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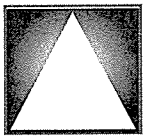
SEVENTH  EDITION

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13 Other Psychotic Disorders

▲ 13.1 Schizoaffective Disorder, Schizophreniform Disorder, and Brief Psychotic Disorder

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There are three disorders in addition to schizophrenia listed in the fourth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) in the section "Schizophrenia and Other Psychotic Disorders." The first, schizoaffective disorder, is a complex illness that has changed significantly over time. In its simplest definition, it is presently conceived as an illness with coexisting, but independent, schizophrenic (psychotic) and mood components. Schizoaffective disorder is seen primarily as part of a schizophrenia spectrum rather than an equal hybrid of mood and schizophrenia disorders. Schizophreniform disorder is a diagnosis that assumes another will replace it after 6 months. Most cases of schizophreniform disorder progress to either schizophrenia or schizoaffective disorder, with some cases rediagnosed as a non–schizophrenia spectrum illness (i.e., schizotypal or schizoid personality disorders), while a few resolve completely. Finally, the diagnosis brief psychotic disorder describes an impairment in reality testing that lasts at least 1 day, but less than 1 month. All three disorders have a psychotic component, are often misunderstood, are incorrectly applied, and are not as well studied as schizophrenia, bipolar I disorder, or major depressive disorder.

SCHIZOAFFECTIVE DISORDER

As the end of the century nears great strides have been made in clarifying the diagnostic criteria for many psychiatric illnesses. However, patients often do not fall neatly into set illness criteria. There are several approaches to dealing with such patients. One is to diagnose the patient with two distinct illnesses and treat those illnesses as separate problems. Another possibility is to consider that the patient has a primary illness and symptoms of a second illness that are not as important and might even resolve when the primary illness is treated. A third approach considers that the patient suffers from a distinct blended illness with its own history, diagnosis, and treatment. This last approach best represents the current orthodoxy in the diagnosis and treatment of patients with the DSM-IV diagnosis of schizoaffective disorder. Unfortunately, this approach is not easily applied, often making the diagnosis confusing and convoluted.

History At the beginning of this century, patients with mental illness were grouped together as suffering from the common illness insanity. With the work of Emil Kraepelin, and Eugene Bleuler, distinct diagnostic groups began to emerge. Kraepelin was able to distinguish an unremitting, dementing illness in young patients that became known as schizophrenia, which he contrasted with an episodic illness of affect now known as bipolar I disorder. However, there were patients who did not fit neatly into either category. Bleuler believed that the presence of any symptoms of schizophrenia even when there was an affective component was still schizophrenia. Patients with mixed features of schizophrenia and affective (mood) disorder were first described by George Kirby and August Hoch in the early part of the century. In 1933, Jacob Kasanin introduced the term "schizoaffective psychosis" to describe a group of patients who had symptoms of both affective and schizophrenic illnesses. While he is credited with introducing the term, on subsequent review of these patients, all would now meet the diagnosis of a pure mood disorder. Nevertheless, the term schizoaffective disorder has survived albeit in several different contexts.

Comparative Nosology One of the difficulties in using a diagnosis that depends on not being another diagnosis is that both depend on changes in the other. Schizoaffective disorder is affected by any changes in the diagnostic criteria of schizophrenia, affective disorder, or both. As psychotic affective disorders and schizophrenia have been better distinguished, those who fall through the "diagnostic cracks" have become clearer. In the second edition of DSM (DSM-II) schizoaffective disorder was a subtype of schizophrenia and denoted patients who had any mood symptoms while meeting the criteria for schizophrenia. In contrast, the Research Diagnostic Criteria (RDC) for schizoaffective disorder allowed as few as one symptom of schizophrenia in a patient who met the criteria for a full affective disorder. The third edition of DSM (DSM-III), influenced by studies in the United States and Great Britain, narrowed the diagnosis of schizophrenia and expanded the diagnosis of bipolar disorder. It allowed symptoms of schizophrenia to coexist with a mood disorder as long as these schizophrenic symptoms did not remain when the mood disorder resolved. Moreover, mood-incongruent psychotic symptoms could now exist in bipolar disorder. Finally, schizoaffective disorder moved from its schizophrenia subtype place to stand alone as a "psychotic disorder not elsewhere classified." The revised third edition of DSM (DSM-III-R) expanded this notion by inserting the criterion that a patient with schizoaffective disorder must meet the criteria for schizophrenia for at least 2 weeks independent of any mood syndrome.

DSM-IV has retained most of the DSM-III-R criteria but has stricter diagnostic criteria for schizophrenia. Patients must meet the symptoms of schizophrenia for at least 1 month as opposed to the previous 1-week criterion. Schizoaffective disorder is now listed in the section "Schizophrenia and Other Psychotic Disorders." The 10th revision of *International Statistical Classification of Diseases*

and Related Problems (ICD-10) essentially describes the same disorder. The ICD-10 schizoaffective disorders describe single as well as recurrent episodes. Subtypes include manic, depressed, and mixed types. Mixed type includes a cyclic schizophrenia and a mixed schizophrenic-mood psychosis.

Epidemiology There is no psychiatric epidemiological study of the incidence or prevalence of schizoaffective disorder in a general population. Even if there were such studies, older reports might not be useful, because the diagnosis (and therefore the incidence and prevalence) would have changed over time. Prevalence rates for consecutive patients diagnosed in a psychiatric treatment setting are available. These numbers range from 2 to 29 percent, a potentially significant cohort requiring treatment. Several lines of evidence support the idea that one might expect an increased prevalence of schizoaffective disorder in women. Women have a higher prevalence of major depressive disorder than men do, and women with schizophrenia express more affective symptoms than men with schizophrenia do. In family studies of patients with schizoaffective disorder, relatives of females with schizoaffective disorder have a higher rate of schizophrenia and depressive disorders than do relatives of males with schizoaffective disorder.

Etiology It is difficult to determine a cause of a disease that has changed so much over time. One might conjecture that the etiology of schizoaffective disorder as currently defined might be similar to the etiology of schizophrenia. Thus etiological theories of schizoaffective disorder would include some genetic and environmental causation. Molecular genetic studies of schizoaffective disorder have lagged behind recent studies of the genetics of schizophrenia and bipolar I disorder. Available family studies have reported that families of schizoaffective probands have significantly higher rates of relatives with mood disorder than families of schizophrenia probands. Similarly, these schizoaffective probands have more psychotic symptoms than families of mood disorder probands. The results of these family studies have argued that schizoaffective disorder is a unique disorder, separate from schizophrenia and mood disorders.

Possible environmental causes of schizoaffective disorder are similar to those of schizophrenia, including in utero insult (including malnutrition and viral causes) and obstetrical complications. One hypothesis considers schizophrenia to be a developmental and progressing disorder that can be seen in the development of brain dysmorphology. This includes less cortical gray matter and more fluid and fluid-filled spaces; however, no definitive study of patients with DSM-IV schizoaffective disorder has been done. One might assume that schizoaffective patients would have similar brain abnormalities, because the disorder mimics many aspects of schizophrenia.

For nearly a half century the prevailing etiologic theory of schizophrenia was the dopamine hypothesis. In its simplest description it postulates that the underlying abnormality is excess dopamine in areas of the brain, leading to psychosis. Thus, successful treatment with antipsychotics is due to their dopamine-blocking properties. With the successful use of clozapine (Clozaril) and other serotonin-dopamine antagonists, the dopamine hypothesis has been amended. Currently, a critical balance between the neurotransmitters dopamine and serotonin is believed to be important for treating schizophrenia. At the same time it is accepted that there are abnormalities of serotonin and norepinephrine in mood disorders. These theories are particularly interesting when considering underlying causes of schizoaffective disorder. Possibly this balance of dopamine and serotonin is particularly affected in schizoaffective disorder, leading to chronic psychosis and intermittent but substantial mood alterations.

Table 13.1-1
DSM-IV Diagnostic Criteria for Schizoaffective Disorder

A. An uninterrupted period of illness during which, at some time, there is either a major depressive episode, a manic episode, or a mixed episode concurrent with symptoms that meet criterion A for schizophrenia.

Note: The major depressive episode must include criterion A1: depressed mood.

B. During the same period of illness, there have been delusions or hallucinations for at least 2 weeks in the absence of prominent mood symptoms.

C. Symptoms that meet criteria for a mood episode are present for a substantial portion of the total duration of the active and residual periods of the illness.

D. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Specify if:

Bipolar type: if the disturbance includes a manic or a mixed episode (or a manic or a mixed episode and major depressive episodes)

Depressive type: if the disturbance only includes major depressive episodes

Diagnostic and Clinical Features DSM-IV diagnostic criteria are provided in Table 13.1-1.

These criteria are a product of several revisions that have sought to clarify several diagnoses including schizophrenia, bipolar disorder, and major depressive disorder. It was hoped that improving these diagnoses would make schizoaffective disorder begin to stand out apart from them. However, the diagnostic criteria still leave much to interpretation. The diagnostician must accurately diagnose the affective illness, making sure it meets the criteria of either a manic or depressive episode but also determining the exact length of each episode (not always an easy or possible task). The length of each episode is critical for two reasons. First, to meet the B criterion (psychotic symptoms in the absence of the mood syndrome) one has to know when the affective episode ends and the psychosis continues. Second, to meet criterion C the length of all mood episodes must be combined and compared with the total length of the illness. If the mood component is present for a substantial portion of the total illness, then that criterion is met. Calculating the total length of the episodes can be difficult, and it does not help that the term "substantial portion" is not defined. In practice, most clinicians look for the mood component to be 15 to 20 percent of the total illness. Patients who have one full manic episode lasting 2 months but who have suffered from symptoms of schizophrenia for 10 years do not meet the criteria for schizoaffective disorder. Instead, the diagnosis would be a mood episode superimposed on schizophrenia. It is unclear whether the bipolar or depressive type specifiers are helpful, although they may direct treatment options. These subtypes are often confused with earlier subtypes (schizophrenic versus affective type) thought to have implications in course and prognosis. As with most psychiatric diagnoses, schizoaffective disorder should not be used if the symptoms are caused by substance abuse or a secondary medical condition.

The ICD-10 diagnostic criteria for schizoaffective disorder are listed in Table 13.1-2.

Table 13.1-2
ICD-10 Diagnostic Criteria for Schizoaffective Disorders

Note. This diagnosis depends upon an approximate "balance" between the number, severity, and duration of the schizophrenic and affective symptoms.

G1. The disorder meets the criteria for one of the affective disorders of moderate or severe degree, as specified for each category.

G2. Symptoms from at least one of the groups listed below must be clearly present for most of the time during a period of at least 2 weeks (these groups are almost the same as for schizophrenia):
(1) thought echo, thought insertion or withdrawal, thought broadcasting (criterion G1(1)a for paranoid, hebephrenic, or catatonic schizophrenia);
(2) delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations (criterion G1(1)b for paranoid, hebephrenic, or catatonic schizophrenia);
(3) hallucinatory voices giving a running commentary on the patient's behavior or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body (criterion G1(1)c for paranoid, hebephrenic, or catatonic schizophrenia);
(4) persistent delusions of other kinds that are culturally inappropriate and completely impossible, but not merely grandiose or persecutory (criterion G1(1)d for paranoid, hebephrenic, or catatonic schizophrenia); e.g., has visited other worlds; can control the clouds by breathing in and out; can communicate with plants or animals without speaking;
(5) grossly irrelevant or incoherent speech, or frequent use of neologisms (a marked form of criterion G1(2)b for paranoid, hebephrenic, or catatonic schizophrenia);
(6) intermittent but frequent appearance of some forms of catatonic behavior, such as posturing, waxy flexibility, and negativism (criterion G1(2)c for paranoid, hebephrenic, or catatonic schizophrenia).

G3. Criteria G1 and G2 above must be met within the same episode of the disorder, and concurrently for at least part of the episode. Symptoms from both G1 and G2 must be prominent in the clinical picture.

G4. *Most commonly used exclusion clause.* The disorder is not attributable to organic mental disorder, or to psychoactive substance-related intoxication, dependence, or withdrawal.

Schizoaffective disorder, manic type

A. The general criteria for schizoaffective disorder must be met.

B. Criteria for a manic disorder must be met.

Other schizoaffective disorders

Schizoaffective disorder, unspecified

Comments

If desired, further subtypes of schizoaffective disorder may be specified, according to the longitudinal development of the disorder, as follows:

Concurrent affective and schizophrenic symptoms only
Symptoms as defined in criterion G2 for schizoaffective disorders
Concurrent affective and schizophrenic symptoms beyond the duration of affective symptoms

Ms. A.D. was a 29-year-old white unmarried woman, with a 10-year history of schizoaffective disorder bipolar type. She was first hospitalized after child protection took her son away for alleged child abuse. When the patient was interviewed at that time, she was described as dressed like a "gypsy" with heavy makeup and pressured speech. She told the treatment team her son had been abused by his father, a well-known rock star. During this time she was stabilized on lithium (Eskalith) and haloperidol (Haldol). A.D.'s manic symptoms resolved, but her belief that she was a rock star's girlfriend remained. Since that first hospitalization she has lost custody of her son. She remains delusional about the child's famous father, and in addition, she believes people are out to get her. She has had three distinct episodes of mania during which she needs little sleep and has racing thoughts and pressured speech. She has been intermittently compliant with medications and is currently receiving haloperidol in a long-acting form. In the 10 years of her illness she has never been free of her delusions. She has not been able to work and receives federal disability assistance.

Differential Diagnosis The psychiatric differential diagnosis includes all the possibilities usually considered for mood disorders and for schizophrenia

In any differential diagnosis of psychotic disorders a complete medical workup should be performed to rule out organic causes of the symptoms. A history of substance use with or without a positive toxicology screening test may indicate a substance-induced disorder. Preexisting medical conditions, their treatment, or both may cause psychotic and mood disorders. Any suspicion of a neurological abnormality warrants consideration of a brain scan to rule out anatomical pathology and an electroencephalogram (EEG) to determine any possible seizure disorders (e.g., temporal lobe epilepsy). Psychotic disorder due to seizure disorder is more common than that seen in the general population. It tends to be characterized by paranoia, hallucinations, and ideas of reference. Epileptic patients with psychosis are believed to have a better level of function than patients with schizophrenic spectrum disorders. Better control of the seizures can reduce the psychosis.

The same hypothetical case is used in the 3 cases below with different outcomes to illustrate the diagnostic decision.

Mrs. B. was a 32-year-old married woman with three children. She reported being relatively happy and free of illness until the birth of her third child. She had the usual "baby blues" that resolved after the first month. When her third child was 14 months old, she began to have trouble sleeping, and her husband noticed that she was sometimes irritable and at other times euphoric. She began to talk rapidly and call family members at all hours of the night. One night her husband received a phone call that his wife was in the county jail. She had secretly left the house, gone to a local bar, and instigated a fight with a female patron. The police thought she was acting wildly and suspected some sort of intoxicant. She was taken to the local psychiatric clinic where a urine toxicology screen was negative. She was admitted to the hospital and treated with the benzodiazepine, lorazepam (Ativan), and the mood stabilizer lithium, and after 2 weeks was completely asymptomatic.

Her diagnosis is bipolar I disorder, manic type.

Discussion The patient suffered from an elevated and euphoric mood alone. She did not exhibit any symptoms of schizophrenia and was appropriately treated with a benzodiazepine, lorazepam, to calm her and long-term treatment with a mood stabilizer, lithium. This patient might have future episodes with hallucinations, delusions, or both. These psychotic symptoms may or may not be congruent with her mood state (e.g., a patient who is depressed and has the delusion of being a terrible person who has committed a crime and deserves to suffer and be punished). However, the psychotic symptom might also be very incongruent with the mood. The critical

distinction for this patient was that the psychotic symptom existed only during the mood episode. Conceptually, the psychosis was fueled by the mood. Correct the mood and there is no fuel for the psychosis and it also disappears.

Mrs. S. was a 32-year-old married woman with three children. She reports that she has been relatively happy and free of illness until the birth of her third child. She had the usual "baby blues" that resolved after the first month. When her third child was 14 months old she began to have trouble sleeping and her husband noticed that she was becoming increasingly isolated and not able to take care of her children. One night her husband received a phone call that his wife was in the county jail. She had secretly left the house, gone to a local bar and instigated a fight with a female patron. The police thought she was acting wildly and suspected some sort of intoxicant. She was taken to the local psychiatric clinic where a urine toxicology screen was negative. At that time she told the staff that she was sure someone was using her social security number and consuming the benefits she would need when she was older. She had gone to the bar because a man's voice had told her that the person who was using her benefits was there. This voice had been talking to her for over a year and often commented on her looks and actions. The patient was admitted to the hospital, treated with the antipsychotic risperidone (Risperdal), and after 2 weeks of treatment was completely asymptomatic.

Her diagnosis is schizophrenia, paranoid type.

Discussion The patient's primary symptoms were delusions and hallucinations without any accompanying mood abnormality. They were of sufficient severity and duration to give her a diagnosis of the paranoid type of schizophrenia, and she was appropriately treated with an antipsychotic agent. Patients suffering from schizophrenia often have both depressive and euphoric symptoms. A common mistake is assuming that a schizophrenic patient presenting with a full range of affect is a patient with schizoaffective disorder. The presence of euphoria or demoralization alone does not meet the criteria for diagnosis of schizoaffective disorder. Patients must both meet the appropriate criteria for the affective disorder and have the affective disorder for a substantial portion of their chronic illness. That said, a patient with schizophrenia suffering from subsyndromal demoralization or disinhibited behavior might benefit from an antidepressant or mood stabilizer, respectively.

Mrs. S.A. was a 32-year-old married woman with three children. She reports that she has been relatively happy and free of illness until the birth of her third child. She had the usual "baby blues" that resolved after the first month. When her third child was 14 months old she began to have trouble sleeping and her husband noticed that she was becoming increasingly irritable, euphoric, isolated and not able to take care of her children. One night her husband received a phone call that his wife was in the county jail. She had secretly left the house, gone to a local bar and instigated a fight with a female patron. The police thought she was acting wildly and suspected some sort of intoxicant. She was taken to the local psychiatric clinic where a urine toxicology screen was negative. At that time she told the staff that she was sure there was someone using her social security number and consuming the benefits she would need when she was older. She also described herself as being one of the 10 smartest people in the world and was sure that the treatment team did not understand her because of their incompetence and she asked to be seen by the head of the hospital. The patient was treated with the antipsychotic risperidone and the mood stabilizer lithium and was completely asymptomatic after 2 weeks of treatment. A year later her husband brought her back to the psychiatric hospital. He reported she had been doing well and was compliant with her medication, which was now lithium carbonate alone. Her mood has been unremarkable, but in the last month she again began to say that someone had stolen her social security benefits. On interview she was calm and cooperative although a little guarded. She reluctantly admitted that the man's voice had returned recently. Risperidone was added back to her regimen, and after 2 weeks she returned to her usual self.

Her diagnosis is schizoaffective disorder, bipolar type.

Discussion The third case (above) displayed symptoms of both a mania and a delusion. She was appropriately treated with an antipsychotic agent and a mood stabilizer. If the vignette had ended there, one might conclude that she had a manic episode with psychotic features. However, she had an exacerbation a year later. This time her mood was totally normal but her delusions and hallucinations returned. She is restarted on the antipsychotic since it appears the mood stabilizer alone was insufficient. It was very appropriate in this circumstance to first taper the patient off the antipsychotic and try the patient on a mood stabilizer alone, aware of the long-term risks of antipsychotics. However, having had the delusional episode while on the mood stabilizer most likely portends a need for intermittent or maintenance antipsychotic treatment.

These 3 women, while having historical details in common, illustrate the differences between a pure mood disorder, schizophrenia, and schizoaffective disorder.

Course and Prognosis

Considering the uncertainty and evolving diagnosis of schizoaffective disorder, determining the long-term course and prognosis is difficult. Given the definition of the diagnosis, one might expect patients with schizoaffective disorder to have either a course similar to an episodic mood disorder, a chronic schizophrenic course, or some intermediate outcome. It has been presumed that an increasing presence of schizophrenic symptoms predicted worse prognosis. Studies using RDC criteria showed that after 1 year patients with schizoaffective disorder had different outcomes depending on whether their predominant symptoms were affective (better prognosis) or schizophrenic (worse prognosis). With the narrower definition of DSM-III-R and DSM-IV, all patients had to have an independent schizophrenic component to meet the diagnosis of schizoaffective disorder. One study that followed patients diagnosed with DSM-III-R schizoaffective disorder for 8 years found that the outcomes of these patients more closely resembled schizophrenia than a mood disorder with psychotic features.

Treatment

There are several extensive reviews of the treatment of schizoaffective disorder, but critical evaluation of the results of these studies is not easy. Because the operational definition of schizoaffective disorder has shifted over the last 30 years, comparing or pooling studies is impossible. The efficacy and selection of treatment for a patient under the broader (more mood disorder inclusive) DSM-II criteria may differ from that of the patient diagnosed with the narrower DSM-III-R criteria. However, there are some general recommendations for treatment. The principle rule is to treat the patient's symptoms, not the diagnostic label.

Mood Stabilizers

Mood stabilizers are a mainstay of treatment for bipolar disorders and would be expected to be important in the treatment of patients with schizoaffective disorder. Few studies have examined the efficacy of mood stabilizers in schizoaffective

disorder, in contrast to the extensive studies of lithium, valproate (Depakote), and to a lesser extent carbamazepine (Tegretol) in bipolar I disorder. A recent study that compared lithium with carbamazepine showed superiority for carbamazepine for schizoaffective disorder, depressive type, but no difference in the two agents for the bipolar type. In practice however, these medications are used extensively alone, in combination with each other, or with an antipsychotic agent. In manic episodes, schizoaffective patients should be treated aggresively with dosages of a mood stabilizer in the middle to high therapeutic blood concentration range. As the patient enters a maintenance phase the dosage can be reduced to low to middle range to avoid adverse effects and potential effects on organ systems (e.g., thyroid and kidney) and to improve ease of use and compliance. Laboratory monitoring of plasma drug concentrations and periodic screening of thyroid, kidney, and hematological functioning should be performed. As in all cases of intractable mania, the use of electroconvulsive therapy (ECT) should be considered.

Psychosis or akathisia must be distinguished from a manic episode. For a psychotic agitation, an antipsychotic agent (often with a benzodiazepine) is indicated. In akathisia, numerous studies have shown that reducing the antipsychotic agent dosage or using benzodiazepine or a β-adrenergic receptor antagonist are helpful.

Antidepressants By definition many schizoaffective patients suffer from major depressive episodes. Treatment with antidepressants mirrors treatment of bipolar depression. Care should be taken not to precipitate a cycle of rapid switches from depression to mania with the antidepressant. The choice of antidepressant should take into account previous antidepressant successes or failures. Selective serotonin reuptake inhibitors (e.g., fluoxetine [Prozac] and sertraline [Zoloft]) are often used as first-line agents because they have less effect on cardiac status and have a favorable overdose profile. However, agitated or insomniac patients may benefit from a tricyclic antidepressant. As in all cases of depression, use of ECT should be considered.

It is very important to try to distinguish psychosis, akinetic syndromes, and primary negative symptoms from depression. Again, psychosis should be adequately treated with an antipsychotic agent. Suspected akinetic treatment can be improved by lowering the dosage of antipsychotic agent, treating with an anticholinergic agent, or switching to a serotonin-dopamine antagonist like clozapine (Clozaril), risperidone, olanzapine (Zyprexa), or quetiapine (Seroquel). Negative symptoms are often difficult to tease out. While there are no definitive studies, these symptoms may improve with the use of serotonin-dopamine antagonists.

Antipsychotic Agents As mentioned above, antipsychotic agents are important in the treatment of schizoaffective disorder. The introduction of chlorpromazine in the 1950s showed antipsychotic agents that block the action of the neurotransmitter dopamine are effective in the treatment of psychosis. Therefore it is not surprising that these compounds are effective in treating the psychotic symptoms that plague patients with schizoaffective disorder. What is not as clear is whether they alone can control both the schizophrenic and the affective symptoms. Because of the complexity and mixed nature of the illness pharmaceutical companies have generally avoided separate studies of antipsychotic agents, with schizoaffective patients. As medications were approved for use in schizophrenia, they were almost immediately used for patients with schizoaffective disorder. With the advent of combined serotonin-dopamine blocking agents, more schizoaffective patients are being recruited for efficacy and safety trials of new antipsychotic agents.

The introduction of the serotonin-dopamine antagonist holds promise for patients with schizophrenia and schizoaffective disorder. While much more data exist on clozapine efficacy in patients with schizophrenia, a few studies have described either comparable or greater efficacy with schizoaffective patients. There may be several reasons why patients diagnosed with schizoaffective disorder respond favorably to clozapine. First, clozapine has been shown to be superior in treating positive symptoms of schizophrenia and therefore the positive symptoms of schizoaffective disorder. Second, akinetic syndromes that can mimic depressive syndromes are greatly reduced with clozapine use. Third, some evidence indicates that clozapine may have mood-stabilizing properties. This hypothesis is based on several studies showing good results using clozapine in patients with difficult cases of bipolar disorder. Data for risperidone, olanzapine, and quetiapine in treating schizoaffective disorder are minimal. One such study showed superiority of haloperidol and amitriptyline over risperidone in a group of psychotic patients (including schizoaffective disorder patients) with depressive symptoms.

Psychosocial Treatment Considering the present notion that schizoaffective disorder as specified in DSM-IV closely resembles schizophrenia, one can assume that psychosocial treatment of schizoaffective disorder should mimic that of psychosocial treatment of schizophrenia. Therefore, patients should benefit from a combination of family therapy, social skills training, and cognitive rehabilitation. Because the psychiatric field has had difficulty deciding the exact diagnosis and prognosis of schizoaffective disorder, this uncertainty must be explained to the patient. Historically, patients and families have been told that schizoaffective illness has a better prognosis than schizophrenia, but this may no longer be true. Patients and their families must contend with an evolving diagnosis; they may be told the patient is suffering from a treatable mood disorder at first and later told that it is a severe psychotic disorder. The range of symptoms can be quite large as patients contend with both ongoing psychosis and varying mood states. It can be very difficult for family members to keep up with the changing nature and needs of these patients. Medication regimens can be more complicated, with multiple medications frequent, and psychopharmacological education is important. However it is often difficult to explain to patients and their families that new medication treatments have been tested in affective and schizophrenic disorders but not schizoaffective disorder.

SCHIZOPHRENIFORM DISORDER

History Gabriel Langfeldt, first used the term *schizophreniform* in 1939, at the University Psychiatric Clinic in Oslo, Norway. As originally used, this diagnosis relied on a tradition of Scandinavian psychiatry, which had identified a condition that had relatively brief and self-contained psychotic intervals. Patients recovered well and had affective and sometimes hysterical components to their illness, and the diagnosis was used to distinguish a group considered to have little relation to true schizophrenia.

Comparative Nosology In contrast to this rather specific role for schizophreniform disorder, the current DSM-IV diagnosis has relatively little to do with the origin of the term and much more to do with the tradition of Kraepelinian schizophrenia as a chronic illness. Prior to the DSM-IV revision of this diagnostic entity, DSM-III and DSM-III-R had used this diagnosis as a "schizophrenia-in-waiting" diagnosis, with the only difference between the two diag-

noses being whether the illness had lasted a total of 6 months including psychotic, prodromal, and residual symptoms. Under the DSM-III and DSM-III-R systems, the psychotic phase of the illness needed to last only 1 week, and less if treated successfully. The remainder of the 6-month-duration criteria for schizophrenia comprised residual or prodromal symptoms. Patients who had an insidious onset with prodromal symptoms preceding the onset of psychotic symptoms by at least 6 months would be given a diagnosis of schizophrenia as soon as the psychotic symptoms lasted 1 week. Those who had limited prodromal symptoms or who had sudden onset of psychosis as the first sign of illness, however, would not be diagnosed as having schizophrenia until the total period of illness reached 6 months. During what for many was a waiting period, the diagnosis of schizophreniform disorder would be used. Because of the relatively brief period of psychosis required (1 week) on the one hand and the similarity with schizophrenia on the other, this category formerly consisted of patients with potentially many types of psychoses—brief reactive psychosis, "schizophrenia-in-waiting," and true schizophreniform disorder. Unfortunately, the true schizophreniform disorder would be difficult to sort out from this diagnostic system, and relative to the other categories it is probably quite rare, although potentially important as a time-limited psychotic illness that returns to baseline functioning without residual symptoms.

The revisions of DSM-IV have made one of the above overlaps less likely—the one with brief reactive psychosis. To separate these two disorders diagnostically, the DSM-IV diagnosis for schizophreniform disorder requires a month of psychotic symptoms rather than 1 week. Further, brief reactive psychosis has changed to brief psychotic disorder because the diagnostic criteria reaction-to-a-stressor was considered too ubiquitous—but DSM-IV includes the concept as a specifier. From the other side, the diagnosis of schizophreniform has moved much closer to its parent diagnosis of schizophrenia with the requirement for 1 month of psychotic symptoms. Although no data are currently available on the course of schizophreniform illness, the requirement for a greater duration of psychotic illness will probably make it less likely that a given patient will recover before 6 months of total illness comprising both psychotic symptoms and residual or prodromal symptoms (now referred to as attenuated symptoms) is reached.

This category now looks exactly like schizophrenia with an unanticipated full recovery before 6 months. Some data suggest that those who indeed do recover before 6 months have better 5- and 10-year outcomes. Whether this represents a separate disorder category or merely one end of a distribution of outcomes in schizophrenia is yet to be determined. There will always be the unusual patient who appears to have schizophrenia but recovers completely. They are exceedingly rare. Further, this category of illness continues to be severely hampered by a lack of research, and indeed the changing criteria for diagnosis makes it difficult to focus on this "moving target." Most data will continue to be anecdotal. ICD-10 does not have a designated schizophreniform disorder, although the concept is included in several categories. The diagnosis acute schizophrenia-like psychotic disorder describes a disorder that would otherwise be considered schizophrenia but with symptoms lasting less than 1 month. If the symptoms persist past the month, the ICD-10 diagnosis of schizophrenia should be used. There is also a subclassification for a schizophreniform psychosis manic or depressed type under "schizoaffective disorders"; however, according to DSM-IV, schizophreniform disorder is subsumed order ICD-10's category of other schizophrenia.

Another reason for having this diagnostic category is that it avoids having to use the term *schizophrenia* with all of its negative connotations early in the diagnostic formulation. Many families require considerable time to reconcile the future of their family member. A gradual introduction to the concept of schizophreniform disorder, with a waiting period during which the family can more realistically orient itself and learn about the illnesses in the schizophrenia spectrum may prove helpful to some. Further, because of the negative connotation of schizophrenia and the stigma currently attached to it, a diagnostic system that avoids a false-positive diagnosis of schizophrenia is desirable. A 6-month duration of illness prior to making the diagnosis of schizophrenia will eliminate virtually all false-positive diagnoses.

As noted above, schizophreniform disorder shares an overlap with schizophrenia with two exceptions: the duration of illness is from 1 to 6 months and social or occupational dysfunction is not required to meet the diagnosis, although it may occur at some point in the illness. Given the requirement of 1 month of psychotic symptoms, however, it seems quite unlikely that a person's social and occupational functioning would not be disrupted. DSM-IV describes two possible conditions for this diagnosis: (1) when a person has recovered within the 6-month period (the "pure" form of schizophreniform disorder) and (2) when a person has not had the illness long enough (6 months) to meet the diagnosis of schizophrenia. For this latter condition, the term "provisional" is used. A guide for clinicians is given as a part of the diagnosis, which should be qualified by the presence or absence of good prognostic signs. The following are listed, and two are required for the qualifier of good prognosis: (1) rapid onset of psychotic symptoms, (2) confusion at the peak of psychotic symptomatology, (3) good premorbid social and occupational functioning, and (4) maintenance of a range of affect.

As with most psychiatric diagnoses, schizophreniform disorder should not be used if substance abuse or a secondary medical condition causes the symptoms.

Epidemiology Because of the significant change in the diagnostic criteria for schizophreniform disorder in DSM-IV, there are currently no epidemiological data from community samples. The risks of drawing from treatment samples are well known in terms of the variability introduced by clinic type, socioeducational variables, urban/rural factors, and even treatment philosophy. The elegance of the Epidemiologic Catchment Area (ECA) study with its five sites, using census track data collection, is not likely to be repeated in the near future, and its data were derived using DSM-III criteria. The significant changes from that period would include changing from 1 week of psychotic symptoms to 1 month, adding the concept of "provisional" diagnosis, and adding the good prognostic signs. Clearly, lengthening the requirement for psychotic symptoms was the most significant change, because it eliminated what most certainly were many cases of brief psychotic disorder. The data from the ECA study indicate a lifetime prevalence of 0.2 percent and a 1-year prevalence of 0.1 percent. Even with inclusion of cases of brief psychosis, this is a relatively small category. One could extrapolate that with the further stringency of DSM-IV, the category would become even smaller.

Etiology Because of the change in the duration of illness, most persons who fall in this category will have underlying pathologies similar to those with schizophrenia. This will certainly be true for those who carry this diagnosis provisionally while waiting for the 6-month time period to elapse before changing the diagnosis to schizophrenia. There has been ample speculation about whether "acute" schizophrenia (rapid onset, good premorbid functioning) differs from

insidious-onset schizophrenia in anything more than severity of such factors as negative symptoms. A rapid and complete response to a treatment intervention may eventually help to differentiate those in this category from standard antipsychotic nonresponders. The concept that the heterogeneity of the underlying biology may be responsible for differential treatment response is not new, but it has been given increasing credibility with the advent of the serotonin-dopamine antagonists (clozapine, risperidone, olanzapine, and quetiapine). It is now probably safe to say that any set of biological, neurophysiological, psychologic or other tests will find this group of patients looking much more closely like schizophrenia than any other category. In fact, the abnormalities consistent with schizophrenia may already be present in schizophreniform disorder. One such abnormality, decreased gray matter volume, has been seen in MRI studies but to a lesser extent than in patients with chronic schizophrenia. The cause of pure schizophreniform disorder will probably not be known for a long time, because a patient group that small will be hard to study.

Diagnostic and Clinical Features The DSM-IV criteria for schizophreniform are listed in Table 13.1-3. Schizophreniform disorder in its typical presentation is a rapid-onset psychotic disorder without a significant prodrome. Hallucinations, delusions, or both will be present; negative symptoms of alogia and avolition may be present. Affect may be flattened, which is seen as a poor prognostic sign. Speech may be grossly disorganized and confused, and behavior may be disorganized or catatonic. The symptoms of psychosis, the negative symptoms, and those affecting speech and behavior will last at least 1 month but may last longer. The patient's degree of perplexity about what is happening should be assessed, as this is a differentiating prognostic sign.

Although the above is the typical presentation, a picture exactly resembling that of schizophrenia may also occur. In that case, the onset may be insidious, premorbid functioning may have been poor, and affect is quite blunted. The only differentiation from schizophrenia for this type of presentation will be duration of the total episode of illness. When it has lasted 6 months, the diagnosis becomes schizophrenia. In making the diagnosis in the case with insidious onset, the "attenuated symptoms" of the acute episode may have lasted for some time. If they have been present for at least 5 months and then the acute episode lasts 1 month, the diagnosis of schizophrenia is appropriate, without a prior diagnosis of schizophreniform disorder.

In the typical form of the disorder, the patient returns to baseline functioning by the end of 6 months. Theoretically, repeated episodes of schizophreniform illness are possible, each lasting less than 6 months, but rarely is functioning not lost with repeated episodes of this severe illness, and schizophrenia is a more likely consideration.

Ms. L.J. was a 29-year-old Hispanic second daughter of an intact and stable family. She completed high school without problems and was described as outgoing and friendly. She considered college but opted to work. She spent several years as factory worker and had decided to go back to school and become a teacher. Five months ago she had a sudden "awareness" that God was present and filling the souls of people around her. She became acutely distressed when she realized God was not going to "touch her." Her family was quite surprised and alarmed by her sudden change in behavior. She was brought to the local emergency room. While she occasionally drank alcohol and had smoked marijuana in the past, the family did not suspect a substance abuse problem. Toxicology screening in the emergency room was negative for substances. She was admitted to the hospital for evaluation. She told the psychiatrist that she felt she had done something wrong and that was why God had abandoned her. She also reported that she felt people on the ward were reading her mind. She was particularly concerned that her critical thoughts about others could be heard and then these angry people would attack her. L.J. was stabilized on haloperidol then switched to risperidone because of side effects. A family meeting was held to discuss her problems. At that time, the psychiatrist recommended a wait-and-see approach. The psychiatrist told the family and patient to follow up with an outpatient doctor and remain on the medication if the outpatient psychiatrist recommended it. Two months after her admission she no longer was distressed by her religious concerns. However, she still felt people could read her mind. Three months after her admission she no longer felt that people could read her mind, and she had returned to her community college. A month later, she stopped taking her antipsychotic agent because she felt she didn't need it. Two weeks ago her family brought her to the emergency room because she was again talking about God and "hiding" from people who could read her thoughts. She initially refused medications but resumed taking them, with some improvement of her psychosis. A family meeting was held to discuss the return of her psychosis and the fact that she may eventually be diagnosed with schizophrenia.

Table 13.1-3
DSM-IV Diagnostic Criteria for Schizophreniform Disorder

A. Criteria A, D, and E of schizophrenia are met.

B. An episode of the disorder (including prodromal, active, and residual phases) lasts at least 1 month but less than 6 months. (When the diagnosis must be made without waiting for recovery, it should be qualified as "provisional.")

Specify if:

Without good prognostic features

With good prognostic features as evidenced by two (or more) of the following:

(1) onset of prominent psychotic symptoms within 4 weeks of the first noticeable change in usual behavior or functioning

(2) confusion or perplexity at the height of the psychotic episode

(3) good premorbid social and occupational functioning

(4) absence of blunted or flat affect

Differential Diagnosis Although the major differential diagnoses are with brief psychotic disorder and schizophrenia, the rapid onset of acute psychosis may be the most important diagnostic point in a patient's course of illness. The clinician should focus on the prior 6 months, taking a detailed history of occupational and social functioning, the pattern of onset, the presence or absence of mood changes, alcohol and substance abuse, and other illness and prescriptive medication. Of special interest will be any family history of psychiatric illness, mood disorders or schizophrenia-like illnesses in particular. A recent study showed a high prevalence of personality disorders after recovery from the psychosis. One could hypothesize that the personality disorder predisposes one to psychosis especially when under stress.

A complete physical examination is always indicated with the presentation of a psychotic illness. Suggestions of endocrinologic

involvement, such as thyroid functioning, should be followed up with laboratory studies. If substance abuse is suspected, however remote a possibility, a toxicology screening test should be performed. Changes in sensorium and the rapid onset of symptoms should raise clinical suspicion of substance toxicity. Alcohol may be involved in a number of ways. Certainly, alcohol withdrawal and the onset of delirium may be associated with psychotic symptoms. Further, alcohol abuse leads to unreliable medication taking, even of prescribed medications, which can lead to psychotic features.

The separation of mood disorders with psychotic features from a rapid-onset schizophreniform disorder may be difficult and tests the clinician's skills. Negative symptoms such as alogia, avolition, and blunted affect may be difficult to distinguish from the loss of interest and pleasure seen with major depressive episodes. Appetite, sleep, and other neurovegetative symptoms may also occur with both. The presence of the psychotic features of the illness, in the absence of these mood features, will assist the clinician in making the diagnosis of schizophreniform disorder, but this may take time to evolve.

To differentiate from brief psychotic disorder, a time cutoff has been established, more than 1 day but less than 1 month. During this period, the diagnosis must be brief psychotic disorder. In diagnostic systems prior to DSM-IV, the presence or absence of a stressor was used to differentiate these two conditions further, but it is no longer used in the nosology, except as a descriptor or modifier. Differentiation is based solely on the time line.

Course and Prognosis The course of schizophreniform disorder is for the most part defined in the criteria. It is a psychotic illness lasting more than 1 month and less than 6 months. The real issue is what happens to persons with this illness over time. Most estimates of progression to schizophrenia range between 60 and 80 percent. What happens to the other 20 to 40 percent is currently not known. Some will have a second or third episode during which they will deteriorate into a more chronic condition of schizophrenia. A few, however, may have only this single episode and then are able to continue on with their lives. While this is clearly the outcome desired by all clinicians and family members, it is probably a rare occurrence and should not be held out as likely.

The prognostic features used to characterize the illness are listed above. Their presence will, indeed, be useful in suggesting some likelihood of a favorable outcome. Clinical experience, however, tempers the confidence in these predictors, as many patients with all four of the descriptors have a deteriorating course and outcome.

Treatment Although no available studies have directly addressed the treatment of schizophreniform disorder, the approach should be that for any psychotic disorder of recent onset. The most important initial evaluation is safety, both for the patient and the patient's environment.

Safety Assessment of safety or danger is a complex series of probabilities, not certainties. The best predictor is, of course, past behavior. Someone suffering from the sudden onset of psychosis may not have any past history if this is the first episode. If so, any evidence of prior violence must be seriously considered in forming the initial treatment plan. The evaluation of predictability and hostile affect becomes critical in deciding whether hospitalization is necessary. With someone suffering from an acute psychotic disorder who shows any signs of hostility, anger, and confusion or has a history of explosive or violent activity, hospitalization should be an important consideration. In the absence of these features, hospitalization may be a consideration if the environment itself, usually the family, cannot comfortably ensure that the treatment plan can be carried out in a safe, stress-reducing manner. For most families this will not be possible.

Inpatient Treatment Plan The inpatient unit is usually a significant part of the initial treatment plan. In addition to pharmacological management, the unit program and philosophy are critical ingredients in helping to stabilize the patient as rapidly as possible. An environment that is critical, intrusive, and overinvolved, with a multistimulus approach to the patient has negative impact on psychosis-prone patients. With this in mind, the patient should not necessarily be required to attend group meetings, therapeutic community, or orientation but should rather be approached in a one-on-one manner with time-limited interactions. Communication should be direct and simple, and the program should be structured with relatively little free time. Visitors should be oriented to this same principle and should be encouraged to visit one at a time.

Outpatient Treatment Plan The patient who has begun to recover from an acute psychotic episode will continue to need a comfortable environment with considerable structured activity. Complex communications and interactions should be kept to a minimum early, although introduction of some simple group work in an attempt to normalize socialization may be carefully planned. Gradual resumption of activities should be attempted one at a time, with mastery achieved before the introduction of new activities. In the case of a student, for example, it would be much better to begin with one course and succeed than with a full course load that would most likely lead to failure. Incremental progress is the goal, and it should extend well beyond the 6 months required for diagnosis.

Role of the Family There is no more significant factor in the successful outcome of a patient with acute onset psychosis than family involvement in the treatment. As reviewed elsewhere, the data are compelling that a clinical treatment program that enlists the family in a positive clinical alliance does better than one that does not, regardless of the other treatment modalities being used. There is no more consistent finding in outcome studies of the late 1980s and 1990s than the positive outcomes found in programs that work with families. In general, most of these programs begin with some form of educational program about schizophrenia, the importance of medication, the expectations of families, and the identification of early signs of impending relapse. Some of the programs have worked elaborately with patients and their families with behavioral paradigms, others have worked with monthly group interactions involving multiple patients and their families. For many of these families this introduction to working as a member of the treatment team enlists them into a long-term positive relationship with the treatment program. For others, it gives them the skills needed to participate in the rehabilitation process. This positive alliance will serve the program, the patient, and the family well. It opens lines of communication and takes a major step toward ensuring that the patient will receive the best monitoring and most appropriate treatment available. Active involvement of a family support group, such as the local chapter of the Alliance for the Mentally Ill, is often quite useful as well. Frequently, however, families experiencing their first episode of psychosis in a family member find association with a group of people who have family members with chronic illnesses to be too threatening. They may wish

to believe that their family member will recover, and certainly for those who have true schizophreniform disorder, this will be true.

Pharmacological Therapy The pharmacological approach to the acutely psychotic patient is one of the most challenging and difficult in all of psychiatry. There was an era in psychiatry when there was time to observe the patient to determine whether there was a transient condition that would be self-limiting. The economic forces of today's psychiatry do not permit such an observation period and demand vigorous pharmacological intervention. Perhaps the sole remaining condition in which it would be reasonable to wait before vigorous pharmacological intervention is one that elicits a high index of suspicion of chronic amphetamine abuse, with a positive toxicology screening test result. With these patients it is probably better to wait and treat the agitation with benzodiazepines; the psychosis will usually resolve. Even among these patients will be a small but significant group who will continue with what looks like a schizophreniform or schizophrenia-like illness. Whether this group represent a subgroup of patients who were already at risk for schizophrenia or whether chronic amphetamine abuse sensitizes dopamine receptors in some patients is not known.

Given that it is not economically feasible to wait before initiating treatment, selection of the most appropriate medication becomes a critical decision. The choices basically come down to selection of an antipsychotic agent. For many years this decision involved selecting the antipsychotic agent whose side-effect profile fit the needs of the patient best. If the patient was agitated, a more sedating antipsychotic agent (e.g., chlorpromazine [Thorazine], thioridazine [Mellaril]) would be selected. If not, a less sedating, high-potency compound would be used (e.g., haloperidol, fluphenazine [Prolixin]). Both strategies, however, exposed the patient to extrapyramidal adverse effects initially and to tardive dyskinesia if long-term continuation was needed. With the use of anticholinergic medications, some of the extrapyramidal symptoms could be reduced. However, anticholinergic medications themselves have been associated with decrements in memory, executive functioning, and new learning. Therefore they are used much less frequently than previously and certainly not used routinely unless adverse effects are present. There are now other choices with the advent of the novel serotonin-dopamine antagonists. These antipsychotic agents, while considerably more expensive, hold out the advantage of fewer extrapyramidal adverse effects. They may rapidly become the medications of first choice for psychosis, because they are much better tolerated by the patient and are thus more likely to be taken over a period of time, eliminating the potential for relapse from noncompliance. The expense of readmission of a patient more than makes up for the difference in cost.

Dosage of any antipsychotic agent should be at the lowest possible level, both for adverse effect prevention and for cost. There is a tendency for medication dosages to climb in an effort to shorten the length of the psychosis. Originally, the concept of "rapid neuroleptization was a method of treatment in which a patient was given antipsychotic medication every hour until sedated. Thorough evaluation of this strategy revealed no therapeutic advantages and considerably increased risk for acute dystonic reaction. It is now widely accepted that the full resolution of a psychotic episode may take anywhere from 3 to 6 weeks. Pressure to discharge a patient well before this time certainly places considerable psychological pressure on the physician to increase the medication dosage. It is not clear that there is any advantage to doing this, and maintaining a lower dosage keeps the patient considerably less uncomfortable with adverse effects. If agitation is a problem, addition of a medium- to long-acting benzodiazepine will usually produce the desired results. Benzodiazepines are much better at sedation than are antipsychotic agents. Data suggest that use of a benzodiazepine reduces the amount of an antipsychotic agent that must be used.

A small subgroup of patients present with an acute psychotic episode that rapidly resolves. The more rapid the resolution, the more likely it is that they have a self-limited disorder. These patients will probably not meet the DSM-IV diagnosis of schizophreniform disorder with its requirement of 1 month of symptomatology.

For those whose symptoms do last 1 month or longer and who meet the criteria for schizophreniform disorder, there is a question of how long do they need to be on medication. Although no study has directly addressed this question with patients who met DSM-IV criteria for schizophreniform disorder, strategies have been tested on patients with schizophrenia who have been recruited in an acute episode. Patients who were taken off medication in the first 6 months did much worse than those who were maintained at standard dosages or those who had an 80 percent reduction of dosage. Currently, the low-dosage strategy for maintenance should be considered with the standard antipsychotic agents and probably with the serotonin-dopamine antagonists as well.

With the standard antipsychotic agents, a completely resolved psychotic episode, and full return to premorbid functioning, the usual decision point has been 6 months. This time frame was driven by the finding that almost no cases of tardive dyskinesia occur before 6 months of continuous medication. Going beyond 6 months does increase this risk. With the serotonin-dopamine antagonists, tardive dyskinesia is presumed to be a much lower risk if at all, and thus clinical judgment is needed. If a gradual tapering strategy is selected, the dosage should not be lowered more frequently than every 3 to 4 months if the physician wishes to see the effect of one dosage lowering before initiating the next. Unlike antibiotic use, for example, the infection may well return quickly after premature discontinuation of the medication, psychosis does not immediately reappear even if the medication is completely eliminated. Relapse curves from dosage-discontinuation studies are quite compelling in this regard.

BRIEF PSYCHOTIC DISORDER

History Brief psychotic disorder is a new diagnosis in DSM-IV that subsumes the former diagnostic category of brief reactive psychosis, which first appeared in DSM-II. Brief psychotic disorder is one of the least understood and least studied types of functional psychosis; most research has had methodological flaws and unclear diagnostic criteria. Historically, Karl Jaspers described the concept of a reactive psychosis in 1913. Jaspers described the essential features, which include presence of an identifiable traumatic stressor, close temporal relation between stressor and psychosis, and generally benign course of the psychotic episode.

Jaspers also believed that the content of the psychosis was related to the trauma and served some therapeutic purpose.

Comparative Nosology Over the past century myriad terms have been used to describe psychotic episodes precipitated by stressful events, including good-prognosis schizophrenia, but brief reactive psychosis had gained prominence until the DSM-IV. Compared with the DSM-III and DSM-III-R criteria that required a precipitating stressor and confusion or emotional turmoil during the episode, the new diagnosis of brief psychotic disorder is less restrictive. With its broader definition, brief psychotic disorder will presumably reduce the use of the classification "psychotic disorder not otherwise speci-

fied." Because stressors and reactions to stressors are so ubiquitous and ill defined, reactivity to a stressor is no longer necessary for the diagnosis and is used instead as a descriptor. Scandinavian researchers have been integral in delineating this disorder, which has been gradually gaining international recognition. Conceptual generalization of the disorder is both supported and challenged by culture-bound syndromes such as koro and amok, which demonstrate significant differences while still falling under the rubric of brief psychotic disorder. The ICD-10 classifies these symptoms as "acute and transient psychotic disorders" (see Table 13.3-1). Subtypes include "acute polymorphic psychotic disorder without symptoms of schizophrenia," which has an overall picture of unstable, highly emotional symptoms with psychotic features that would not justify a diagnosis of schizophrenia. In contrast, the diagnosis acute polymorphic psychotic disorder with symptoms of schizophrenia also describes an unstable clinical picture, but symptoms of schizophrenia are also present for a major part of the time. If the acute picture is marked by delusions, only a diagnosis of "other acute predominately delusional psychotic disorders" can be used. Finally, any unspecified transient psychotic disorder can be designated as other or unspecified acute and transient psychotic disorders.

Epidemiology Relatively uncommon in DSM field trials, brief psychotic disorder has large discrepancies in reported incidence and prevalence rates because of methodological flaws and diagnostic variability in the literature. Its age of onset is most commonly reported to be in the late 20s or early 30s. Although reliable data on sex and sociocultural determinants are limited, preliminary data suggest a higher incidence in women and persons in developing countries. Such epidemiological patterns are sharply distinct from those of schizophrenia.

Etiology Little is known about the etiology of brief psychotic disorder. The existence of one or many events becomes the identified causative agent in psychotic disorder with marked stressor (brief reactive psychosis). Both the magnitude and the multiplicity of such stressors are posited to be important, but no well-controlled studies assessing the causal role of various types of stressors are available. Severe intrapsychic conflict (an internal stressor) may be the etiological agent for brief psychotic disorder without a marked stressor. Preexisting characterological psychopathology of either cluster A or B variety may predispose a person to development of the disorder. Many explanatory models of this increased vulnerability exist, but most are based on immature defenses and ego development as major contributors. Family studies support a genetic vulnerability to brief reactive psychosis but do not support a genetic link between this disorder and schizophrenia.

Diagnostic and Clinical Features The DSM-IV diagnostic criteria are listed in Table 13.1-4. DSM-IV defines brief psychotic disorder as impairment in reality testing lasting at least 1 day but not more than 1 month. An eventual full return to premorbid levels of functioning is required; if the diagnosis is made without waiting for the anticipated recovery, then the qualifier provision must be added. At least one of the following symptoms is present during the circumscribed illness: delusions, hallucinations, disorganized speech, disorganized behavior, or catatonia. Exclusionary criteria include the presence of a mood disorder with psychotic features, schizoaffective disorder, schizophrenia, and any psychotic disorder secondary to the direct physiological effects of a substance or a general medical condition. If symptoms occur in response to one or more events that would be markedly stressful to almost anyone in similar circumstances and within the same cultural context, then the illness bears the specifier *with marked stressor* (formerly referred to as brief psychotic disorder). Conversely, if symptoms are not in response to such an event, the specifier *without marked stressor* is applied. An additional specifier, *with postpartum onset,* indicates the onset of psychotic symptoms within 4 weeks postpartum.

Table 13.1-4
DSM-IV Diagnostic Criteria for Brief Psychotic Disorder

A. Presence of one (or more) of the following symptoms:
   (1) delusions
   (2) hallucinations
   (3) disorganized speech (e.g., frequent derailment or incoherence)
   (4) grossly disorganized or catatonic behavior

   Note: Do not include a symptom if it is a culturally sanctioned response pattern.

B. Duration of an episode of the disturbance is at least 1 day but less than 1 month, with eventual full return to premorbid level of functioning.

C. The disturbance is not better accounted for by a mood disorder with psychotic features, schizoaffective disorder, or schizophrenia and is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Specify if:

With marked stressor(s) (brief reactive psychosis): if symptoms occur shortly after and apparently in response to events that, singly or together, would be markedly stressful to almost anyone in similar circumstances in the person's culture

Without marked stressor(s): if psychotic symptoms do *not* occur shortly after, or are not apparently in response to events that, singly or together, would be markedly stressful to almost anyone in similar circumstances in the person's culture

With postpartum onset: if onset within 4 weeks postpartum

Patients with brief psychotic disorder typically have rapid-onset psychotic symptomatology and often demonstrate emotional turmoil, confusion, or both. Prompt recovery with a full return to premorbid level of functioning within a month is dictated by definition. It is imperative to assess the impact of culture on symptom presentation prior to making the diagnosis. In the case of brief reactive psychosis, the precipitant may be one or a series of life stressors, such as the loss of an important relationship, familial disruption, or combat-related trauma. In such cases, environmental adversity combines with cultural expectations and support systems to manifest symptoms distinctly.

R.S. was a 44-year-old Haitian male admitted for observation at the local emergency room. He was agitated and combative, requiring restraints and several intramuscular doses of droperidol and lorazepam. The psychiatrist could not interview him under these acute circumstances. His mother arrived soon after and was able to give corroborative history. According to his mother the patient had just learned that his wife and two children had died in a natural disaster in Haiti. Several hours after his first evaluation, the patient was calmer. He told staff that he was hearing his wife talking to him and he wished to "join her." He also believed the Haitian secret police were coming to arrest him. He was admitted to the inpatient ward and began a course of an antipsychotic agent. By the third day of his hospitalization there was no evi-

dence of the previous psychosis. He was discharged from the hospital and given a follow-up appointment in 1 month. When he returned the next month he had been medication free for that time. He was grieving the loss of his family but was not psychotic. He was referred to a grief group, which he attended for the next 6 months. In that time he remained sad, but there were no other episodes of paranoia or hallucinations.

Differential Diagnosis Sharing rapid onset of symptoms, brief psychotic disorder must be differentiated from substance-induced psychotic disorders and psychotic disorders due to a general medical condition. A thorough medical evaluation including a physical examination, laboratory studies, and brain imaging will help rule out many of those conditions. With only cross-sectional information, brief psychotic disorder is difficult to differentiate from other types of functional psychosis.

The relationship between brief psychotic disorder and both schizophrenia and affective disorders remains uncertain. As noted above, DSM-IV has made the distinction between brief psychotic disorder and schizophreniform disorder clearer by now requiring a full month of psychotic symptoms for the latter. If psychotic symptoms are present longer than 1 month, the diagnoses of schizophreniform disorder, schizoaffective disorder, schizophrenia, mood disorders with psychotic features, delusional disorder, and psychotic disorder not otherwise specified need to be entertained. If psychotic symptoms of sudden onset are present for less than a month in response to an obvious stressor, the diagnosis of brief psychotic disorder is strongly suggested. Other diagnoses to differentiate include factitious disorder, malingering, and severe personality disorders, with consequent transient psychosis possible.

Course and Prognosis The course of brief psychotic disorder is found in the diagnostic criteria of DSM-IV. It is a psychotic episode that lasts more than 1 day but less than 1 month, with eventual return to premorbid level of functioning. Approximately half of patients diagnosed with brief psychotic disorder retain this diagnosis; the other half will evolve into either schizophrenia or a major affective disorder. There are no apparent distinguishing features between brief psychotic disorder, acute-onset schizophrenia, and mood disorders with psychotic features on initial presentation. Several prognostic features have been proposed to characterize the illness, but they are inconsistent across studies. The good prognostic features are similar to those found in schizophreniform disorder: acute onset of psychotic symptoms, confusion or emotional turmoil at the height of the psychotic episode, good premorbid functioning, the presence of affective symptoms, and short duration of symptoms. There is a relative dearth of information on the recurrence of brief psychotic episodes, however, so the course and prognosis of this disorder have not been well characterized.

Treatment Although no available studies directly address the treatment of brief psychotic disorder, the treatment approach should focus on the acute onset of psychotic symptoms. In particular, patient safety is of paramount importance. Depending on the danger the patient represents to self and others, psychiatric hospitalization is often warranted. A patient demonstrating acute psychotic symptoms who also displays a hostile affect or has a history of violence is particularly likely to require hospitalization. In addition to providing a safe and structured environment, hospitalization permits observational monitoring and a medical examination investigating potential etiological factors.

If medication is necessary, a high-potency antipsychotic agent in low dosage is typically recommended. An antiparkinsonism agent may be added if extrapyramidal adverse effects occur. A benzodiazepine used in combination with an antipsychotic agent can act synergistically, thereby lowering the necessary doses of each and reducing the risk of side effects. Benzodiazepines can also be used as monotherapy to reduce agitation without obscuring the clinical picture. The role of other psychotropic medications such as mood stabilizers and antidepressants is not yet clear.

After the acute episode has subsided, long-term treatment is required. An individualized treatment strategy based on increasing problem-solving skills while strengthening the ego structure through psychotherapy, appears to be the most efficacious. Involvement of the family in the treatment process is crucial to a successful outcome and is reviewed elsewhere in this chapter. There is no role for maintenance antipsychotic treatment in brief psychotic disorder; if such treatment is required, the diagnostic assumptions must be questioned.

SUGGESTED CROSS-REFERENCES

A more detailed review of schizophrenia is presented in Chapter 12; acute and transient psychotic disorders are presented in Section 13.3. Mood disorders are covered in Chapter 14. Personality disorders are discussed in Chapter 24.

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▲ 13.2 Delusional Disorder and Shared Psychotic Disorder

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Once viewed as too rare to warrant a separate classification, delusional disorder has emerged in recent years as a focus of clinical research and treatment innovation. Better definition and a growing literature have revitalized the efforts to characterize, understand, and treat these conditions. Limited but growing evidence supports not only its occurrence, but its distinctiveness from schizophrenia and mood disorder as well as its treatability. Delusional disorder refers to a group of disorders, the chief feature of which is the presence of a nonbizarre delusion. It is the delusion and the relative absence of other psychopathology that unifies these disorders in terms of natural history and impact on functioning. Once called *paranoia,* this condition as defined in the fourth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) and the 10th revision of *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) is easier to recognize and less subject to misdiagnosis.

Despite such advances, clinicians are relatively ill-informed about delusional disorders and many have only seen an occasional example. There are several possible reasons why this is so. Persons with this condition do not regard themselves as mentally ill and actively oppose psychiatric referral. Because they may experience little impairment, they generally remain outside hospital settings, appearing reclusive, eccentric, or odd, rather than ill. If they do have contact with professionals, it is more likely to be with lawyers regarding litigious concerns; with medical specialists regarding health concerns; or with the police regarding complaints of trespass, persecution, or threat, rather than with psychiatric clinicians regarding complaints of emotional disorder. A hallmark of these disorders is that the patient does not believe that he or she is deluded or in need of psychiatric assistance. In the infrequent psychiatric encounter, clinicians tend to diagnose these disorders as other conditions, often as schizophrenia or mood disorders.

Although delusional disorders are uncommon, they are probably not as rare as previously thought. While many individuals with such disorders seek assistance from other medical specialists, judges, or the police, they are increasingly being recognized as psychiatrically ill. The relationship of these disorders to other psychoses remains unclear, and much about them is puzzling. The DSM-IV requirement of excluding other conditions is prudent given the special importance of differential diagnosis. Armed with newer and better criteria, clinical research is ongoing in areas such as natural history, pathogenesis, neuropsychology, neuroimaging, treatment, and even genetics. Although the DSM-IV criteria are not definitive, they have provided a sound basis for clinical and research investigation. Systematic studies based on larger samples of these disorders are needed to anchor classification with sound information; however, such studies may be difficult to conduct because of the large numbers of patients required and their reluctance to participate in research. A biological basis for these disorders is proposed on many grounds, but its definition remains elusive. The study of misidentification syndromes (e.g., the Capgras's syndrome) has led to interesting hypotheses and methods that draw on neuropsychological and clinical insights that may inspire progress in delusional disorders. Treatment remains an obstacle, although recent reports suggest that favorable responses to psychopharmacologic and psychotherapeutic interventions are more common than previously thought.

DEFINITION

Delusional disorder is the current classification for a group of disorders of unknown cause, the chief feature of which is the delusion (Table 13.2-1). Although the specific content of the delusion may vary from one case to the next, it is the occurrence of the delusion, its persistence, its impact on behavior, and its prognosis that unifies these seemingly different disorders. In considerable agreement with Emil Kraepelin's concept of paranoia, the revised third edition of DSM-III-R provides reliable criteria for identifying cases and collecting systematic information about these conditions. This development in classification helped to reestablish the clinical importance of this group of disorders and may have reversed a trend of infrequent diagnosis. The criteria use the term *delusional* to avoid the ambiguity of the term *paranoid* used earlier in the third edition of DSM (DSM-III) classification, *paranoid disorders,* as well as to emphasize that the category includes disorders in which delusions other than those of the persecutory or jealous type are present. Although these changes were initially confusing, especially in terms of comparisons to diagnostic approaches elsewhere, they have gained acceptance and have created a more level playing field for further empirical contributions.

In 1994 DSM-IV refined the definition and the boundaries with other disorders, including substance-induced disorders, mental disorders due to general medical conditions, mood disorders, and schizophrenia. No laboratory test exists to assist in diagnosis. The DSM-IV definition, like its predecessors, hinges on the presence of a nonbizarre delusion. DSM-IV acknowledges the difficulty of judging whether a delusion is bizarre, meaning clearly implausible, not understandable, and not derived from ordinary life experiences. In contrast, the nonbizarre delusion involves situations or circumstances that can occur in real life (e.g., being followed, infected, or deceived by a lover). DSM-IV also emphasizes the differential diagnoses of schizophrenia, mood disorders, substance-induced disorders, and mental disorders due to a general medical condition before the diagnosis of delusional disorders can be made. These conceptual refinements and demarcations from other conditions have increased the usefulness of the criteria for delusional disorder.

Delusional Disorder According to DSM-IV, the diagnosis of delusional disorder can be made when a person exhibits nonbizarre delusions of at least 1 month's duration that cannot be attributed to other psychiatric disorders. Definitions of the term *delusion* and types relevant to delusional disorders are presented in Table 13.2-1. *Nonbizarre* means that the delusions must be about situations that can occur in real life, such as being followed, infected, loved at a distance, and so on; that is, they usually have to do with phenomena that, although not real, are nonetheless possible. There are several types of delusions, and the predominant type is specified when the diagnosis is made.

Table 13.2-1
DSM-IV Definition of Delusion and Certain Common Types Associated With Delusional Disorders

Delusion A false belief based on incorrect inference about external reality that is firmly sustained despite what almost everyone else believes and despite what constitutes incontrovertible and obvious proof of evidence to the contrary. The belief is not one ordinarily accepted by other members of the person's culture or subculture (e.g., it is not an article of religious faith). When a false belief involves a value judgment, it is regarded as a delusion only when the judgment is so extreme as to defy credibility. Delusional conviction occurs on a continuum and can sometimes be inferred from an individual's behavior. It is often difficult to distinguish between a delusion and an overvalued idea (in which case the individual has an unreasonable belief or idea but does not hold it as firmly as is the case with a delusion).

Delusions are subdivided according to their content. Some of the more common types are listed below:

Bizarre—A delusion that involves a phenomenon that the person's culture would regard as totally implausible.

Delusional jealousy—The delusion that one's sexual partner is unfaithful.

Erotomanic—A delusion that another person, usually of higher status, is in love with the individual.

Grandiose—A delusion of inflated worth, power, knowledge, identity, or special relationship to a deity or famous person.

Mood-congruent—See mood-congruent psychotic features.

Mood-incongruent—See mood-incongruent psychotic features.

Of being controlled—A delusion in which feelings, impulses, thoughts, or actions are experienced as being under the control of some external force rather than being under one's own control.

Of reference—A delusion whose theme is that events, objects, or other persons in one's immediate environment have a particular and unusual significance. These delusions are usually of a negative or pejorative nature, but also may be grandiose in content. This differs from an idea of reference, in which the false belief is not as firmly held nor as fully organized into a true belief.

Persecutory—A delusion in which the central theme is that one (or someone to whom one is close) is being attacked, harassed, cheated, persecuted, or conspired against.

Somatic—A delusion whose main content pertains to the appearance or functioning of one's body.

Thought broadcasting—The delusion that one's thoughts are being broadcast out loud so that they can be perceived by others.

Thought insertion—The delusion that certain of one's thought are not one's own, but rather are inserted into one's mind.

Mood-congruent psychotic features—Delusions or hallucinations whose content is entirely consistent with the typical themes of a depressed or manic mood. If the mood is depressed, the content of the delusions or hallucinations would involve themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment. The content of the delusion may include themes of persecution if these are based on self-derogatory concepts such as deserved punishment. If the mood is manic, the content of the delusions or hallucinations would involve themes of inflated worth, power, knowledge, or identity, or a special relationship to a deity or a famous person. The content of the delusion may include themes of persecution if these are based on concepts such as inflated worth or deserved punishment.

Mood-incongruent psychotic features—Delusions or hallucinations whose content is not consistent with the typical themes of a depressed or manic mood. In the case of depression, the delusions or hallucinations would not involve themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment. In the case of mania, the delusions or hallucinations would not involve themes of inflated worth, power, knowledge, or identity, or a special relationship to a deity or a famous person. Examples of mood-incongruent psychotic features include persecutory delusions (without self-derogatory or grandiose content), thought insertion, thought broadcasting, and delusions of being controlled whose content has no apparent relationship to any of the themes listed above.

In general, the patient's delusions are well systematized and have been logically developed. The person may experience auditory or visual hallucinations, but these are not prominent features. Tactile or olfactory hallucinations may be present and prominent if they are related to the delusional content or theme, examples are the sensation of being infested by bugs or parasites, associated with delusions of infestation, and the belief that one's body odor is foul, associated with somatic delusions. The person's behavioral and emotional responses to the delusion appear to be appropriate. Impairment of functioning is not marked and personality deterioration is minimal, if it occurs at all. General behavior is neither obviously odd nor bizarre.

Shared Psychotic Disorder This unusual condition has also been called *folie à deux* and *induced or shared psychotic disorder.* It develops in an individual in the context of a close relationship with another person who has an established delusion that he or she also believes, and requires an absence of psychotic disorder prior to the onset of the induced delusion; it is usually classified with paranoid disorders.

HISTORY

Nineteenth-century psychiatry devoted much attention to the description of paranoid disorders, in which delusions are a cardinal feature. Karl Ludwig Kahlbaum's description of paranoia in 1863 was the first in a series of contributions that culminated in the classification of paranoia, and inspired that of folie à deux, morbid jealousy, the better-known schizophrenias, and mania. His work also led to a recognition that paranoid features are nonspecific characteristics of many medical diseases. Subsequent work has led to refined criteria for paranoid and related disorders and has reestablished awareness of less common paranoid presentations such as delusional disorder.

Many clinicians remember being taught that paranoia is so rare that most would not see a single such patient during an entire career. This widespread belief has compromised interest in paranoid disorders. The fact that most persons with delusional disorder live in the community and do not generally seek psychiatric care has made it difficult to carry out systematic case studies. Indeed, knowledge of these conditions has grown slowly. However, case series such as those of Alistair Munro (for delusional disorder, somatic type) or those of Nils Retterstol have been influential in shaping understanding and awareness. What they reveal is that there are persons with these disorders, that the disorders are complex forms of psychiatric illness, and that much remains to be learned.

A major change in the classification of delusional disorders in DSM-III-R and DSM-IV has been to emphasize the central role of delusions in those disorders and to steer away from the vague label of *paranoid,* which has become synonymous with *suspicious* and has come to apply largely to a personality disorder. Indeed, suspiciousness occurs in only some of these disorders. The history of the concept of paranoia indicates that lack of clarity in its use is not

new. The word *paranoia* was coined by the ancient Greeks from roots meaning *beside* and *self.* Hippocrates applied this term to delirium associated with high fever, but other writers used it to describe demented conditions and madness. It sometimes meant thinking amiss, folly, and the like; hence, its meaning was unclear. For centuries the term fell into disuse until a revival of interest in the nineteenth century.

In 1863 Karl Kahlbaum classified paranoia as a separate mental illness: "a form of partial insanity, which throughout the course of the disease, principally affected the sphere of the intellect." Influenced by the new scientific methods of empirical medicine, Kahlbaum emphasized the importance of natural history in mental illness and restricted the use of the term *paranoia* to a persistent delusional illness that remained largely unchanged throughout its course. He noted that delusions could occur in other medical and psychiatric conditions.

Emil Kraepelin found the paranoid concept troublesome and altered his thinking on it with each edition of his influential textbook. His final view advocated three types of paranoid disorder. Like Kahlbaum, Kraepelin based his conclusions on an analysis of the natural history of mental disorders, particularly on outcome, because etiology was obscure. He restricted the definition of paranoia to an uncommon, insidious, chronic illness (he saw 19 cases) characterized by a fixed delusional system, an absence of hallucinations, and a lack of deterioration of the personality. The types of delusions included persecutory, grandiose, jealous, and possibly hypochondriacal. He considered this illness to derive from defects in judgment, a disorder of personality caused by constitutional factors and environmental stress. Paraphrenia was a second paranoid disorder that developed later than dementia precox and was milder. Hallucinations (auditory in particular) occurred, but there was no mental deterioration (dementia). Finally, there was *dementia paranoides,* an illness that initially resembled paranoia but had an earlier onset and showed a deteriorating course. Because of this latter feature, Kraepelin considered dementia paranoides a form of dementia precox that arose from disorders of thought, cognition, and emotion. Kurt Mayer's follow-up of Kraepelin's 78 paraphrenia cases challenged the validity of this category because the vast majority of patients showed an outcome indistinguishable from that of dementia precox, casting doubt on the separability of this group. Karl Kolle's follow-up of Kraepelin's paranoia cases indicated some overlap with dementia precox. Kraepelin also emphasized that isolated paranoid symptoms occurred in a variety of psychiatric and medical illnesses.

Eugen Bleuler also recognized paranoia; he broadened its definition to include cases with hallucinations—a paranoid form of dementia precox for which he coined the term *schizophrenia*—and an intermediate group. However, he thought that the paranoia described by Kraepelin was so rare that it did not warrant a separate classification. Further, he argued that schizophrenic symptoms must be suspected and carefully sought even in those cases. He believed that paraphrenia and intermediate conditions were forms of schizophrenia linked by "much that was identical," and particularly by a common disturbance in associative processes. He also emphasized that paranoid symptoms occurred in other conditions and that to label the symptoms schizophrenic required at least one of the fundamental symptoms: loosened associations, ambivalence, inappropriate affect, and autism. Bleuler's contributions reinforced a trend toward the diagnosis of paranoid illness as a form of schizophrenia.

Sigmund Freud used the autobiographical writings of Judge Daniel Schreber to illustrate the role of psychological defense mechanisms in the development of paranoid symptoms. He proposed that Schreber's illness involved a process of denial or contradiction of repressed homosexual impulses toward his father. Persecutory and other delusions result from projecting these denied yearnings onto the environment. Freud did not differentiate subtypes of paranoid disorder, and confused the issue somewhat by proposing that the term *paraphrenia* be substituted for the term *dementia precox* or *schizophrenia.* The major impact of Freud's work was to suggest hypotheses that indicated the relationship between certain delusions and personality.

Ernst Kretschmer's work on the theory of paranoia emphasized that certain sensitive personalities, characterized by depressive, pessimistic, and narcissistic traits, developed paranoid features acutely when key or precipitating experiences occurred at critical moments in their lives. He observed that these individuals did not develop schizophrenia and had a favorable prognosis. A number of other observations, predominantly but not exclusively emanating from European clinicians (e.g., the American concept of *hysterical psychosis*), proposed connections between personality and delusion development. Those efforts, based on various theories of the cause of paranoid disturbance, have persisted despite modest empirical support. Out of such work have come terms, such as *reactive* and *psychogenic psychosis,* which have figured in various classification schemes, undermining the effort to bring international consistency in definition.

Many barriers remain to international agreement on definition. For example, the term *paraphrenia,* unlike *paranoia,* has slipped into near obscurity in North America. In the United Kingdom, however, the diagnosis of late paraphrenia is often used and it is occasionally used in the United States. This term refers to cases of late-onset paranoid symptomatology not characterized by the presence of dementia, confusion, or mood disorder. Interestingly, Kraepelin did not identify a late age of onset in his cases. The potential overlap with late-onset cases of schizophrenia has been a focus of investigation and controversy. With the removal of the DSM-III age criterion for schizophrenia (upper limit of age of onset at 45) in DSM-III-R, cases of late-onset symptoms have tended to be diagnosed as schizophrenia in the United States. Nevertheless, clinical research continues to address the puzzle of whether late-onset cases, despite considerable overlap in clinical features, arise from a variety of causes.

Current controversy is based on these historical antecedents and contemporary practices. DSM-III introduced greater rigor in the assessment by requiring clearer criteria boundaries among the varied disorders with delusions. Increased awareness that delusions result from numerous conditions has had a positive influence on the diagnostic process. Yet much of current clinical and research writing on paranoid conditions has characteristically avoided defining the terms *paranoid* and *delusion,* apparently because everyone was assumed to know what these terms mean. In popular and literary usage the term *paranoid* has come to mean insane, angrily suspicious, distrustful, or irrationally irritable. However vague the concept may be, it continues to be used in clinical work. Because it is necessary to differentiate conditions with paranoid features, a useful concept of the term is fundamental. However, the nature and definition of delusions upon which modern psychopathology and psychiatry are built remain unclear.

Shared Psychotic Disorder Jules Baillarger first described the syndrome in 1860, calling it *folie à communiquée,* although the first description is commonly attributed to Ernest Charles Lasègue and Jules Falret, who described the condition in 1877 and gave it the name of *folie à deux.* The syndrome has also been called *communicated insanity, contagious insanity, infectious insanity, psychosis*

Table 13.2-2
Conditions and Agents Associated With Delusions and Other Paranoid Features

- Neurological disorders
  - Adrenoleukodystrophy
  - Arteriosclerotic psychoses
  - Blunt head trauma
  - Brain tumors
  - Cerebrovascular disease
  - Cerebral anoxia
  - Complex partial seizure disorder
  - Delirium
  - Dementia
  - Fat embolism
  - Hearing loss
  - Huntington's disease
  - Hydrocephalus
  - Hypertensive encephalopathy
  - Idiopathic basal ganglia calcification
  - Idiopathic Parkinson's disease
  - Intracranial hemorrhage
  - Marchiafava-Bignami disease
  - Menzel-type ataxia
  - Metachromatic leukodystrophy
  - Migraine
  - Motor-neuron disease
  - Multiple sclerosis
  - Muscular dystrophy
  - Narcolepsy
  - Postencephalitic parkinsonism
  - Presenile dementia (Alzheimer's and Pick's diseases)
  - Roussy-Levy syndrome
  - Senile psychoses
  - Spinocerebellar degeneration
  - Subarachnoid hemorrhage
  - Subdural hematoma
  - Sydenham's chorea
  - Temporal arteritis
- Metabolic and endocrine disorders
  - Acute intermittent porphyria
  - Addison's disease
  - Complication of surgical portacaval anastomosis for cirrhosis
  - Cushing's syndrome
  - Folate deficiency
  - Hemodialysis
  - Hypercalcemia
  - Hypoglycemia
  - Hyponatremia
  - Hypopituitarism
  - Liver failure
  - Malnutrition
  - Niacin deficiency
  - Pancreatic encephalopathy
  - Parathyroid disorders
  - Pellagra
  - Pernicious anemia
  - Phenylketonuria
  - Systemic lupus erythematosus
  - Thiamine deficiency
  - Thyroid disorders
  - Uremia
  - Vitamin B_{12} deficiency
  - Wilson's disease
- Sex chromosome disorders
  - 47 XXY
  - Klinefelter's syndrome
  - Turner's syndrome
- Infections
  - Acquired immune deficiency syndrome
  - Encephalitis lethargica
  - Creutzfeldt-Jakob disease
  - Malaria
  - Syphilis
  - Toxic shock syndrome
  - Trypanosomiasis
  - Typhus
  - Viral encephalitides
- Psychiatric disorders
  - Brief psychotic disorder
  - Delusional disorder (including classic paranoia)
  - Shared psychotic disorder
  - Mood disorders
  - Psychotic disorders not otherwise specified
  - Schizoaffective disorder
  - Schizophrenia (all types)
  - Schizophreniform disorder
- Alcohol and other substances
  - Alcohol withdrawal
  - Amphetamine
  - Anesthetic nitrous oxide
  - Atropine toxicity
  - Barbiturate
  - Chronic alcohol hallucinosis
  - Chronic bromide intoxication
  - Cocaine
  - Ephedrine
  - Marijuana
  - Mescaline and other hallucinogens
  - Perbitine
  - Withdrawal from minor tranquilizers and hypnotic medications
- Toxic agents
  - Arsenic
  - Carbon monoxide
  - Manganese
  - Mercury
  - Thallium
- Pharmacological agents
  - Adrenocorticotropic hormone
  - Amphetamine and related compounds
  - Antiparkinson agents
  - Anabolic steroids
  - Antiarrhythmic drugs
  - Antibiotics (cephalosporin, penicillin)
  - Anticholinergic drugs
  - Antihypertensive agents
  - Antimalarials
  - Antitubercular drugs
  - Bromocriptine
  - Bupropion
  - Chemotherapeutic agents (asparaginase)
  - Cimetidine
  - Corticosteroids
  - Diphenylhydantoin
  - Disulfiram
  - Imipramine and other tricyclic drugs
  - Levodopa
  - Mephentermine
  - Methyldopa and imipramine (combination)
  - Pentazocine
  - Phenylpropanolamine and sympathomimetic agents
  - Propylhexedrine

of association, and *double insanity.* Marandon de Montyel divided *folie à deux* into three groups (*folie imposée, folie simultanée,* and *folie communiquée*), and Heinz Lehmann added a fourth group, *folie induite.*

PARANOID CONCEPT

Paranoid signs and symptoms are among the most dramatic and serious disturbances in psychiatry and medicine but the term *paranoid* refers to a variety of behaviors that may not be psychopathological nor indicative of schizophrenia; hence, the meaning of the term has become obscure. Some clinicians label ordinary suspiciousness paranoid; others restrict use of the term to persecutory delusions; still others apply the term only to grandiose, litigious, hostile, and jealous behavior, despite the fact that those behaviors may be within the normal spectrum. To make the paranoid concept useful and less vague requires consideration of several points:

1. The term *paranoid* is a clinical construct used to interpret observations, and in order to apply this construct effectively, the clinician must know its meaning and be able to make accurate observations of potentially paranoid behavior.
2. Use of the term *paranoid* means the clinician has judged that the person's behavior is psychopathological. This judgment is usually based on the discovery that the person who displays such features is either disturbed or disturbing to others.
3. Although many contributions to understanding paranoid phenomena have focused on conditions in which paranoid features are central (e.g., schizophrenia for Bleuler, paranoia and dementia paranoides for Kraepelin), those features are not necessarily associated with schizophrenia and can appear in other psychiatric and medical disorders. Hence, paranoid features indicate psychopathology, but no specific cause or outcome (Table 13.2-2).
4. The observations that form the basis for judging behavior to be paranoid are of two kinds: subjective (part of the private mental experience of the patient, e.g., a delusion) and objective (observable as a manifest form of behavior, such as litigiousness, guardedness, and grandiosity). Table 13.2-3 is a list of the subjective and objective features that have traditionally been labeled paranoid and that are frequently found in association; some of these features can be manifestations of normal behavior. The judgment that such features are paranoid may rest on how extreme or inappropriate they are, their presence in combination or association with other behaviors on the list, and the presence of delusions.
5. The term *paranoid delusion* has traditionally referred to a wide variety of delusions, not simply those of grandeur, persecution, or jealousy. Because of recent confusion that term probably should not be used. The term *paranoid* and related terms are defined in Table 13.2-4.

Delusions When Karl Jaspers formulated the concept of delusion widely used today, he suggested three criteria: (1) subjective certainty, (2) incorrigibility, and (3) falsity of content. He viewed these criteria as tentative, preferring to consider them as approximations to a definition in that they provided practical suggestions for detecting delusions rather than actually defining them. This and later contributions emphasized a certain humility about the delusion concept that has not been sustained in contemporary formulations of this psychopathological feature. Numerous, often ignored, problems compromise the clinical research utility of the delusion concept. For example, according to DSM-III-R and DSM-IV, delusion is "an incorrect inference about external reality." This definition has certain

Table 13.2-3
Paranoid Features

Objective features
- Anger
- Critical, accusatory behavior
- Defensiveness
- Grandiosity or excessive self-importance
- Guardedness, evasiveness
- Hate
- Hostility
- Humorlessness
- Hypersensitivity
- Inordinate attention to small details
- Irritability, quick annoyance
- Litigiousness (letter writing, complaints, legal action)
- Obstinacy
- Resentment
- Seclusiveness
- Self-righteousness
- Sullenness
- Suspiciousness
- Violence, aggressiveness

*Subjective features**
- Delusions of self-reference, persecution, grandeur, infidelity, love, jealousy, imposture, infestation, disfigurement
- Overvalued ideas

* Part of private mental experience. The patient often discloses those features during the clinical interview, but may not do so, even with specific questioning.

Table 13.2-4
Terminology Connected with Paranoia

Delusional disorders DSM-III-R category emphasized that the cardinal feature of these conditions is delusions; DSM-IV criterion is one or more nonbizarre delusions lasting for more than 1 month

Paranoia Old term for an insidiously developed disorder in which persons suffer from an unshakable delusional system but have no disturbance in the clarity or form of their thinking; also known as *paranoia vera, simple delusional disorder, delusional monomania*

Paranoic or paranoiac Old adjectives used to describe persons with paranoia

Paranoid Broad term meaning suspicious to most people. In psychiatry it is a clinical construct used to describe various objective and subjective features of behavior deemed to be psychopathological; refers to no specific condition (e.g., to be paranoid does not mean that schizophrenia is present)

Paranoid delusion Older term used to refer to persecutory and grandiose delusions because of their occurrence in the paranoid subtype of schizophrenia; this term has suffered from the confusion associated with the paranoid concept; DSM-III-R recommended that it no longer be used

Paranoid disorders DSM-III term for an idiopathic group of conditions including paranoia, acute paranoid disorder, shared paranoid disorder, and atypical paranoid disorder; no longer used

Paranoid personality Enduring traits of paranoid behavior not due to schizophrenia or other mental disorder; generally, there is no evidence of delusions or other features of psychosis

Paranoid syndrome Term applied to constellations of paranoid features that occur together and can arise from multiple sources including depression, general medical conditions, substance-induced disorders, and schizophrenia

Paraphrenia Old term for conditions lying theoretically between schizophrenia and paranoia and sharing features of both (hallucinations but no deterioration). It, too remains controversial and probably should not be used until research validates its meaning. In use in U.K. Designate patients with late-onset paranoid features without confusion, dementia, or mood disorder

implicit and complicating features: (1) there is a process of inference separable from the belief that the process produces, (2) this same process is used by normal persons to generate beliefs about the world, and (3) this process is impaired in delusional patients. As pointed out later in this chapter, the validity of the latter two assertions is questionable. Also, central to the concept of delusional disorder is the distinction between *bizarre* (impossible) and *nonbizarre* (possible) delusions. This distinction has been difficult to apply reliably in clinical assessment, yet on it rests considerable weight in making the diagnosis of delusional disorder. Further examples of difficulties concerning the definition of delusion have been discussed by Manfred Spitzer, who has traced the movement from philosophy to empirical science in the evolution of the definition of delusion. Awareness of the vagaries and imprecise nature of the definition of delusion is essential to clinical and research efforts.

Since the early nineteenth century delusions have been classified by content or theme. Other descriptive dimensions have gained acceptance through clinical use and some empirical research: understandability, degree of certainty, systemization, complexity, relevance to patient's life, plausibility, onset, associated psychopathology, and time course. These features are used to grasp the nature of the delusional experience, translate clinical observations into diagnostic and treatment interventions, and design research.

In clinical encounters delusions are usually easy to detect. Certain features (Table 13.2-3) of the patient's behavior may suggest the presence of delusions or help confirm the impression that the beliefs are delusional. In subtle cases, however, this task is more challenging. The clinician must make a judgment, based on the behavior and reported private mental experience of the patient, of whether or not delusional beliefs are present. Attempts to present counterevidence and argument may be useful to determine whether the patient's views can be influenced by evidence that is usually sufficient to alter the belief of a normal person. This judgment often depends on deciding whether a threshold indicative of psychopathological disorder has been passed, possibly reflected in the inappropriateness or extreme nature of the patient's behavior, rather than the simple truth or falsity of the belief. In practice, the only effective approach to assessing delusions is to put together as comprehensive a picture as possible regarding the nature of the patient's condition. Lacking laboratory tests for delusions, clinical judgment will be required to some degree in virtually all cases. At the theoretical level, the definition of delusions is moving gradually away from its roots in philosophy and phenomenological description toward a more empirically derived set of features. This process will take considerable time to achieve a satisfactory resolution of the many issues plaguing this aspect of psychopathology.

COMPARATIVE NOSOLOGY

Certain advances have been made in the nosology of delusional disorders, but the variety of current definitions illustrates that consensus has not yet been achieved. The reasons for such differences are multiple: the principal reason is the lack of relevant data—delusional disorders occur infrequently. Typically, patients continue to function and live in the community without ever seeking clinical intervention. When they do, the condition is easily misdiagnosed because patients may have minimal overt identifying characteristics. Limited knowledge, based largely on case reports, exists; systematic, larger-scale studies are uncommon. Most of these studies are European and have employed varied classifications. Also, the fundamental concept that these disorders are distinct from schizophrenia and mood disorders has until recently been unrecognized by many psychiatrists.

Kahlbaum was the first to use the term *paranoia* to designate a diagnostically separate group of disorders. Kraepelin developed this diagnostic concept further by emphasizing the chronic and unremitting nature of paranoia and the lack of other features such as hallucinations that distinguished it from schizophrenia. In 1952 the first edition of DSM (DSM-I) defined paranoid reactions as conditions in which there are persecutory or grandiose delusions, with emotional responses and behavior consistent with the delusions, but generally lacking hallucinations. The subtypes were *paranoia* (a chronic disorder with systematized delusions) and *paranoid state* (a more acute, less persistent condition with less systematized delusions). In 1968 DSM-II largely preserved these concepts.

DSM-III Although new definitions were established in DSM-III in 1980, earlier concepts are still evident. The essential features of paranoid disorders according to DSM-III were persistent persecutory delusions or delusional jealousy not due to any other mental disorder. Included in the group of paranoid disorders were paranoia, shared paranoid disorder, acute paranoid disorder, and a residual category called atypical paranoid disorder. The boundaries between these conditions and other disorders, such as paranoid personality disorder or paranoid schizophrenia, were noted to be vague. Different types of paranoid disorders were classified on the basis of chronicity. The criteria narrowed the bounds of previous classifications by not including cases with marked hallucinations or certain delusions (e.g., hypochondriacal, erotomanic, and others).

DSM-III-R In 1987 DSM-III-R simplified the DSM-III definition, attempted to minimize the confusion associated with the term *paranoid,* and highlighted the view that the formation of delusions in the absence of schizophrenia, mood disorder, or organic disorder is the essential feature of these conditions. In contrast to DSM-III, diagnosis in DSM-III-R and DSM IV requires a month-long duration of symptoms. Subtyping is based on the predominant type of delusion, which is specified (such as jealous, erotomanic, or somatic). This latter feature broadens the category to include a variety of unusual delusions as well as the more common persecutory type. In many respects these criteria are virtually identical to Kraepelin's definition of paranoia. The two exceptions were Kraepelin's reluctance to endorse a subtype of somatic or hypochondriacal paranoia or to permit cases with hallucinations to fall within this diagnosis. Kraepelin believed that cases with hypochondriacal delusions rarely occurred in this pattern.

Shared paranoid disorder was renamed *induced psychotic disorder* in DSM-III-R and was placed in the category of psychotic disorders not elsewhere classified, along with schizophreniform, schizoaffective disorders, and brief reactive psychosis. This represents a fundamental departure from DSM-III, which classified this disorder among the paranoid disorders. The delusional content of patients with this disorder may concern not only persecution or jealousy but virtually any form of delusion, hence the change in terminology. The term *induced* may better describe the nature of the condition, but hardly resolves the puzzle of causation.

DSM-IV In 1994 a revised classification made modest changes in the DSM-III-R criteria in an attempt to refine the definition of delusional disorders. In DSM-III-R the distinction between schizophrenia and delusional disorders had been unclear and controversial. In DSM-III-R this boundary was defined by the nonbizarre qualities of delusions in delusional disorder and the absence of other active-phase symptoms of schizophrenia. Also important was the required

absence of other odd or bizarre behavior apart from the delusion. Because the distinction between *bizzare* and *nonbizarre* is difficult to define and therefore to apply reliably, other terms such as *systematized* and *prominent* were suggested. In practice, however, those terms also have limitations. This problem has helped to promote the case for modifying the criteria in another way: specifically, to use the level of impaired functioning as a means of characterizing the distinction between schizophrenia (considerable impairment) and delusional disorders (relatively less impairment). However, the variability of outcomes in both disorders undermines this strategy somewhat. DSM-IV suggests that when poor functioning occurs in delusional disorder, it is the result of the delusional beliefs themselves. For example, a person quits a job because he or she believes that the fumes in the workplace are causing a cancerous growth. That person's financial situation worsens and preoccupation with repeated medical consultations enhances a downward spiral. In contrast, poor functioning in schizophrenia usually results from cognitive compromise and positive and negative symptoms, especially avolition. The resolution of how to make modifications, however, depends on the effectiveness of the criteria in defining homogeneous and valid subsets of psychotic disordered patients. For this purpose, field trials and data analyses have been used to inform the decision scientifically. Although the DSM-IV criteria reflect progress, their validity remains only partly established.

Another unsettled issue that DSM-IV attempts to resolve is the classification of delusional variants of somatoform disorder, specifically body dysmorphic disorder. In this condition the patient suffers from preoccupation with imagined or slight defects in appearance (such as skin blemishes, the size of one or more body parts); it is accompanied by impairment in social and occupational functioning, shame, and repetitive, often ritualistic behaviors. These may include skin picking, mirror checking, requests for reassurance, and attempts to camouflage the supposed deformity. In some cases, the preoccupation appears to be delusional. However, the relationship between nondelusional and delusional variants is unclear; whether the disorders are distinct or overlapping remains unknown. DSM-IV permits dual diagnosis of body dysmorphic disorder and delusional disorder when a delusional belief is present in the former condition. This resolution, in which the same symptoms are given two diagnoses, accurately reflects the available research data on the relationship of these two disorders and also underlines the need for further research to clarify these distinctions. A similar problem arises with respect to delusional variants of hypochondriasis and of obsessive-compulsive disorder, and a similar solution is applied: obsessive-compulsive disorder patients may also be diagnosed as delusional disorder.

Shared Psychotic Disorder DSM-IV renamed the DSM-III-R category *induced psychotic disorder,* calling it *shared psychotic disorder.* This change reflects the attempt to avoid the term *paranoid* and to identify the condition without reference to any presumed cause or mechanism. The goal is to define the boundaries between this condition and more common ones, such as other psychotic disorders, mood disorders with psychotic features, substance-induced psychotic disorders, and psychotic disorders due to a general medical condition.

ICD The ninth revision of *International Statistical Classification of Diseases* (ICD-9) contained more categories for paranoid disorder than the American schemes. Most paranoid disorders fall under the rubric *paranoid state,* including simple paranoid state, paranoia, paraphrenia, and induced psychosis. Additional subcategories include other and unspecified paranoid states. Acute paranoid reactions and psychogenic paranoid psychosis are classified separately. DSM-III, DSM-III-R, and DSM-IV generally reflect an atheoretical position with respect to the causes of these disorders whereas ICD-9 was less neutral. For example, psychogenic paranoid psychosis implies a kind of causal mechanism. The categories of paranoid disorder according to these classifications are summarized in Tables 13.2-5.

ICD-10 pays more attention to creating classifications similar to DSM-III-R and DSM-IV. Paraphrenia, for example, is subsumed under persistent delusional disorder but delusions must be present for about 3 months in order to diagnose delusional disorder. The subtypes of the disorder overlap with DSM-IV subtypes. For those conditions of less duration, acute and transient psychotic disorder is diagnosed. Induced (shared) delusional disorder is considered a separate designation with a phenomenology similar to persistent delusional disorder.

EPIDEMIOLOGY

Delusional disorder has been considered an uncommon if not rare condition from its earliest descriptions even though epidemiological information is meager. Recent demographic evidence covering a period from 1912 to the 1970s provides an estimate of incidence, preva-

Table 13.2-5
Comparative Nosology of Delusional Disorder

ICD-9 (1979)	DSM-III (1980)	DSM-III-R (1987)	ICD-10 (1993)	DSM-IV (1994)
Paranoid state, simple			Delusional disorder	
Paranoia	Paranoia	Delusional (paranoid) disorder	Delusional disorder	Delusional disorder
Paraphrenia (involutional paranoid state, late paraphrenia)			Delusional disorder	
Induced psychosis (folie á deux, induced paranoid disorder)	Shared paranoid disorder	Induced psychotic disorder	Induced delusional disorder	Shared psychotic disorder
Other specified states (paranoia querulans, Sensitiver Beziehungswahn)			Delusional disorder	
Unspecified paranoid states	Atypical paranoid disorder		Persistent delusional disorder, unspecified	
Acute paranoid reaction (bouffée délirante)	Acute paranoid disorder		Paranoid reaction	
Psychogenic paranoid psychosis (protracted reactive paranoid psychosis)				

Table 13.2-6
Epidemiological Features of Delusional Disorder

Incidence*	0.7–3.0
Prevalence*	24–30
Age at onset (range)	18–80 (mean 34–45 years)
Type of onset	Acute or gradual
Sex ratio	Somewhat more frequently female
Prognosis	Best with early, acute onset
Associated features	Widowhood, celibacy often present; history of substance abuse, head injury not infrequent

Portions of the table adapted from K S Kendler: Demography of paranoid psychosis (delusional disorder). Arch Gen Psychiatry *39:* 890, 1982.
* Incidence and prevalence figures represent cases per 100,000 population.

lence, and related statistics (Table 13.2-6). However, this evidence was assembled using definitions that are not the same as those of DSM-III, DSM-III-R, or DSM-IV. Subsequent data will in all likelihood be somewhat different using the newer criteria. It is clear that the estimates are merely indications, but can be useful guidelines to future appraisals.

However, certain features of the data are remarkable. For example, the stability of estimated incidence has been striking over extended periods of time in this century. The prevalence of these disorders substantiates the widely held clinical impression that they are uncommon conditions (compared with mood disorders and schizophrenia) but are not rare. Some studies indicate that delusional disorder accounts for a surprising 2 to 8 percent of inpatient psychiatric admission for "functional psychosis." Patients with delusional disorders are somewhat more likely to be women (but this is an inconsistent feature), and to be more socially and educationally disadvantaged as compared to patients with mood disorders. Women tend to be older than men at the time of diagnosis. While the onset age range is wide (18 to 80), most patients are middle-aged. There is suggestive evidence that immigrant status, celibacy among men, and widowhood among women are associated with delusional disorder but all such observations need to be unambiguously replicated.

ETIOLOGY

The cause of delusional disorder is unknown. The epidemiological and clinical literature suggests that certain risk factors may be relevant to etiology and deserve further research elaboration. These risk factors are found in Table 13.2-7. Whether they are risk predictors or simply characteristics or markers of the disorder is unknown. Familial psychiatric disorder, including delusional disorder, is the best documented risk factor at present.

Genetic or family studies that have begun to appear in the literature indicate the possible specific family transmission of delusional disorder. A recent study of genetic variation in deoxyribonucleic acid (DNA) sequence coding for dopamine type 4 (D_4) receptor proteins strongly suggests the involvement of the relevant gene in conferring susceptibility to delusional disorder. The comparison subjects either had schizophrenia or were normal controls.

Paranoid features, including the types of delusions encountered in these disorders, occur in a large and growing number of conditions (Table 13.2-2). Differences in classifying idiopathic delusional disorder add to the problems of understanding causation. Theories and explanations of delusions abound in the literature but empirical evidence to support those theories is limited. With so many uncertainties, any conclusions concerning the cause of delusional disorder must be made cautiously.

Delusional disorder is an uncommon, probably heterogeneous, group of illnesses whose validity has been questioned since Kahlbaum published his views. The major phenomenological feature of these conditions is the formation and persistence of delusions. It is well known that delusions occur in a variety of psychiatric and medical conditions, and that the pathogenesis of delusions is not fully understood. Hence, discussion of etiology in the delusional disorders can proceed along two lines: (1) determining the distinctiveness of the category itself, (2) examining the theories proposed to account for the pathogenesis of delusion formation per se, and (3) integrating the available evidence into testable proposals.

Distinctiveness of Delusional Disorder An issue that is central to attributing causation is whether delusional disorder represents a separate group of conditions or is an atypical form of schizophrenic and mood disorders. The relevant data come from a limited number of studies and is inconclusive. Epidemiological data suggest that delusional disorder is a separate condition; it is far less prevalent than schizophrenic or mood disorders; age of onset is later than in schizophrenia although men tend to experience the illness at earlier ages than women; and the sex ratio is different from that of mood disorder, which occurs disproportionately among women. Findings from family or genetic studies also support the theory that delusional disorder is a distinct entity. If delusional disorder is simply an unusual form of schizophrenic or mood disorders, the incidence of these latter conditions in family studies of delusional disorder patient probands should be higher than that of the general population. However, this has not been a consistent finding. A recent study concluded that patients with delusional disorder are more likely to have family members who show suspiciousness, jealousy, secretiveness, even paranoid illness, than families of controls. Other investigative efforts have found paranoid personality disorder and avoidant personality disorder to be more common in the relatives of patients with delusional disorder than in the relatives of controls or of schizophrenic patients. A recent study documented modest evidence for an increased risk of alcoholism among the relatives of patients with delusional disorder as compared to probands with schizophrenia, probands with psychotic disorder not otherwise specified, and probands with schizophreniform disorder.

Investigations into patient's natural history also lend support to the suggestion that delusional disorder is a distinct category: age of onset appears to be later than in schizophrenia and outcome generally is better for delusional disorder patients than for schizophrenia patients. Although fraught with methodological shortcomings, premorbid personality data indicate that schizophrenia patients and patients with delusional disorder differ early in life. The former are more likely to be introverted, schizoid, and submissive; the latter extroverted, dominant, and hypersensitive. Delusional disorder patients may have below-average intelligence. Precipitating factors, especially related to social isolation, conflicts of conscience, and immigration, are more closely associated to delusional disorder than schiz-

Table 13.2-7
Risk Factors Associated With Delusional Disorder

Advanced age
Sensory impairment/isolation
Family history
Social isolation
Personality features (e.g., unusual interpersonal sensitivity)
Recent immigration

ophrenia. These characteristics support Kraepelin's view that environmental factors may play an important etiological role. Clinical characteristics such as greater intensity of delusions, uncommon occurrence of negative symptoms, and possible association with cerebrovascular disorder in late-onset cases also suggest differences from late-onset schizophrenia. Recent observations of successful treatment with pimozide (Orap) in several subtypes of delusional disorders suggest the possibility of a common pathogenetic mechanism in these disorders. Follow-up studies indicate that the diagnosis of delusional disorder remains fairly stable: only a small proportion of cases (3 to 22 percent) are diagnosed later as having schizophrenia, and even fewer (6 percent) are diagnosed later as having a mood disorder. Outcome in terms of hospitalization and occupational adjustment is markedly more favorable for delusional disorder than for schizophrenia. When social or occupational functioning is poor in delusional disorder, it generally occurs as the result of the delusional beliefs themselves, not because of cognitive impairment or negative symptoms.

The evidence argues in favor of the distinctiveness of delusional disorder, but it is likely that at least some patients diagnosed as having delusional disorder will develop schizophrenia or mood disorders. Hence, current clinical criteria have limitations and need improvement, which may be possible with the use of laboratory techniques or more specified clinical definitions. Furthermore, the data suggest that delusional disorder is relatively chronic and is probably biologically distinct from other psychotic disorders.

PATHOGENESIS

Although a clear understanding of the pathogenesis of delusions remains an unfulfilled hope, several major theories have been advanced. Any adequate hypothesis for delusion formation must deal with certain facts: (1) delusions occur in a variety of medical and psychiatric diseases; (2) not all persons with such conditions develop delusions; (3) the types of delusions are relatively few and strikingly repetitious despite the variety of diseases; (4) delusions can clear rapidly with treatment of the underlying condition or its termination; (5) delusions can persist, and even become systematized; (6) delusions often accompany perceptual changes such as hallucinations or impaired sensory input; (7) delusions may be highly encapsulated features in persons such that their functioning may not be compromised socially, intellectually, or emotionally. Also, any adequate hypothesis must respond to two questions. First, why does the patient have a delusion? This is a question concerning the form of the psychopathology. Second, why does the patient have this particular delusion? This is a question concerning the content of the psychopathology.

There are three categories of theory in delusion formation.

1. Delusions arise in an otherwise intact cognitive system because a deviant pattern of motivational interest is present (psychodynamic mechanism, social attribution theory).
2. Delusions arise as the result of a fundamental cognitive defect that impairs the patient's capacity to draw valid conclusions from evidence (disorder of reasoning).
3. Delusions arise from normal cognitive processes directed at explaining abnormal perceptual experiences (psychobiological mechanism, anomalous experience hypothesis).

These theories need not be mutually exclusive. Delusional beliefs probably are the result of different processes involving one or more of the proposed mechanisms.

Psychodynamic Mechanism In 1911 Freud published "Psychoanalytic Notes Upon an Autobiographical Account of a Case of Paranoia (Dementia Paranoides)." His interpretation of this case, which became the foundation of the psychodynamic theory of paranoia, was based on his reading of the memoirs of the presiding judge of a Dresden appeals court, Daniel Paul Schreber, who had suffered episodes of psychiatric illness in 1884, 1885, and 1893. The second episode led to two prolonged hospitalizations from which the patient obtained discharge in 1902 following legal action, although he was still delusional. Freud asserted that Schreber's 1903 account, *Memoirs of My Nervous Illness,* offered a legitimate basis for theory, as "paranoiacs cannot be compelled to overcome their internal resistances, and . . . in any case they only say what they choose to say. . . ." Freud argued that the written case report can take the place of personal acquaintance, and in the case of Schreber, Freud never saw the patient. Freud asserted that Schreber's case illustrated a general mechanism of delusion formation involving denial or contradiction and projection of repressed homosexual impulses that break out from the unconscious. The forms of delusion in paranoia can be represented as contradictions of the proposition "I (a man) love him (a man)." The following examples illustrate the forms of illogic.

1. Delusion of persecution. In the contradiction 'I do not love him, I hate him," a hatred that persons deem unacceptable at the conscious level is transformed and becomes instead: "He hates (elaborated to "persecutes") me." Patients can then rationalize their anger by consciously hating those persons whom they perceive to hate them.
2. Delusion of erotomania. The proposition "I do not love him—I love her" is transformed through projection to "She loves me—and so I love her."
3. Delusional jealousy. To protect against unwarranted, threatening impulses the patient transforms the proposition in this manner: "I do not love him—she (a wife, lover) loves him." Hence, jealous delusions represent the transformed attractions of the deluded for the lover.
4. Delusion of grandiosity (megalomania). Here the contradiction made is, "I do not love him, I love myself."

The essence of the theory is that delusions represent attempts to manage the stirrings of unconscious homosexuality. According to the classic theory, the dynamics of unconscious homosexuality are similar for female as well as male patients.

Comment Many theorists have added to the psychodynamic lore on delusion formation from the standpoint of understanding personality factors. For example, some of the vulnerability to delusion formation may be related to deficiently developed trust, narcissistic dynamics, or exaggerated traits such as hypersensitivity.

Critique Freud's mechanism of delusions sidesteps the distinction between form and content in psychopathology. He proposes an inferential process to account for the particular delusion but does not clearly address the issue of why a delusion is formed rather than another symptom, such as hallucination. Verification of the hypothesized mechanism clearly rests on finding evidence that delusions are associated with indications of homosexual tendencies. The theory has been perpetuated in part because an absence of homosexuality can never be proved, and such tendencies can be used as a pillar, even if not a scientifically or empirically demonstrable pillar, in the psychodynamic argument. The few experimental attempts made to test the hypothesis have been inconclusive or equivocal. Although

homosexual concerns have been found among some delusional patients, the variety of conditions with similar delusions argues against a common mechanism of unconscious homosexuality in all. Persons who delusional patients say are persecuting them are not always known by them, nor is the persistence of such delusions adequately accounted for in that formulation. Nevertheless, the classic approach has had immense influence and has provided important psychoanalytical concepts, such as projection, and an awareness that developmental experiences may operate to influence the content of delusional thinking. Systematic empirical study would be valuable.

Disordered Reasoning Because the definition of delusion (Table 13.2-1) emphasizes the operation of reasoning processes that have gone haywire, it is not surprising that a number of attempts have been made to establish that disorder of reasoning is related to delusion formation and that such disorders can be observed among deluded patients. Related to the psychodynamic formulation is the proposal that delusions arise on the basis of defects in formal logical reasoning. Popular in the 1950s and 1960s, this view, promulgated by Eilhard von Domarus among others, suggested that errors in logic such as the principle of identity (two subjects are identical on the grounds of identical predicates) have an etiological role. For example, "Charles Manson used drugs; I use drugs, therefore I am Charles Manson." The empirical assessment of that proposal has failed to establish that deluded patients exhibit more defects in reasoning; rather it appears that normal and deluded persons both make similar errors of reasoning with comparable frequencies.

Two other proposals involving disturbance in reasoning have been studied recently. The first portrays the difficulty underlying delusion formation as a failure in the application of Bayesian reasoning. According to this model of developing beliefs, making choices, and drawing conclusions, delusional patients accept conclusions at levels of probability too low for acceptance by nondelusional persons. However, attempts to demonstrate that failure have had equivocal results. The second proposal suggests that the reasoning processes of delusional patients are influenced by the subject's tendency to assign meaning in a biased manner. The bias arises in making judgments about one's own behavior and that of another person by assigning motives and characteristics to the person involved. Application of this model reflecting motivational and reasoning difficulties (based on social attribution theory) has been tested, but the results do not provide sound support for the formulation.

Other Psychological Mechanisms In *Manic Depressive Insanity and Paranoia,* Kraepelin considered the delusions of paranoia to be the "morbidly transformed expression of the natural emotions of the human heart" and, more specifically, "a kind of psychological compensation for the disappointments of life." He dismissed the Freudian psychodynamic mechanism on the grounds that it did not refer to a clear concept of paranoia and that it was not supported by evidence. He also emphasized consitutional factors, especially disturbances of judgment, in his formulation. Other authors have made similar suggestions about the role of need fulfillment in the development of paranoia. For example, delusions of persecution might serve to maintain the self-esteem of the deluded person, according to a social attribution view about delusion formation in which a normal bias—that of assigning blame for negative outcomes to other persons or circumstances—is exaggerated.

Critique These contributions do not address the issue of pathogenesis rigorously. They explain the content of the delusion but not its form. The commonness of the risk factors or antecedent features cited repeatedly as central to delusion formation contrasts dramatically with the uncommonness of delusional disorder.

Psychobiological Mechanisms The French neurologist Gaëtan G. de Clerambault proposed in 1942 that chronic delusions resulted from abnormal neurological events. Infections, lesions, intoxication, and other forms of damage produce automatisms that puzzle or distress the patient initially and eventually demand explanation. The explanations take the form of delusions. Automatisms include hallucinations, a constant parade of memories, feelings of familiarity, false recognition, arresting of thought, disturbances in attention, bizarre tactile sensations, and even kinesthetic sensation. The view that delusions are an explanation for hallucinations is an old concept in psychiatry that has not been well formulated. The fact that hallucinations have been introduced into and retracted from the definition of paranoia over the years also reflects a lack of clarity regarding a possible connection between the two forms of psychopathology.

In 1974 Brendan Maher proposed a similar hypothesis that conceptualized delusions as explanations of anomalous experiences that arise in the environment, the peripheral sensory system, or the central nervous system. A central tenet of his view is that the processes whereby delusional beliefs are formed are similar in their essential nature to those that operate in the formation of normal beliefs and even of scientific hypotheses. Integral to the hypothesis is the assumption that components of this normal operational sequence have a neural substrate that may be activated either by sensory input (as in the hallucinatory effects of drugs) or by the effects of brain damage (as in alcoholism). The activation of any part of the sequence demands explanation and may thus give rise to delusions. The sequence, activated by disturbances in sensory experience, emotional incongruity, or central nervous system abnormalities, has the following stages: (1) anomalous experience, (2) feelings of significance, (3) testing for reality of experience, (4) developing tentative hypotheses, (5) additional observation, (6) exploring insights, and (7) confirmation of the insight by selective observation. In Maher's explanation, the patient is delusional because he or she actually experiences anomalies that demand explanation. The particular content of the delusion is drawn from the past or current circumstances, experience, and the personal and cultural background of the patient. The explanation answers questions such as the following: What is happening? Why? Why do other people deny it is happening? Why is it only happening to me? Who is responsible for it? The delusional explanation offers relief from puzzlement, and that relief works against abandonment of the explanation.

Critique The psychobiological formulation has gone largely unstudied, but there is supporting evidence in the form of studies of altered perception among patients and healthy controls experiencing sensory impairment or sensory deprivation, and among persons taking various drugs of abuse. These studies have demonstrated a high incidence of delusion formation. The failure to detect a fundamental defect in the cognitive process of delusional patients or to identify basic differences in belief formation between persons with delusions and normal controls provides indirect support as well. Indeed, delusions are formed in persons with a range of levels of intelligence and education, further supporting the view that a disturbance in the cognitive processes is not the source of the problem. Also a number of medical conditions show evidence of delusions but no history of cognitive impairment. Clearly, this hypothesis warrants further

examination, and it remains to be seen how applicable it is to conditions, such as delusional disorder, in which the occurrence of hallucinations is debated. Sensory impairment and central nervous dysfunction, although apparently likely, have not been firmly established for the disorder. The anomalous experience hypothesis focuses on the psychological mechanisms underlying delusion formation, but a complementary proposal concerns the anatomic loci associated with delusional thinking. Jeffrey Cummings and others have used the growing data on the psychopathological consequences of neurological disease to suggest that delusions occur in diseases involving the limbic system—in particular, temporal lobe structures and caudate nuclei. Diseases characterized by excessive dopaminergic activity or reduced cholinergic activity also carry a heightened risk of delusion formation. Cummings further hypothesizes that the common locus of delusion formation is limbic dysfunction that predisposes the individual to misinterpretation of the environment accompanied by inappropriate perception of threat. Both disease- and patient-related factors influence the content, complexity, and timing of the delusion.

PATHOGENESIS

Although limited by the spareness of research in the area, observations of pharmacological treatment provide complementary insights into the pathogenetic puzzle. Data from treatment reports on delusional disorder suggest that pimozide (Orap) a highly specific dopamine-blocking agent, has greater effectiveness than typical antipsychotic drugs in this condition; some data even suggest that it has a unique role. There are several pharmacological effects of pimozide, in addition to dopamine receptor blockade, that may help explain its effectiveness: (1) relative lack of nonadrenergic blocking action (2) calcium channel antagonism, and (3) opioid receptor blockade. The effect of opiated receptor blockade has been proposed as relevant to reported specific effectiveness in delusional infestation partly based on observations of opiate receptor blocking interventions in delusional disorder somatic type, with delusions of infestation. Intravenous administration of the opioid agonist fentanyl (sublimaze) led to intensified cutaneous sensations whereas administration of naloxone (Narcan) an opioid antagonist, resulted in complete remission of the patient's cutaneous sensation. That pimozide is especially effective in delusional disorder, somatic type, supports the notion that its opiate receptor antagonism blocks central recognition of abnormal peripheral sensation; such a view is consistent with the anomalous experience hypothesis.

Other Relevant Factors Delusions have been linked to a variety of additional factors such as social and sensory isolation, socioeconomic deprivation, and personality disturbance. The deaf, the visually impaired, and possibly immigrants with limited ability in a new language may be more vulnerable to delusion formation than the normal population. Vulnerability is heightened with advanced age. Delusional disturbance and other paranoid features are common in the elderly. In short, multiple factors are associated with the formation of delusions, and the source and pathogenesis of delusional disorders per se have yet to be specified.

Integration The pathogenesis of delusions in general and delusional disorder in particular remains a field of hypotheses with little firm grounding. A variety of theories exist, but empirical support for any theory is markedly limited. Of those available, however, the anomalous experience hypothesis appears to be the best supported and certainly is the most consistent with research findings from other domains. Given the research explosion in neuroscience and psychopathology, this hypothesis should be explored as fully as possible. In delusional disorder, for example, the anomalous experience hypothesis needs to be further specified, for example, on what kinds of anomalous experience could lead to the jealousy delusion, the erotomanic delusion, and so forth. Studies now under way in the misidentification delusions, such as the Capgras's syndrome, provide a model for how such research might be directed. Progress may result from further studies of the neurobiology underlying successful treatment strategies in delusional disorder as well.

DIAGNOSIS AND CLINICAL FEATURES

Delusional Disorder

Diagnosing delusional disorders requires that the clinician match the features of the case to the appropriate criteria (Table 13.2-8). When the clinician has successfully ruled out other disorders, certain features of the case can help to substantiate the diagnosis of delusional disorder. The ICD-10 criteria for delusional disorder are listed in Table 13.2-9.

DSM-IV defines the core psychopathological feature of delusional disorder as persistent, nonbizarre delusions not explained by other psychotic disorders. Onset can be sudden, following a precipitating event that the patient often reports, or the disorder may emerge

Table 13.2-8
DSM-IV Diagnostic Criteria for Delusional Disorder

A. Nonbizarre delusions (i.e., involving situations that occur in real life, such as being followed, poisoned, infected, loved at a distance, or deceived by spouse or lover, or having a disease) of at least 1 month's duration.

B. Criterion A for schizophrenia has never been met. **Note:** Tactile and olfactory hallucinations may be present in delusional disorder if they are related to the delusional theme.

C. Apart from the impact of the delusion(s), or its ramifications, functioning is not markedly impaired and behavior is not obviously odd or bizarre.

D. If mood episodes have occurred concurrently with delusions, their total duration has been brief relative to the duration of the delusional periods.

E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Specify type (the following types are assigned based on the predominant delusional theme):

Erotomanic type: delusions that another person, usually of higher status, is in love with the individual

Grandiose type: delusions of inflated worth, power, knowledge, identity, or special relationship to a deity or famous person

Jealous type: delusions that the individual's sexual partner is unfaithful

Persecutory type: delusions that the person (or someone to whom the person is close) is being malevolently treated in some way

Somatic type: delusions that the person has some physical defect or general medical condition

Mixed type: delusions characteristic of more than one of the above types but no one theme predominates

Unspecified type

Table 13.2-9
ICD-10 Diagnostic Criteria for Delusional Disorders

Delusional disorder

A. A delusion or a set of related delusions, other than those listed as typically schizophrenic in criterion G1(1)b or d for paranoid, hebephrenic, or catatonic schizophrenia (i.e., other than completely impossible or culturally inappropriate), must be present. The commonest examples are persecutory, grandiose, hypochondriacal, jealous (zelotypic), or erotic delusions.

B. The delusion(s) in criterion A must be present for at least 3 months.

C. The general criteria for schizophrenia are not fulfilled.

D. There must be no persistent hallucinations in any modality (but there may be transitory or occasional auditory hallucinations that are not in the third person or giving a running commentary).

E. Depressive symptoms (or even a depressive episode) may be present intermittently, provided that the delusions persist at times when there is no disturbance of mood.

F. *Most commonly used exclusion clause.* There must be no evidence of primary or secondary organic mental disorder as listed under organic, including symptomatic, mental disorders, or of a psychotic disorder due to psychoactive substance use.

Specification for possible subtypes

The following types may be specified if desired: persecutory; litiginous; self-referential; grandiose; hypochondriacal (somatic); jealous; erotomanic.

Other persistent delusional disorders

This is a residual category for persistent delusional disorders that do not meet the criteria for delusional disorder. Disorders in which delusions are accompanied by persistent hallucinatory voices or by schizophrenic symptoms that are insufficient to meet criteria for schizophrenia should be coded here. Delusional disorders that have lasted for less than 3 months should, however, be coded, at least temporarily, under acute and transient psychotic disorders.

Persistent delusional disorder, unspecified

gradually and may become chronic. Behavioral and emotional responses are generally appropriate: neither a mood disorder nor the volitional, thinking, and emotional disturbances of schizophrenia are present (including hallucinations, which are quite restricted in delusional disorder). In general, patients with delusional disorder show little disorganization or impairment in their behavior or in the clarity of their thinking.

The delusions are unusual yet they refer to aspects of life that might occur, such as being conspired against, cheated on, physically ill, in love, jealous, and so forth. They are, as George Winokur has suggested, "possible," rather than totally incredible and bizarre as are many of the delusions of schizophrenia. Delusions are categorized according to their content; the most common are characterized by persecution, disease, and jealousy. The delusions are fixed (persistent) and unarguable. Patients interpret facts to fit the delusion rather than modifying the delusion to fit the facts. There is systematization in the delusional thinking, meaning that a single theme or series of connected themes is present with links to the predominant delusion. Normal life and functioning gradually give way to the dominance of delusional concerns.

Many have proposed that there is a descriptive continuum between paranoid personality disorder, delusional disorder, and the paranoid subtype of schizophrenia in terms of degrees of disorganization and impairment. However, there is little evidence to support the concept that these disorders share more than overlapping psychopathology.

The presence of hallucinations in delusional disorder has been debated, with some theorists arguing that schizophrenia is a more likely diagnosis in such cases and others not, so long as the hallucinations are not marked and persistent. The resolution of this issue remains distant, but it is reasonable to consider infrequent, poorly organized, and simple hallucinations that are not a prominent part of the psychopathology to be a feature of delusional disorder. The hallucinations are usually auditory but may be visual and tend to be more common in acute cases. Other types of hallucinations may occur; however, tactile or olfactory hallucinations may be present and may even be prominent if they are related to the delusional theme.

The person's emotional contact and behavior are generally intact. The emotional response is usually consistent with the delusional concern, and the mood is often appropriately depressed, frustrated, or even intensely angry or elated. Restlessness and agitation may be present. Loquaciousness and circumstantiality, usually accompanying descriptions of the delusions, are found in some patients, but formal thought disorder as sometimes found in schizophrenia is absent. Persons with delusional disorder may behave in a remarkably normal way much of the time; they become strikingly different when the delusion is focused on, at which time thinking, attitude, and mood may change direction abruptly. A. Munro has called this shift in response a characteristic, possibly unique feature of delusional disorder. In the delusional mode the patient is hyperalert, preoccupied, and driven by the delusional concern. In the normal mode, the patients mood becomes calm, the conversation neutral, and the patient finds it easier to focus on other issues. The shift between modes can be difficult for lay persons to comprehend. Social and marital functioning are more likely to be compromised than intellectual and occupational functioning.

Associated features in delusional disorder include those of the paranoid syndrome (Table 13.2-3). The degree of hostility and suspiciousness may be such that violent or aggressive behavior results. Litigious behavior is common among such patients. However, some patients, notably those with somatic delusions, may not display hostility, anger, or even suspiciousness to any considerable degree.

MENTAL STATUS EXAMINATION The patient's complaints are brought to the attention of the clinician by the patient or a third party, such as police, family, neighbors, or a consulted physician or attorney. The patient may have attracted attention by asking for protection, quarreling with neighbors, visiting too many clinics, or similar behavior. The complaint focuses on the distressing behavior and possibly on incidental symptoms. The patient will not complain of a psychiatric condition; in fact, he or she will deny that or the presence of any psychiatric symptoms. Often to the surprise of those expecting to observe a range of mental deviances, examination leads to the discovery that thinking, orientation, affect, attention, memory, perception, and personality are intact. The patient's thinking is so clear and the delusional features are so central to his or her concerns that the clinician begins to anticipate the interview responses of the patient to the point that accurate predictions of specific actions and reactions are possible. Such predictability may distinguish the behavior of the patient with delusional disorder from behavior associated with other psychotic conditions. The patient's behavior and responses to the interview are consistent with the range of features in other paranoid conditions. There may be hostility, anger, lack of cooperation, and a sarcastic or challenging quality in most of what the patient says.

The capacity to act in response to delusions is an important dimen-

sion of the evaluation. Level of impulsiveness should be assessed and related to any potential for violent or suicidal behavior. The patient's self-righteousness, the intensity of the delusional experience, and its emotional impact on the patient may be clues to possible violent behavior; any plans for harming others, including homicide, should be inquired about. Suicidal behavior is an equally important concern. Impulses for self-harm arise in settings of frustration, demoralization, and even depression. If such thoughts exist, the patient should be asked how they were handled in the past. Jealousy and erotomania are perhaps especially important concerns in the assessment of possible aggression and violence. Stalking, history of abuse, and arrest records should be inquired about. Careful judgment and diplomatic interviewing are especially important in such presentations.

ASSESSMENT OF DELUSIONS The detection of delusions solidifies the judgment that a paranoid condition is present. Delusions are usually easy to detect. Features of behavior (Table 13.2-3) may suggest their presence. Associated psychopathological symptoms such as hallucinations, disturbed form of thought, and mood disorder may also indicate that delusions are part of the clinical picture.

The clinical challenge is clear in subtle cases. Fundamentally, the clinician must make a judgment based on available observations and the reported private mental experience of the patient. Attempts to dissuade the patient with counterevidence and counterarguments may be useful in determining whether the patient's beliefs can be influenced in ways that are usually sufficient to change a nondelusional person's mind. Spending time in discussion with the patient to grasp the nature of delusional thinking in terms of its themes, impact on the patient's life, complexity, systematization, and related features may be crucial in making the judgment. The most sensible guideline for all cases of suspected delusional thinking is to establish as comprehensive a picture as possible concerning the condition of the patient, including the patient's subjective private experience and evidence of psychopathological symptoms. Such information should reduce much of the uncertainty of the evaluative process.

PERSECUTORY TYPE The delusion of persecution is a classic symptom of delusional disorder; persecutory type and jealousy type delusions are probably the forms seen most frequently by psychiatrists. In contrast to persecutory delusions in schizophrenia, the clarity, logic, and systematic elaboration of the persecutory theme in delusional disorder leave a remarkable stamp on this condition. The absence of other psychopathology, of deterioration in personality, or of deterioration in most areas of functioning also contrasts with the typical manifestations of schizophrenia.

A 56-year old woman, X-ray technician who had emigrated as an adult from Europe, and married late in life, presented to the emergency room. Her complaints were that her husband's business partner of many years intended to get her husband to resign from the business and to destroy their home. Over a number of months she had become gradually aware that a variety of apparently inconsequential incidents (such as unusual cars parked on her isolated residential street, seeing individuals she knew at restaurants, and feeling as if she were being followed each time she drove her car) pointed to a conspiracy to disrupt and ultimately destroy their lives. Her delusion of persecution was remarkably systematized and detailed; her mood in describing this was tense and irritable. There was no evidence of hallucinations, confusion, thought disorder, or mood disorder. Cognition was intact. The patient was quite intelligent and saw the clinical consultation as a means of assisting her husband to deal with the distress of being targeted in such a manner. (The husband had accompanied his wife on these consultations. He also had experienced some delusional thinking in accord with hers.)

The patient showed no evidence that suggested suicidality or potential for violence toward others. She initially refused all medication but gradually over several months of therapy and parallel frequent legal consultations agreed reluctantly to take risperidone (Risperda) and later, for postpsychotic depression, paroxetine (Paxil). She responded within weeks to 0.5 to 1 mg of risperidone administered daily or on alternate days; she refused to take the medication continuously. Within a year, she began to focus on other issues and the emotional intensity of the delusional concerns diminished although they could be aroused with modest stimulation in conversation or from happenings in her home or neighborhood.

JEALOUS TYPE Delusional disorder with delusions of infidelity has been called *conjugal paranoia* when it is limited to the delusion that a spouse has been unfaithful. The eponym *Othello syndrome* has been used to describe morbid jealousy that can arise from multiple concerns. The delusion usually afflicts men, often those with no prior psychiatric illness. It may appear suddenly and serve to explain a host of present and past events involving the spouse's behavior. The condition is difficult to treat and may diminish only on separation, divorce, or death of the spouse.

Richard Krafft-Ebing described the symptom of delusional jealousy in alcoholics in 1891 and believed that extreme jealousy was pathognomonic for alcoholism. Other disorders with this symptom were later described. A recent retrospective analysis of 8134 psychiatric inpatients disclosed a prevalence of delusional jealousy of 1.1 percent among the major diagnostic groups. Among ICD-9 paranoid disorders, a 6.7 percent lifetime point prevalence was determined. Delusional disorder with alcohol dependence frequently shows the single delusion of jealousy, a persistent feature that sometimes remits if alcohol abuse is brought under control. In personality disorders the symptom may be confused with extreme jealousy, but other psychotic features should be absent. The prevalence of delusional jealousy among hospitalized patients with mood disorder was a surprisingly low 0.1 percent. A study of 26,000 psychiatric inpatients using DSM-III-R criteria yielded a 0.17 percent rate of delusional disorder, jealous type. Jealous delusions occur much more frequently in other disorders than in delusional disorder.

Marked jealousy (usually termed *pathological* or *morbid jealousy*) is thus a symptom of many disorders including schizophrenia (where female patients more commonly display this feature), epilepsy, mood disorders, drug abuse, and alcoholism—for which treatment is directed at the primary disorder. Jealousy is a powerful emotion; when it occurs in delusional disorder or as part of another condition it can be potentially dangerous and has been associated with violence, notably both suicide and homicide. The forensic aspects of the symptom have been noted repeatedly, especially its role as a motive for murder. However, physical and verbal abuse occur more frequently than extreme actions among individuals with this symptom. Caution and care in deciding how to deal with such presentations are essential not only for diagnosis, but also from the point of view of safety.

A 47-year-old carpenter was brought for psychiatric examination following complaints by neighbors about his loud yelling and verbal abuse of his girlfriend. The patient resented the psychiatric referral, but was willing to give an account of his concerns. His girlfriend, he complained, was having an affair with someone,

but he was not sure who the interloper was. On his own, however, he had begun gathering evidence: strands of hair found in the apartment, photographs of soiled sheets, and suspicious items from the trash—all of which he claimed proved that an affair was ongoing. He revealed plans to tape-record, possibly videotape, his girlfriend's activities while he was on the job. Upon admitting that he had told his girlfriend that he would kill her if the affair persisted, he was admitted to the hospital. He was treated with a serotonin–dopamine antagonist in low dosages and responded with a reduction in the intensity of his rage and preoccupation. Eventually, he left the hospital, but only after his girlfriend had moved away. He still harbored suspicions but accepted the termination of the relationship without voluble opposition.

EROTOMANIC TYPE Patients with erotomania have delusions of secret lovers. Most frequently the patient is a woman, but men are also susceptible to the delusion. The patient believes that a suitor, usually more socially prominent than herself, is in love with her. The delusion becomes the central focus of the patient's existence and the onset can be sudden.

Erotomania, the *psychose passionelle,* is also referred to as *de Clérambault's syndrome* to emphasize its occurrence in different disorders. Besides being the key symptom in some cases of delusional disorder, it is known to occur in schizophrenia, mood disorder, and other organic disorders. There is no mention of erotomania in DSM-III: the condition was termed *atypical psychosis.* DSM-III-R reinstated the condition, and it remains in DSM-IV.

Patients with erotomania frequently show certain characteristics: they are generally but not exclusively women, unattractive in appearance, in low-level jobs, and they lead withdrawn, lonely lives being single and having few sexual contacts. They select secret lovers who are substantially different from themselves. They exhibit what has been called *paradoxical conduct,* the delusional phenomenon of interpreting all denials of love, no matter how clear, as secret affirmations of love. The course may be chronic, recurrent, or brief. Separation from the love object may be the only satisfactory means of intervention. Although men are less commonly afflicted by this condition than women, they may be more aggressive and possibly violent in their pursuit of love. Hence, in forensic populations men with this condition predominate. The object of aggression may not be the loved individual but companions or protectors of the love object who are viewed as trying to come between the lovers. The tendency toward violence among men with erotomania may lead initially to police rather than psychiatric contact. In certain cases resentment and rage in response to an absence of reaction from all forms of love communication may escalate to a point that the love object is in danger.

A 29-year-old male financial analyst, while having lunch in a downtown restaurant observed the arrival of a well-known local media personality, an attractive woman about his age. He experienced several moments of eye contact with the woman and became convinced that she had fallen in love with him. There ensued a barrage of flowers, letters, phone calls, and even several attempts to meet with her at her workplace. The woman rebuffed all such efforts and eventually called the police. The man was arrested on a stalking charge after he was observed following the woman to her residence. He was angry and threatening to the police, finally admitting that he had purchased a handgun but refusing to give a reason for the purchase. He was remanded to a forensic psychiatric unit, treated with pimozide, and eventually discharged on a court-supervised probation.

SOMATIC TYPE Delusional disorder with somatic delusions has been called *monosymptomatic hypochondriacal psychosis.* The condition differs from other conditions with hypochondriacal symptoms in degree of reality impairment. In delusional disorder the delusion is fixed, unarguable, and presented intensely, because the patient is totally convinced of the physical nature of the disorder. In contrast, persons with hypochondriasis often admit that their fear of illness is largely groundless. The content of the somatic delusion may vary widely from case to case. Munro has described the largest series of cases and has used the content of delusions to define three main types: (1) delusions of infestation (including parasitosis); (2) delusions of dysmorphophobia, such as of misshapenness, personal ugliness, or exaggerated size of body parts (this category seems closest to that of body dysmorphic disorder); and (3) delusions of foul body odors or halitosis. This latter category, sometimes referred to as *olfactory reference syndrome,* appears somewhat different from the category of delusions of infestation in that patients with the former have an earlier age of onset (mean 25 years), male predominance, single status, and absence of past psychiatric treatment. Otherwise the three groups, although individually low in prevalence, appear to overlap.

The frequency of these conditions is low, but they may be underdiagnosed because patients present to dermatologists, plastic surgeons, and infectious disease specialists more often than to psychiatrists in the unremitting search for curative treatment. This may partially account for Kraepelin's skepticism about the occurrence of this form of paranoia. Several recent reports indicate that pimozide (a diphenylbutyliperidine and highly specific dopamine blocker) and certain serotonin-specific reuptake inhibitors may be effective in treatment of such disorders, even in cases with a variety of delusional themes. There may be a heightened association of shared psychotic disorder involving primary cases of hypochondriacal delusion; one series reported a quarter of cases with such an association.

Patients with this condition have a poor prognosis without treatment. It affects both sexes roughly equally. A previous history or family history of psychotic disorder is uncommon. In younger patients, a history of substance abuse or head injury is frequent. Although anger and hostility are commonplace, shame, depression, and avoidant behavior are even more characteristic. Suicide, apparently motivated by anguish, is not uncommon.

A 40-year-old single unemployed man is referred by his primary care physician because of repeated consultations related to his complaint of hair loss. A dermatologist evaluated the patient, found no pathology, and told the patient that the minimal hair loss was normal. The patient refused to accept this judgment and demanded a further consultation. Because of managed-care restrictions, the patient consulted two additional specialists with his own (meager) funds with similar results. He had quit his job because of embarrassment about the hair loss and had become increasingly indebted financially. The psychiatric consultation infuriated him but he cooperated because he thought that the hair loss had begun with some "pills" he had been prescribed several years previously for anxiety and insomnia and that a psychiatrist might have something to add to understanding his case, including perhaps an antidote that might relieve the loss of hair. Treatment with an antidepressant agent proved unsatisfactory and the patient was started on an atypical antipsychotic drug with modest success. He complained less frequently about the hair loss and eventually began to express concern about his loneliness and his fear of being a burden to his aging parents, whom he lived with for financial reasons. His insight, however, remained limited and he

intermittently voiced his concerns about his appearance and hair loss to his psychiatrist.

GRANDIOSE TYPE Delusions of grandeur (*megalomania*) have been noted for years. They were described in Kraepelin's paranoia and have been associated with conditions fitting the description of delusional disorder. Whether this subtype occurs in clinical practice sufficiently enough to warrant a classification is debatable.

A 51-year-old man was arrested for disturbing the peace. Police had been called to a local park to stop him from carving his initials and those of a recently formed religious cult into various trees surrounding a pond in the park. When confronted, he had scornfully argued that, having been chosen to begin a new town-wide religious revival, it was necessary for him to publicize his intent in a permanent fashion. The police were unsuccessful at preventing the man from cutting another tree and made the arrest. Psychiatric examination was ordered at the state hospital, and the patient was observed there for several weeks. He denied any emotional difficulty and had never received psychiatric treatment. There was no history of euphoria or mood swings. The patient was angry about being hospitalized and only gradually permitted the doctor to interview him. In a few days, however, he was busy preaching to his fellow patients and letting them know that he had been given a special mandate from God to bring in new converts through his ability to heal. Eventually, his preoccupation with special powers diminished and no other evidence of psychopathology was observed. The patient was discharged, having received no medication at all. Two months later he was arrested at a local theater, this time for disrupting the showing of a film that depicted subjects he believed to be satanic.

MIXED TYPE The category of mixed type applies to patients with two or more delusional themes. However, this diagnosis should be reserved for cases in which no single delusional type predominates.

UNSPECIFIED TYPE The category of unspecified type is reserved for cases in which the predominant delusion cannot be subtyped within the previous categories. A possible example is certain delusions of misidentification, for example, Capgras's syndrome, named after the French psychiatrist who described the *illusion des sosies* or the illusion of doubles. The delusion in Capgras's syndrome is the belief that a familiar person has been replaced by an impostor or persons. Others have described variants of the Capgras's syndrome, namely the delusion that persecutors or familiar persons can assume the guise of strangers (*Frégoli's phenomenom*) and the very rare delusion that familiar persons could change themselves into other persons at will (*intermetamorphosis*). Each disorder is not only rare but is highly associated with schizophrenia, dementia, epilepsy, and other organic disorders. Reported cases have been predominantly in women, have had associated paranoid features, and have included feelings of depersonalization or derealization. The delusion may be shortlived, recurrent, or persistent. It is unclear whether delusional disorder can appear with such a delusion. Certainly, the Frégoli and intermetamorphosis delusions have bizarre content and are unlikely, but the delusion in Capgras's syndrome is a possible candidate for delusional disorder. The role of hallucination or perceptual disturbance in this condition needs to be explicated.

Shared Psychotic Disorder

Shared psychotic disorder (also referred to over the years as *shared paranoid disorder, induced psychotic disorder, folie à deux,* and *double insanity*) was first described by Lasegue and Falret in 1877. It is probably rare, but incidence and prevalence figures are lacking and the literature consists almost entirely of case reports. The disorder is characterized by the transfer of delusions from one person to another. Both persons are closely associated for a long time and typically live together in relative social isolation. In its most common form, *folie imposée* (which is covered by the DSM-IV criteria in Table 13.2-10), the individual who first has the delusion (the primary case) is often chronically ill and typically is the influential member of a close relationship with a more suggestible person (the secondary case) who also develops the delusion. The secondary case is frequently less intelligent, more gullible, more passive, or more lacking in self-esteem than the primary case. If the pair separates, the secondary case may abandon the delusion, but this outcome is not uniformly seen. The occurrence of the delusion is attributed to the strong influence of the more dominant member. Old age, low intelligence, sensory impairment, cerebrovascular disease, and alcohol abuse are among the factors associated with this peculiar form of psychotic disorder. A genetic predisposition to idiopathic psychoses has also been suggested as a possible risk factor. The ICD-10 criteria for induced delusional disorder are given in Table 13.2-11.

Other special forms have been reported, such as *folie simultanée,* where two people become psychotic simultaneously and share the same delusion. Occasionally, more than two individuals are involved (e.g., *folie à trois, quatre, cinq*; also *folie à famille*), but such cases

Table 13.2-10
DSM-IV Diagnostic Criteria for Shared Psychotic Disorder

A. A delusion develops in an individual in the context of a close relationship with another person(s), who has an already-established delusion.
B. The delusion is similar in content to that of the person who already has the established delusion.
C. The disturbance is not better accounted for by another psychotic disorder (e.g., schizophrenia) or a mood disorder with psychotic features and is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Table 13.2-11
ICD-10 Diagnostic Criteria for Induced Delusional Disorder

A. The individual(s) must develop a delusion or delusional system originally held by someone else with a disorder classified in schizophrenia, schizotypal disorder, persistent delusional disorder, or acute and transient psychotic disorders.
B. The individuals concerned must have an unusually close relationship with one another, and be relatively isolated from other people.
C. The individual(s) must not have held the belief in question before contact with the other person, and must not have suffered from any other disorder classified in schizophrenia, schizotypal disorder, persistent delusional disorder, or acute and transient psychotic disorders in the past.

are especially rare. The most common relationships in *folie à deux* are sister-sister, husband-wife, and mother-child, but other combinations have also been described. Almost all cases involve members of a single family.

There is some question whether patients with such conditions are truly delusional rather than highly impressionable, as frequently there is merely passive acceptance of the delusional beliefs of the more dominant person in the relationship until they are separated, at which point the unusual belief may remit spontaneously. In the DSM-IV criteria the requirement that the secondary case not have a psychotic disorder prior to onset of the induced delusion illustrates the relevance of this question. Also, the psychopathology of secondary cases varies. In DSM-III such patients were required to meet the criteria for paranoid disorder (i.e., show evidence of disturbed personality and perhaps evidence of other psychiatric disorder, mental subnormality, or dementia); some cases may fit the definition of delusional disorder.

A 40-year-old woman consulted physicians to help cure her problem of disagreeable body odor. The physicians failed to satisfy the woman's hopes of diagnosis and treatment, because they found nothing wrong with her. They did occasionally recommend psychiatric consultation, which she refused. Her husband, a quiet, retiring man of 35, accompanied his wife to all medical specialist consultations. When questioned, he shared his wife's concerns about body odor and provided many examples of how distressing this problem had become. When he was told that there really was nothing wrong with his wife, he objected repeatedly and proclaimed that the doctors were incompetent. A psychiatrist was called to the clinic to see the couple and found consistent stories from both. The woman accepted a recommendation for hospitalization on the psychiatry-medical unit, and the husband returned home. After weeks of evaluation and treatment, the woman was discharged. The husband had stopped visiting her, and when informed that his wife would be coming home he said that he thought she had been cured of her problem. However, 3 months later the couple was once again visiting different specialists.

A 52-year-old man was referred by the court for inpatient psychiatric examination after being charged with disturbing the peace. He had been arrested for disrupting a trial, complaining of harassment by various judges. He had walked into a courtroom, marched to the bench, and begun to berate the probate judge. While in the hospital, he told in detail of conspiratorial goings-on in the local judiciary. A target of certain judges, he claimed he had been singled out for a variety of reasons for many years: he knew what was going on; he had kept records of wrongdoings; and he understood the significance of the whole matter. He refused to elaborate on the specific nature of the conspiracy. He had responded to it with frequent letters to newspapers, the local Bar association, and even to a Congressional subcommittee. His mental state, apart from his story and a mildly depressed mood, was entirely normal. A family interview revealed that his wife and several grown children had shared the belief in a judicial conspiracy directed against the patient for a number of years. There was no change in delusional thinking in the patient or the family after 10 days of observation and the patient refused follow-up treatment.

The intensity of conviction is governed by the presence of the primary case in the life of the secondary case. Protection is provided by others who share the delusion and believe that the response is reasonable. Munro has found that shared psychotic disorder is frequently associated with delusional disorder, somatic type. In the second case described for persecutory delusional disorder, the husband, a somewhat passive and isolated man, shared his wife's convictions. With her treatment, he also became less concerned about a conspiracy and began to share his doubts about the whole matter with his therapist.

A recent summary of the Japanese literature indicated that in 97 cases of *fulie à deux,* the phenomenology and epidemiology were similar to those in western reports.

PATHOLOGY AND LABORATORY EXAMINATION

Pathology As in most psychiatric conditions, there is no evidence of localized brain pathology to correlate with clinical psychopathology in patients with delusional disorder. These patients seldom die early and show no consistent abnormalities on neurological examination. Delusions can complicate many disorders and virtually all brain disorders. Certain disorders produce delusions at rates greater than that expected in the general population: for example, epilepsy (especially of the temporal lobe), degenerative dementias (dementia of the Alzheimer's type and vascular dementia), cerebrovascular disease, extrapyramidal disorders, and traumatic brain injury.

Although many types of delusions have been reported in patients with brain disorders, there appear to be particular connections between delusion phenomenology and certain kinds of brain dysfunction. For example, patients with more severe cortical impairment tend to experience more simple, transient, persecutory delusions. This type of delusional experience is characteristic of conditions such as Alzheimer's disease, dementia and metabolic encephalopathy that are also associated with significant cognitive disturbance. More complex (i.e., elaborate and systematic) delusional experiences tend to be more chronic, intensely held, resistant to treatment, and associated with neurological conditions producing less intellectual impairment and strong affective components. Those features occur in patients with neurological lesions involving the limbic system or subcortical nuclei rather than cortical areas. That, coupled with the observation of response of some patients to drug treatment, such as pimozide and other medications, provides a rational basis on which to hypothesize the presence of subcortical pathology, possibly involving systems subserving temporolimbic areas. Available evidence suggests that if there is a lesion, it will be subtle.

Imaging studies have begun to yield subtle findings about delusional disorder. In one study using quantitative volumetry in magnetic resonance imaging, 16 patients with delusional disorder showed lateral ventricle enlargement greater than in subjects with schizophrenia ($N = 31$) and almost twice that of age-matched healthy controls ($N = 35$). Although this study showed no evidence of cortical infarcts (cerebrovascular injury), other studies have suggested that unsuspected cerebral infarction may occur in a high proportion of late-onset cases with delusional disorder. A further examination of these 16 delusional disorder subjects revealed that the degree of physiological right-left asymmetry was significantly greater in the temporal lobes.

Another study has tentatively concluded that eye-tracking dysfunction in the saccadic system is present in delusional disorder, possibly reflecting some attentional impairment related to voluntary saccadic eye movement areas. Despite the subtle nature of such findings, future empirical studies, guided by etiological hypotheses, could lead to breakthroughs. Given the low incidence of delusional disorder, intensive studies of specific cases and of conditions with delusions from known causes (and with identifiable neuropatholo-

gies) offer useful beginning points. Recent studies of misidentification syndromes (e.g., Capgras's syndrome) offer the prospect of developing more refined models of neuropathological mechanisms for delusional disorder.

Laboratory Examination A range of assessments is often necessary, but several have a high likelihood of detecting key factors in the case. The use of drug-screening measures is particularly valuable given the marked delusional responses induced by a number of substances, especially alcohol, amphetamines, cocaine, and other central nervous system stimulants.

Neuropsychological assessment may help to disclose evidence of impaired intellectual functioning suggestive of brain abnormalities. The assessment of intelligence may show discrepancies between verbal and performance scores as well as scatter in overall performance. Limited data on delusional disorder (especially the more chronic forms) suggest that average or marginally low intelligence is characteristic of patients with this condition. A preliminary comparison of patients with late-onset delusional disorder and schizophrenia has indicated neuropsychological impairment to be somewhat less for the former group. Projective testing such as the Rorschach test has limited value in making the diagnosis but may confirm features consistent with it. Deviation on the paranoia scale of the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) has strong correlations to paranoid features and may help substantiate the diagnosis or raise it as a possibility.

DIFFERENTIAL DIAGNOSIS

Delusional Disorder Because delusional disorders are uncommon, idiopathic, and possess features characteristic of the full range of paranoid illnesses, differential diagnosis has a clearcut logic: delusional disorder is a diagnosis of exclusion. There are many conditions to consider (Table 13.2-4), especially the more common disorders associated with paranoid features (Table 13.2-12). To avoid premature diagnosis, careful evaluation is required.

Clinical assessment of paranoid features requires three steps. Initially, the clinician must recognize, characterize, and judge as pathological the presence of paranoid features. Next, the clinician should determine whether they form a part of a syndrome or are isolated. Finally, a differential diagnosis should be developed. The first of the three steps must be pursued thoroughly. The clinician must be aware that a range of objective traits or behaviors (Table 13.2-3) is often found in paranoid illness and may constitute the only clue that a paranoid illness is present. Patients with paranoid symptoms are frequently unwilling to reveal their subjective experiences to examiners or to cooperate in the clinical investigation. Careful interviewing of the patient and other informants may disclose evidence that the behavior is clearly psychopathological; in other cases, however, that conclusion must await further observations. Sometimes investigation is required to determine whether the belief is indeed delusional or not. Premature acceptance that the patient has delusional disorder has at times been an embarrassment to some clinicians who learn that the patient was not deluded. If the judgment that the patient is delusional seems unassailable, then careful elaboration of the nature of the delusion is called for. The delusional thinking should be examined for its fixity, logic, encapsulation, degree of systematization and elaboration, and its effect on planning and action.

Table 13.2-12
More Common Disorders Associated With Paranoid (Delusional) Features

Alcohol abuse
Drug abuse (especially CNS stimulants)
Anticholinergic toxicity
Sedative-hypnotic withdrawal
Delirium
Dementia
HIV infection
Brain tumor
Epileptic disorder
Mood disorders
Schizophrenia/schizoaffective disorders

Having determined that a paranoid condition is present, the clinician should attend to premorbid characteristics (personality, adjustment, symptom development, medical problems, and so forth), the course, and associated symptoms to detect patterns of syndromic psychopathology or isolated symptom presentations—this is step two. The discovery of clouded consciousness, perceptual disturbance, other psychopathology, physical signs, or confusing symptoms may suggest different causes for paranoid features. Isolated acute paranoid symptoms, on the other hand, often appear early in medical illness.

Finally, the clinician should resist the temptation to make the diagnosis of schizophrenia or delusional disorder prematurely in cases where paranoid features are present because these features occur regularly in a variety of psychiatric and medical illnesses. Consequently, awareness of the multiple causes of paranoid features (step one) is essential to completing the differential diagnosis (step three).

Certain principles should guide effective assessment. First, it is important to have knowledge of the paranoid features and patterns of the clinical disorders in which they occur. For example, a small percentage (perhaps 10 percent) of schizophrenia cases have their onset after age 40, and most idiopathic psychiatric conditions do not begin after age 50. Second, the premorbid status of the patient should be determined. Generally, a normal premorbid state suggests that acute paranoid features are the consequence of medical disease. Third, an abrupt change in personality, mood, ability to function, and mental state should be noted because this may indicate complications resulting from medical disease. Fourth, in those cases in which there is evidence that the patient has been refractory to psychotropic medication or psychotherapy, the continuing presence of paranoid features should alert the clinician to consider alternative diagnoses.

The final diagnosis in cases where paranoid features are prominent should be made only following: (1) a complete medical and psychiatric history with special attention (because of their high prevalence) to alcohol and other drug substance use (including drugs of abuse, prescribed drugs, and over-the-counter medication use history); (2) a thorough physical examination, including neurological and mental status examinations; (3) appropriate laboratory studies, particularly serological, toxicological, endocrine, microbiological, radiological, and electroencephalographic studies.

There are certain delusional conditions that, because of their frequency and seriousness, should be routinely considered in the differential diagnosis, as among the most likely sources of delusions (Table 13.2-13). For example, delirium, dementia, psychotic disorder due to a general medical condition, and substance-induced psychotic disorder should receive special attention. Awareness of the potential for patients with each of these disorders to present with delusions in a state of clear consciousness prior to the elaboration of the defining syndromal symptoms should be kept in mind.

Table 13.2-13
Differential Diagnosis of Delusional Disorder

Disorder	Delusions	Hallucinations	Awareness	Other Features
Delusional disorder	+	Occasionally	Alert	Relatively free of psychopathology
Psychotic disorder due to a general medical condition, with delusion	+	+	May be impaired	Cognitive changes; perceptual changes; substance abuse history; impairment of functioning frequent
Substance-induced psychotic disorder	+(can be bizarre)	+	Acute: impaired Chronic: may be alert	History of substance abuse; impaired functioning likely
Schizophrenia	+(bizarre)	+	Alert	Emotional changes, pervasive thought disorder; role impairment
Major depressive episode	+(mood congruent)	±	Alert	Concerted changes in mood and neurovegetative features
Manic Episode	+(mood congruent)	±	Alert	Concerted changes in mood, need for sleep activity, energy, lack of inhibition
Obsessive-compulsive disorder	–	–	Alert	Not psychotic; impaired functioning likely
Personality disorder	–	–	Alert	Not psychotic
Somatoform disorder	–	–	Alert	Not psychotic
Shared psychotic disorder	+	–	Alert	Close associate has same delusions

Psychotic Disorder Due to a General Medical Condition, With Delusions Delusions arise in a number of organic diseases and syndromes, many of which are listed in Table 13.2-2. What they frequently have in common is a disturbance of perception, particularly of visual and auditory functioning. Physical, neurological, and mental status studies as well as laboratory examinations will usually detect the organic causes of delusions. Each evaluation should focus on perceptual disturbance. Medical conditions associated with delusions should be searched for according to the guidelines outlined concerning differential diagnosis.

Substance-Induced Psychotic Disorder, With Delusions Drug intoxications are particularly relevant to this disorder. Substances of abuse, such as amphetamines, hallucinogens, phencyclidine, and cocaine; over-the-counter drugs, such as sympathomimetics; and prescribed drugs, such as steroids, methyldopa (Aldomet) and levodopa (Dopar, Larodopa) can cause psychotic disorder, with delusions, sometimes without prominent cognitive impairment. In acute states, confusion, disorientation, and clouding of consciousness may be evident; in chronic cases the picture may be more difficult to distinguish from delusional disorder because cognitive changes are less pronounced. A careful drug history and screen may establish the diagnosis. A history of alcohol abuse or dependence is so common that it should always be considered; alcoholism is often associated with jealousy, persecutory ideas, and poor impulse control.

Cognitive Disorders Dementia should be considered when paranoid features occur, particularly in older persons. Mental status examination should uncover characteristic cognitive changes absent in delusional disorder. Delirium, with its fluctuating course, confusion, memory impairment, and transient delusions, contrasts with the clarity of mental functioning and the persistence of delusions in delusional disorder and should be considered in acute cases with paranoid features.

Schizophrenia Delusions may be the presenting feature of schizophrenia and this diagnosis should be considered when the delusions are implausible or bizarre, affect is blunted or incongruous with thinking, auditory and possibly visual hallucinations are prominent, thought disorder is pervasive, or role functioning is impaired. Patients with paranoid schizophrenia may have somewhat less bizarre delusions, but role functioning is impaired; also prominent auditory hallucinations are often present, unlike in delusional disorder.

Shared Psychotic Disorder The delusions and symptoms of shared psychotic disorder may resemble those of delusional disorder; however, the delusions arise in the context of a close relationship with a delusional person, are identical in content to the delusions of that person, and diminish or disappear when secondary and primary cases are separated.

Mood Disorders With Psychotic Features The persistent and profound dysphoric mood of patients with depression often points to the proper diagnosis; in delusional disorder, affect may be intense, but is not itself an overwhelming or preoccupying experience to the patient. Delusions in depression, if present, are frequently related to mood (mood-congruent delusions) and usually indicate *severe* depression. For example, patients with feelings of worthlessness or guilt may consider that persecution against them is justified as a punishment for their evil ways. Somatic delusions may be puzzling to differentiate if the clinician fails to consider associated psychopathological features. If delusions occur exclusively during mood episodes, the diagnosis is mood disorder with psychotic features. *Depression* refers to a host of signs and symptoms, and usually has a constellation of neurovegetative features (affecting appetite, sleep, libido, energy, and so forth) that are not part of delusional disorder. Moreover, depression is frequently cyclical and is often associated with a positive family history of mood disorder. Patients with delusional disorder, in contrast, are remarkably free of symptoms other than the delusion. Chronic demoralization may result from repeated failure to obtain the kind of response desired in delusional disorder. Not infrequently, mood symptoms that meet the criteria for a mood episode are present in a delusional condition. Delusional disorder is diagnosed only if the total duration of all mood episodes remains brief relative to the total duration of the delusional disturbance. There is some evidence to suggest that depression is the most common comorbid condition in delusional disorder.

Manic Episode Manic delusions, often grandiose and therefore mood congruent, occur in the severest stages of this illness. This could mislead the diagnostician, but the cyclical nature, the marked change in mood (often euphoric or irritable at a very intense level), the reduced need for sleep, increased energy, easy distractibility, lack of focused concentration ability, lack of social inhibition, and increased activity level of manic episodes should be decisive in distinguishing that condition from delusional disorder.

Obsessive-Compulsive Disorder Severe forms of this disorder should be considered in the differential diagnosis, especially obsessive-compulsive disorder with poor insight. Preoccupation with fear, unusual rituals, and obsessional beliefs may be puzzling, yet the pervasive effects of the condition on functioning differ from the experience of delusional disorder. Moreover, delusions and hallucinations should be absent. In practice, this differential diagnosis may be difficult to determine without a period of observation. In some cases it may be necessary to make the diagnosis and that of delusional disorder.

Somatoform Disorders Severe forms of body dysmorphic disorder may be difficult to distinguish from delusional disorder. The degree of conviction about imagined physical disfigurement may be the only guide for differential diagnosis. Lack of other features of psychopathology, often present in such cases, may also help to make the distinction.

Hypochondriasis may also be distinguished on the basis of absence of delusions, although many of the behaviors associated with delusional disorders, somatic type, may occur. Usually such patients reveal some doubt or uncertainty about the validity of their health preoccupations. Their overvalued beliefs about disease or affliction may clearly resemble delusional disorder, somatic type; severe cases may require considerable diagnostic effort, and as in obsessive compulsive disorder, also require a second diagnosis of delusional disorder.

Paranoid Personality Disorder Individuals with paranoid personality disorder by definition have abundant paranoid features. They are persistently oversensitive, ready to take offense, suspicious, resentful, rigid, and frequently self-centered. Rather than delusions, such persons tend to report strongly held ideas (overvalued ideas); generally, however, they are believed to be free of delusions, which is the most useful differential feature. There is some evidence that this personality pattern occurs often enough in families of probands with delusional disorder to suggest a possible genetic connection between the two.

Schizoid Personality Disorder and Schizotypal Personality Disorder Paranoid features may occur in patients with these personality disorders as well. The pervasive disturbance in personality functioning and the absence of delusions and other psychotic features are usually definitive distinguishing characteristics. Delusional disorder has generally not been associated with this type of premorbid pattern of personality.

Disorders of Aging Any discussion of differential diagnosis of paranoid features is incomplete unless consideration is given to the occurrence of paranoid features in the elderly. Paranoid features develop frequently in the elderly, and assessment in such cases should be particularly thorough because information about paranoid features among the aged is limited. There are several facts worth knowing: (1) the association of depressive illness with paranoid features is high enough to warrant suspicion of mood disorder in all cases with paranoid features: (2) there appears to be a late-onset syndrome sometimes labeled *late paraphrenia* or *late-onset schizophrenia* in which paranoid characteristics and hallucinosis frequently occur (this diagnosis, however, is warranted only when no other disorder can be diagnosed): (3) the sudden onset of acute paranoid features in the elderly can be a sign of cerebrovascular injury or other medical illness; (4) many of the medical conditions associated with delusions have increased incidence in the elderly population; for example, delusions can arise in the early course of presenile dementia and senile dementia conditions when deficits in clinical examination probes or neuropsychological performance may be inconspicuous; (5) perhaps most important for the general clinician is to recognize sources of increased risk of paranoid disorder among older individuals. It is now known that many factors contribute to the incidence of paranoid features in the aged, including lack of stimulating company, isolation, physical illness, the aging process itself, loss of hearing, and loss of visual acuity, each of which should be carefully assessed. Delusional disorder may be present in the elderly, may even have its onset in the elderly, but the frequency of other causes of paranoid features calls for a prudent, systematic search.

Shared Psychotic Disorder Malingering, factitious disorder with predominantly psychological signs and symptoms, psychotic disorder due to a general medical condition, and substance-induced psychotic disorder need to be considered in the differential diagnosis of shared psychotic disorder. The boundary between shared psychotic disorder and generic group madness, such as among the victims of the Jonestown massacre in Guyana, is unclear.

COURSE AND PROGNOSIS

Delusional Disorder Onset can begin in adolescence but generally occurs from middle to late adulthood with variable patterns of course, including lifelong disorder in some cases. Studies generally indicate that delusional disorder does not lead to severe impairment or change in personality, but rather to a gradual, progressive involvement with the delusional concern. Suicide has been associated with such disorders, although most patients live a normal life span. The base rate of spontaneous recovery may not be as low as previously thought, especially because only the more severely afflicted patients are referred for psychiatric treatment. Retterstol's personal follow-up investigation of a large series of cases has provided much of the viewpoint on the natural history of the disorder.

The more chronic forms of the illness (patients presenting with features for more than 6 months) tend to have their onset early in the fifth decade. Onset is acute in nearly two-thirds of the cases, and gradual in the remainder. In 53 percent the delusion has disappeared at follow-up, is improved in 10 percent, and is unchanged in 31 percent. In more acute forms of the illness the age of onset is in the fourth decade, a lasting remission occurs in over half of patients, and a pattern of chronicity develops in only 10 percent; a relapsing course has been observed in 37 percent.

Thus the more acute and earlier the onset of the illness, the more favorable the prognosis. The presence of precipitating factors signifies a positive outcome, as does female sex and being married. In terms of prognosis, the persistence of delusional thinking is most

favorable for cases with persecutory delusions, and somewhat less favorable for delusions of grandeur and jealousy. However, outcome in terms of overall functioning appears somewhat more favorable for the jealousy subtype. Such patients may experience fewer hospitalizations and are less likely to have severe psychotic or schizophrenic deteriorations. Work status at follow-up has indicated that the majority of patients are employed. These observations, although limited to few cases, provide some basis for optimism: perhaps half of cases with delusional disorders may remit, but relapse and chronicity are common.

Comorbidity Depression can be diagnosed as a coexistent disorder in the course of delusional disorder. Evidence indicates that depression is an independent disorder in such cases, that is, the disorders appear to be coincidental in their combination rather than related etiologically. This judgment must be regarded as somewhat tentative, but the clinical value of recognizing comorbid (and often treatable) conditions is straightforward.

Shared Psychotic Disorder The nature of the disorder suggests that separation of the submissive person who has shared psychotic disorder (the secondary case) from the dominant person (the primary case) should result in the resolution and disappearance of the psychotic symptoms in the submissive person. Often, the submissive person requires treatment with antipsychotic drugs, just as the dominant person needs antipsychotic drugs for the psychotic disorder. Because the persons are almost always from the same family, they usually live together after being released from hospital. If separated, the patient will experience a possible remission; if not separated, the patient may have a similar prognosis as the primary case.

TREATMENT

Delusional Disorder Delusional disorder has generally been regarded as resistant to treatment and interventions have often focused on managing the morbidity of the disorder by reducing the impact of the delusion on the patient's (and family's) life. However, in recent years the outlook has become less pessimistic or restricted in planning effective treatment for these conditions. The goals of treatment are to establish the diagnosis, to decide on appropriate interventions, and to manage complications (Table 13.2-14). Fundamental to the success of these goals is an effective and therapeutic doctor-patient relationship, which is far from easy to establish. The patients do not complain about psychiatric symptoms and often enter treatment against their will; even the psychiatrist may be drawn into their delusional nets.

Table 13.2-14
Diagnosis and Management of Delusional Disorder

Rule out other causes of paranoid features
Confirm the absence of other psychopathology
Assess consequences of delusion-related behavior
Demoralization
Despondency
Anger, fear
Depression
Impact of search for "medical diagnosis," "legal solution," "proof of infidelity," etc. (i.e., financial, legal, personal, occupational, etc.)
Assess anxiety and agitation
Assess potential for violence, suicide
Assess need for hospitalization
Institute pharmacological and psychological therapies
Maintain connection through recovery

Psychosocial Treatments There is not enough evidence to substantiate the claims for any particular school or approach in talking with the patient. Insight-oriented therapy is usually contraindicated, but a combination of supportive psychotherapeutic approaches and possibly cognitive-behavioral interventions is sensible. It is unlikely that there is any psychiatric condition that requires greater diplomacy, openness, and reliability from the therapist. Considerable skill is required to deal with the profound and intense feelings that accompany these disorders.

Awareness of the fragile self-esteem and unusual sensitivity of these patients is essential for general management and somatic treatment. Clinical experience indicates that direct questioning about the veracity of the delusion, apart from carefully establishing its nature and the evidence to support it during clinical evaluation, is seldom helpful. Although forging an alliance may be especially difficult, responding to the patient's distress rather than to the delusion itself may be effective. Understanding that fear and anxiety serve to stimulate hostility may be the key to adopting a flexible approach that promotes empathy but maintains physical and emotional distance. Patients with the disorder suffer; they often feel demoralized, miserable, isolated, and abandoned. They may face rejection at home, from police or medical specialists, or on the job. However, they can be approached, and their treatment can focus on these experiences.

The goals of supportive therapy are to allay anxiety and initiate discussion of troubling experiences and consequences of the delusion, thereby gradually to develop a collaboration with the patient. In some patients this strategy allows the psychiatrist to suggest means of coping more successfully with the delusional thinking. For example, psychiatrists might encourage patients to keep their delusions to themselves because others might feel surprised, dismayed, or amazed, all at considerable cost to the patient. It may be possible to provide educational intervention to help amenable patients to understand how factors such as sensory impairment, social and physical isolation, and stress contribute to making matters worse. In all such approaches, the overriding aim is to assist in a more satisfying general adjustment.

Cognitive approaches have attempted to reduce delusional thinking through modification of the belief itself, focusing on the associated reasoning or the reality testing of the deluded patient. Unlike noncognitive behavioral approaches that center attention on reduction of verbal behavior (talking about the delusion), this strategy seeks a more lasting and clinically meaningful intervention through multiple techniques that keep the relationship with the patient collaborative. These techniques include distancing, homework, and exploration of emotions associated with various delusions. The effectiveness of cognitive and behavioral therapies has not been studied enough to justify recommendation. Additionally, it is important to determine the long-term as well as the short-term impact of these treatments; nevertheless, they are promising enough to justify continued assessment.

Somatic Treatment Delusional disorder is a psychotic disorder by definition, and the natural presumption has been that the condition would respond to antipsychotic medication. Because controlled studies are limited and the disorder is uncommon, the results required to support this practice empirically have been only partially obtained.

The disparate findings in the recent literature on delusional disor-

der treatment have been summarized recently, with several qualifications. Of approximately 1000 articles published since 1961, the majority since 1980, 257 cases of delusional disorder (consistent with DSM-IV criteria) of which 209 provided sufficient treatment detail to make comparison, were assessed. Overall treatment results indicated that 80.8 percent of cases either recovered fully or partially. Pimozide (the most frequently reported treatment) produced full recovery in 68.5 percent and partial recovery in 22.4 percent of cases ($N = 143$) treated whereas there was full recovery in 22.6 percent and partial recovery in 45.3 percent of cases ($N = 53$) treated with typical neuroleptic agents [e.g., thioridazine (Mellaril), haloperidol (Haldol), chlorpromazine loxapine (Thorazine), perphenazine (Trilafon), and others]. The remaining cases ($N = 13$) were noncompliant with any treatment, a finding the authors regard as an underestimation (6.2 percent). There were no specific conclusions drawn regarding treatment with selective serotonin reuptake inhibitors, (SSRIs), although a number of such reports have been published. While treatment of the somatic subtype generated the largest number of reports, these authors' meta-analysis indicated that the patterns of response were similar across all subtypes of delusional disorder. Follow-up data and personal experience indicated that long-term, possibly permanent, administration of medication is necessary to maintain remission.

The results of treatment with the serotonin-dopamine antagonists (i.e., clozapine [Clozaril], risperidone olanzapine [Zyprexa], and others) is preliminary. Two known cases of the persecutory subtype have been treated successfully with risperidone and there are published reports of clozapine effectiveness in the persecutory subtype ($N = 2$) and the somatic subtype ($N = 2$), and of risperidone effectiveness in the somatic subtype ($N = 1$). Unfortunately, systematic case series will develop slowly, but these preliminary results suggest that the atypical neuroleptic agents may add to the available treatment options.

Given the limited samples available, case reports are especially valuable; although many authors recommend multisite trials (to augment the small numbers of cases available at any one site), it would be beneficial for further single case reports to be published in the meanwhile. The existing literature could be improved with more attention paid to diagnosis, prior treatments, outcome, and level of compliance, as well as dosage schedules, adverse effects, length of treatment, as well as the reasons for selecting or changing particular agents. Use of ($N = 1$) single case research design strategies might also enhance the generalizability of findings.

The impression is growing that antipsychotic drugs are effective, and a trial, especially with pimozide or a serotonin-dopamine antagonist is warranted. Certainly, trials of antipsychotic medication make sense when the agitation, apprehension, and anxiety that accompany delusions are prominent.

Delusional disorders respond less well generally to electroconvulsive treatment than do major mood disorders with psychotic features. Some cases may respond to SSRIs, especially cases of body dysmorphic disorder with delusional concerns (Table 13.2-15). Where differential diagnosis is unclear between delusional disorder and psychotic depression, a trial of combined therapy with antipsychotic and antidepressant medications therapy may be worthwhile. When standard strategies are unsuccessful, trials of lithium (Eskalith) or of anticonvulsant medication such as carbamazepine (Tegretol) probably should be considered. However, no systematic information to support such approaches is yet available.

Somatic treatment is difficult to implement on two levels, The patients' insistence on lack of psychiatric problems may be an insurmountable barrier to initiating treatment, and their sensitivity to all adverse effects may constitute an additional frustrating factor in their care. Noncompliance continues to be a frequent observation in published clinical studies. An open and clear approach to warn patients about and to assist them through possible unpleasant experiences is essential, but the intrinsic nature of active resistance to psychiatric intervention also requires attention. In general, some patients, especially younger patients with delusional disorder, respond to supportive management and somatic treatment. Unfortunately, others, especially the elderly, may be refractory to attempts to reduce their delusional thinking. In all cases goals that are realistic and modest are the most sensible. As most of the difficulty of this disorder results from the effects of the patient's actions concerning the delusions, any preventive approach in that domain has considerable value.

Hospitalization Most delusional disorder patients can be treated effectively in outpatient settings; hospitalization may be necessary when there is potentially dangerous behavior or unmanageable aggressiveness. The patient may show signs of poor impulse control, excessive motor and psychic tension, unremitting anger, brooding, suicidal tendencies, and even threats of self-harm or aggression toward others. Suicidal ideation and planning are also potential grounds for hospitalization. Follow-up studies report suicide above the population base rate; patients with erotomania, jealousy, and persecutory delusions are particularly at risk. Once the psychiatrist decides to hospitalize the patient, it is preferable to inform the patient tactfully that voluntary hospitalization is necessary. If this strategy fails, legal means must be undertaken to commit the patient to a hospital.

Shared Psychotic Disorder

The initial step in treatment is minimally the temporary separation of the affected person from the source of the delusions, the dominant partner. This step may not only be therapeutic but diagnostic when evidence of reduced delusional thinking and preoccupation accrue. The patient may need significant support to compensate for the loss of that person. The patient with shared psychotic disorder should therefore be carefully observed for the remission of the delusional symptoms. Antipsychotic drugs can be used if the delusional symptoms have not abated in 1 or 2 weeks.

Psychotherapy with nondelusional members of the patient's family should be undertaken, and psychotherapy with both the patient with shared psychotic disorder and the dominant partner may be indicated later in the course of treatment. In addition, the mental disorder of the dominant partner should be treated. The clinician might use family therapy and social support to modify the family dynamics and to prevent the recurrence of the syndrome. It is often useful to make sure that the family unit is exposed to input from outside sources to decrease the family's isolation. In short, a comprehensive approach emphasizing support and, when necessary, medication is useful.

Table 13.2-15
Pharmacological Agents With Reports of Successful Use in Delusional Disorder

Dopamine receptor antagonists (particularly pimozide)
Serotonin-dopamine antagonists
Selective serotonin reuptake inhibitors

SUGGESTED CROSS-REFERENCES

Conditions to be differentiated from delusional disorders are discussed in Chapter 12 on schizophrenia, in Chapter 14 on mood disorders, in Chapter 16 on somatoform disorders, in Chapter 24 on paranoid personality disorder, in Chapter 5 on obsessive-compulsive disorder, and in Chapter 10 on mental disorders due to a general

medical condition. Aging and psychiatric disorders in the elderly is covered in Chapter 51.

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▲ 13.3 Acute and Transient Psychotic Disorders and Culture-Bound Syndromes

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While schizophrenia and mood disorders have commanded attention for many years and are likely to continue doing so for the foreseeable future, several other types of psychotic conditions are emerging as significant. Among these are psychotic disorders associated with general medical diseases and with the use of psychoactive substances as well as a complex group of acute and brief psychotic disorders.

Interest in the latter group stems from several factors. One concerns the phenomenological intricacy of disorders in this group. While all basically share loss of touch with reality or bizarre behavior as core psychopathology, they may diverge extensively in other aspects of their symptomatological profile. Another factor involves geographical epidemiology, with a disproportionately high frequency of acute and brief psychoses reported in the developing countries of the Americas, Asia, and Africa. A third factor involves cultural framework. Most of the syndromic or nosological predecessors of the acute and brief psychoses have been described in defined cultural contexts, whether as *bouffée délirante* in France, psychogenic psychosis in Scandinavia, cycloid psychosis in Germany, or the variety of transient psychoses reported in the traditional societies of the developing world.

The crucial role of the last factor connects the nosological category of acute transient psychoses to the culture-bound syndromes. The importance of cultural framework is certainly relevant to the full range of psychiatric disorders, both from clinical psychopathological and epidemiological perspectives, but it is most distinctive and illustrative in reference to culture-bound syndromes of both psychotic and nonpsychotic types.

DEFINITION AND COMPARATIVE NOSOLOGY

ICD-10 The acute psychoses described in northern European countries and in developing countries have been, for the first time, accommodated and organized in the 10th revision of the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10), under the category of acute and transient psychotic disorders. The conditions are formulated and arranged according to the following principles, in order of priority:

1. An acute onset (less than 2 weeks) as the key criterion for the whole group. Acute onset denotes a change within 2 weeks or less from a state without psychotic features to a clearly abnormal psychotic state (not necessarily at its peak severity).
2. The presence of typical syndromes. Those include, first, a rapidly changing and variable state called polymorphic, prominent in acute psychoses described in several countries, and, second, the presence of typical schizophrenic symptoms.
3. The presence or absence of associated acute stress (within 2 weeks of the first psychotic symptoms).

Complete recovery usually occurs within 1 to 3 months (depending on the specific disorder), often within a few weeks or days.

Only a small proportion of patients with these conditions develop persistently disabling states.

DSM-IV The evaluation of a psychotic patient requires consideration of the possibility that the psychotic symptoms result from a general medical condition (e.g., a brain tumor) or the ingestion of a substance (e.g., phencyclidine). Those two situations are classified in the fourth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) as psychotic disorder due to a general medical condition and substance-induced psychotic disorder, respectively. DSM-IV also includes a diagnosis of catatonic disorder due to a general medical condition to emphasize the special considerations regarding the differential diagnosis of catatonic symptoms.

DSM-IV also includes psychotic disorder not otherwise specified for psychotic disorders that do not meet the criteria for any other specific psychotic disorder. In previous editions of DSM these were called atypical psychoses.

ETIOLOGY

Both psychosocial and biological factors appear to play significant roles in the causation of acute brief psychoses and culture-bound syndromes. More than one factor may be present in any particular case, including a combination of psychosocial and biological factors.

Psychosocial Factors The diagnosis of psychotic disorders depends primarily on an accurate and thoughtful assessment of delusions, hallucinations, and bizarre psychomotor behaviors. Culture profoundly influences the meaning and nature of symptoms in the psychotic disorders reviewed in this chapter as well as the characteristics and meaning of the context and the consequences of the behaviors at hand. Attention to cultural framework can help one interpret behaviors properly and minimize misdiagnosis and diagnostic ambiguity in cross-cultural clinical situations. Lacking adequate information on what constitutes normal behavior patterns or culturally sanctioned idioms of distress, clinicians evaluating patients with different cultural, ethnic, or religious backgrounds are likely to misidentify less severe complaints or behaviors as delusional, hallucinatory, or bizarre. Similarly, they are likely to suspect the existence of major psychopathology in patients with fleeting psychotic manifestations.

Spiritual and religious beliefs can present major diagnostic dilemmas for clinicians. Beliefs in witchcraft and sorcery are common in many societies and may or may not be delusional. Spiritism, Santeria, and various other religious movements and different forms of shamanism practiced in many parts of the world encourage and sanction personal communication and active involvement with the dead, with spirits, and with the various deities. Such supernatural and mystical practices and experiences do not necessarily indicate psychopathology. However, such culturally congruent beliefs often also exert substantial pathoplastic influences on symptom formation in psychotic patients. Similarly, possession and trance phenomena are frequently seen in most non-Western societies, and it is often difficult to determine whether those experiences, in a particular case, are part of an ongoing psychotic process or are culturally and contextually appropriate.

Among the social factors that have been the subject of empirical research in recent years is (particularly among women) departure from the parental village for a number of reasons (e.g., marriage) and return to the parental village, including participation in events such as births and weddings. Investigators have also found a history of job stress (particularly among men) associated with the emergence of clinical manifestations.

Other social factors can also significantly influence symptom formation in psychiatric patients, thereby complicating the diagnosis of psychotic conditions. Sustained exposure to racist and discriminatory behaviors tends to increase vigilance and suspiciousness among members of ethnic minorities, and it may contribute to a higher propensity for paranoid symptoms in such persons. Paranoid symptoms are also more prevalent among those, such as refugees, who are forced to live in an unfamiliar cultural milieu. Fear of political persecution is a reality of life for persons living under oppressive regimes, and it may contribute to a higher prevalence of paranoid ideation in such societies. Because of those complications, it is often difficult to determine whether paranoid experiences among recent immigrants and sojourners are reactive or indicate a more serious and enduring psychotic process.

Biological Factors A variety of biological factors can have etiological involvement in the development of acute grief psychoses and culture-bound syndromes. One is infectious diseases, especially prevalent in developing countries. Empirical research documents the presence of fever in a disproportionately high number of patients with acute transient psychotic disorders.

Physical conditions (e.g., cerebral neoplasms, particularly of the occipital or temporal areas) can induce hallucinations. Sensory deprivation, as occurs in blind and deaf persons, can also result in hallucinatory or delusional experiences. Lesions involving the temporal lobe and other cerebral regions, especially the right hemisphere and the parietal lobe, are often associated with delusions.

Psychoactive substances are common causes of psychotic syndromes. The most commonly involved substances are alcohol, indole hallucinogens (e.g., lysergic acid diethylamide [LSD], amphetamines, cocaine, mescaline, phencyclidine [PCP], and ketamine. Many other substances, including steroids and levothyroxine (Levoxyr, synthroid) can be associated with substance-induced hallucinations.

DIAGNOSIS AND CLINICAL FEATURES

ICD-10 ICD-10 provides general criteria for acute and transient psychotic disorders as well as criteria for four specific disorders (Table 13.3-1). ICD-10 also includes two residual categories for acute and transient psychotic disorders.

Acute Polymorphic Psychotic Disorder Without Symptoms of Schizophrenia Acute polymorphic psychotic disorder without symptoms of schizophrenia is characterized by obvious but variable, rapidly changing hallucinations, delusions, and perceptual disturbances, often accompanied by emotional turmoil (happiness and ecstasy or anxiety and irritability). The criteria for manic episode, depressive episode, or schizophrenia are not met. The disorder tends to have an abrupt onset (less than 48 hours) and then a rapid resolution of symptoms. If symptoms persist for more than 3 months, the diagnosis should be changed (e.g., to persistent delusional disorder or some other nonorganic psychotic disorder). The diagnosis accommodates *bouffée délirante* and cycloid psychosis, both either unspecified or without symptoms of schizophrenia, as the following excerpt from the *ICD-10 Casebook* illustrates.

Mrs. Charrière is a 25-year-old Frenchwoman.

Problem Mrs. Charrière was brought by ambulance to a hospital emergency department in the city where she lived. Her husband reported that she had been perfectly normal until the previous evening, when she had come home from work complaining that "strange things were going on" at her office. She had noticed that her colleagues were talking about her, that they had

Table 13.3-1
ICD-10 Diagnostic Criteria for Acute and Transient Psychotic Disorders

G1. There is acute onset of delusions, hallucinations, incomprehensible or incoherent speech, or any combination of these. The time interval between the first appearance of any psychotic symptoms and the presentation of the fully developed disorder should not exceed 2 weeks.

G2. If transient states of perplexity, misidentification, or impairment of attention and concentration are present, they do not fulfill the criteria for organically caused clouding of consciousness as specified for delirium, not induced by alcohol and other psychoactive substances, criterion A.

G3. The disorder does not meet the symptomatic criteria for manic episode, depressive episode, or recurrent depressive disorder.

G4. There is insufficient evidence of recent psychoactive substance use to fulfill the criteria for intoxication, harmful use, dependence, or withdrawal states. The continued moderate and largely unchanged use of alcohol or drugs in amounts or with the frequency to which the individual is accustomed does not necessarily rule out the use of acute and transient psychotic disorders; this must be decided by clinical judgment and the requirements of the research project in question.

G5. *Most commonly used exclusion clause.* There must be no organic mental disorder or serious metabolic disturbances affecting the central nervous system (this does not include childbirth).

A fifth character should be used to specify whether the acute onset of the disorder is associated with acute stress (occurring 2 weeks or less before evidence of first psychotic symptoms):

Without associated acute stress

With associated acute stress

For research purposes, it is recommended that change of the disorder from a nonpsychotic to a clearly psychotic state is further specified as either abrupt (onset within 48 hours) or acute (onset in more than 48 hours but less than 2 weeks).

Acute polymorphic psychotic disorder without symptoms of schizophrenia

A. The general criteria for acute and transient psychotic disorders must be met.

B. Symptoms change rapidly in both type and intensity from day to day or within the same day.

C. Any type of either hallucinations or delusions occurs, for at least several hours, at any time from the onset of the disorder.

D. Symptoms from at least two of the following categories occur at the same time:
(1) emotional turmoil, characterized by intense feelings of happiness or ecstasy, or overwhelming anxiety or marked irritability;
(2) perplexity, or misidentification of people or places;
(3) increased or decreased motility, to a marked degree.

E. If any of the symptoms listed for schizophrenia, criterion G(1) and (2), are present, they are present only for a minority of the time from the onset; ie, criterion B of acute polymorphic psychotic disorder with symptoms of schizophrenia is not fulfilled.

F. The total duration of the disorder does not exceed 3 months.

Acute polymorphic psychotic disorder with symptoms of schizophrenia

A. Criteria A, B, C, and D of acute polymorphic psychotic disorder must be met.

B. Some of the symptoms for schizophrenia must have been present for the majority of the time since the onset of the disorder, although the full criteria need not be met, ie, at least one of the symptoms in criteria G1(1)a to G1(2)c.

C. The symptoms of schizophrenia in criterion B above do not persist for more than 1 month.

Acute schizophrenia-like psychotic disorder

A. The general criteria for acute and transient psychotic disorders must be met.

B. The criteria for schizophrenia are met, with the exception of the criterion for duration.

C. The disorder does not meet criteria B, C, and D for acute polymorphic psychotic disorder.

D. The total duration of the disorder does not exceed 1 month.

Other acute predominantly delusional psychotic disorders

A. The general criteria for acute and transient psychotic disorders must be met.

B. Relatively stable delusions and/or hallucinations are present but do not fulfill the symptomatic criteria for schizophrenia.

C. The disorder does not meet the criteria for acute polymorphic psychotic disorder.

D. The total duration of the disorder does not exceed 3 months.

Other acute and transient psychotic disorders

Any other acute psychotic disorders that are not classifiable under any other category in acute and transient psychotic disorders (such as acute psychotic states in which definite delusions or hallucinations occur but persist for only small proportions of the time) should be coded here. States of undifferentiated excitement should also be coded here if more detailed information about the patient's mental state is not available, provided that there is no evidence of an organic cause.

Acute and transient psychotic disorder, unspecified

been quite different all of a sudden, and that they had started behaving as if they were acting a part. Mrs. Charrière was convinced that she had been put under surveillance and that someone was listening in on her telephone conversations. All day she had been feeling as if she were in a dream. When she looked in the mirror, she had seemed unreal to herself. She had become increasingly anxious, incoherent, and agitated during the course of the day and had not been able to sleep at all during the night. She had spent most of the night looking out of the window. Several times she pointed at the crows in a nearby tree and told her husband, "The birds are coming."

In the morning, Mr. Charrière found his wife on her knees as if she were praying. She knocked her head repeatedly against the floor and talked in a rambling way, declaring that she had been entrusted with a special mission, that her boss was a criminal, there were spies everywhere, and something terrible would happen soon. All of a sudden she calmed down, smiled at her husband, and told him that she had decided to convert from Catholicism to Islam. At that stage she became quite elated, started laughing and shouting, and declared that she and her husband could pray to the same god from then on. Shortly afterward she was terrified again and accused her husband of trying to poison her.

History Mrs. Charrière was brought up in a town in the west of France, where her parents owned a small restaurant. She did well in school, went on to college, and trained as an interpreter. During her training she met her future husband, who had come to France from Algeria to train as an interpreter himself. Because both she and her husband were agnostics, the fact that they came from different religious backgrounds had never been a problem. She took a job with an administration related to the European Communities, and her husband found a position with an international interpreting company. The couple were doing well, they

had bought a nice house on the outskirts of Mrs. Charrière's home town, and were planning to have a child in the near future.

Mrs. Charrière's parents were in good health. She had a brother and two sisters. At age 18 her younger sister had had a nervous breakdown and in the ensuing years had been hospitalized repeatedly in a psychiatric hospital with a diagnosis of schizophrenia.

Both Mrs. Charrière and her husband refrained from drinking alcohol and were strongly opposed to any kind of drugs, including prescription medicines.

Mr. Charrière described his wife as an outgoing, sociable, and perfectly normal woman. However, he was quite worried about what was happening, all the more since she appeared to have symptoms resembling those he had observed in his sister-in-law.

Findings On admission Mrs. Charrière was frightened and bewildered but was oriented in time, place, and person. She was restless and constantly changed position, standing and sitting, moving about the room, shouting and screaming, weeping and laughing. She talked in a rambling way, shifting from one subject to another without any transition. Something criminal was going on at her office, she said, and she had discovered a secret plot. There were microphones hidden everywhere, she added, and "the birds are coming." She wondered whether the physician was a real physician or "a spy in disguise." She went on to speak about "my mission," declared that Jesus had been a false prophet, that Muhammad was the real prophet, and that she would convince the world of what was right and wrong. She then began to explain that the truth was to be found in numbers. The digit "3" signifies good, she said, and the digit "8" represents evil. Suddenly she started to weep, explaining that her parents had died and that she wished to join them in heaven.

During the first days of hospitalization, Mrs. Charrière continued presenting a rapidly changing symptomatology. Her mood frequently shifted from sadness to elation, and the content of her delusions changed from persecution to mysticism. On several occasions she came out of her room and complained that she had heard people speaking about her, even when there was no one in the vicinity. When asked to describe what she was hearing, she spoke of voices coming from the corridor. She firmly denied that the voices might emanate from within her own body.

The physical examination did not reveal any abnormality. Results of blood tests, including thyroid function, were within normal limits, as were all other special investigations such as an electroencephalogram and brain scan.

Course Mrs. Charrière was treated with 30 mg of haloperidol (Haldol) during the first week, and with half this dose for the following week. After 2 weeks all of her symptoms had disappeared, and she was discharged on medication. She was seen once a week in the outpatient department for another month, during which the medication was progressively reduced and then stopped completely. Two months after the onset of the delusional episode, the patient continued to be free of symptoms.

Discussion The significant features of Mrs. Charrière's disorder were acute polymorphous delusions, rapidly changing mood disturbances, perplexity, depersonalization, and derealization without clouding of consciousness, and occasional auditory hallucinations. The disorder developed to its peak in 24 hours and was resolved in a few weeks, with complete recovery within 6 weeks. The patient had no psychiatric history.

The psychiatrist who dealt with this case made a diagnosis of *bouffée délirante.* This concept goes back to the French psychiatrist Valentin Magnan, whose pupil Paul Legrain, proposed the following diagnostic criteria: an acute onset of the disorder "like a bolt from the blue" in the absence of a psychosocial stressor; the presence of unsystematized and rapidly changing "polymorphic" delusions; the presence of emotional turmoil with intense and changing feelings of anxiety, happiness, or sadness; the presence of perplexity, depersonalization, or derealization without clouding of consciousness; and resolution of the disorder with complete recovery within 2 months.

In the ICD-10, the subtyping of acute and transient psychotic disorders rests on the acuteness of onset, the presence of typical syndromes, and the presence of associated stress. In the case of Mrs. Charrière, the onset was abrupt (i.e., the symptoms appeared within less than 48 hours), the syndrome was polymorphic, there were no typically schizophrenic symptoms, and the onset of the disorder was not associated with acute stress. Therefore, Mrs. Charrière's disorder must be coded as acute polymorphic psychotic disorder, without symptoms of schizophrenia, and without associated acute stress. (Reprinted with permission from *ICD-10 Casebook.*)

Acute Polymorphic Psychotic Disorder With Symptoms of Schizophrenia Acute polymorphic psychotic disorder with symptoms of schizophrenia is as polymorphic as the preceding disorders, but is additionally characterized by the consistent presence of typical schizophrenic symptoms. If the schizophrenic symptoms last more than 1 month, the diagnosis should be changed to schizophrenia. The disorder accomodates the concepts of *bouffée délirante* and cycloid psychosis, both with symptoms of schizophrenia.

Acute Schizophrenia-Like Psychotic Disorder Acute schizophrenia-like psychotic disorder is characterized by the consistent and stable presence of typical schizophrenic symptoms, without the polymorphic character of the foregoing disorders. If the schizophrenic symptoms last more than 1 month, the diagnosis should be changed to schizophrenia.

Other Acute, Predominantly Delusional Psychotic Disorders The other disorders are characterized by relatively stable delusions or hallucinations, without fulfilling the criteria for either schizophrenia or the acute polymorphic psychotic disorders. If the delusions persist for more than 3 months, the diagnosis should be changed to persistent delusional disorder and, if only the hallucinations persist, to other nonorganic psychotic disorder. The disorder accommodates the concepts of psychogenic paranoid psychosis and paranoid reaction.

Halime is a 22-year-old student. She is in her first year of medical school in Egypt.

Problem Accompanied by her mother, Halime came to see the physician at the psychiatric outpatient clinic. She was complaining about her nose. For the preceding week, from time to time she could smell a foul odor and was very afraid that it came from herself. She reported hearing voices talking about her behavior and telling her what to do. She had become extremely irritable and was unable to sleep. All these problems began 10 days after returning to her home in Alexandria on summer vacation from the medical school. She could find no obvious reason for the foul smell and the voices, but she thought the condition

might be the result of witchcraft. She had developed a friendship with a young man, a fellow student at the medical school, and suddenly, just before the vacation, he had asked her to marry him. She was very surprised, became frightened, and had refused, which had upset him. She now suspected that her boyfriend had caused a spell to be cast on her because of her refusal. Halime's family said her condition was gradually getting worse. The foul smell and the voices seemed to affect her more each day.

History Halime was the first of two children born to a family of average income in Alexandria. Her father was a mechanic and seemed to be a rather shy and gentle person. The mother was ambitious and expressed great concern for her daughter's education. Her family reported that they had great hope that their first child would be a boy. The parents treated Halime as if she were a boy for the first 3 years of her life until the birth of a second child, which was a son. There was no information about mental disorders in the family.

Halime was introverted, thoughtful, and rather stubborn, with only a few friends. She had a high moral standard and had never dated or had sexual relations. She was doing very well at medical school and was determined to become a great physician in a culture where there is still some resistance to women physicians.

She had always been physically strong and had excellent health.

Findings On admission to the clinic, Halime was found to be very self-conscious and tried to avoid being seen by other people. She appeared tense and sad and seemed close to tears. She was reluctant and mentioned with hesitation some "extraordinary experiences." These included the foul smell, which was like burned meat, and the voices that kept commenting on her behavior. She said the voices described what she was doing "here and now" and added comments. One example she gave of what the voices were saying was, "You are now speaking to the physician. You hope that he can help you, don't you? No hope. We shall overcome." She explained that she believed this was the result of the witchcraft to which she had been subjected. She seemed able to differentiate in her mind between normal and abnormal perceptual experiences. She stated that she was able to make this distinction but was unable to do anything about the voices.

She showed emotional response of normal modulation, and no abnormalities of speech were observed. She was fully oriented as to time, place, and person and showed no impairment of memory. Her attention seemed sharpened, but her concentration was slightly diminished.

Careful physical and neurological examinations revealed no abnormality. An electroencephalogram with nasopharyngeal electrodes and a computed tomography scan also showed only normal results, and laboratory investigations, including thyroid parameters, were all normal.

Course Halime was prescribed haloperidol (3 mg per day) and a hypnotic. In the course of 4 days, the voices and the foul smell gradually disappeared. At the next visit to the clinic a week later, she complained of drowsiness and fatigue, aching and stiffness in the muscles, and difficulties with concentration. Her haloperidol was reduced to 1 mg per day, and the hypnotic was discontinued. After this she gradually improved, and after an additional 2 weeks she appeared well and was able to manage without medication.

Discussion After a sudden proposal of marriage less than 2 weeks before, Halime developed within just a few days a psychotic disorder with olfactory and auditory hallucinations and with commenting voices mentioning her in the third person. Her explanation about witchcraft cannot for certain be considered delusional in a culture where there is widespread belief in this phenomenon, although someone of her educational level would be expected to consider such belief as a superstition. Otherwise, Halime showed remarkable insight into the nature of her condition, with little or no impairment of her sense of reality. She showed no major disturbance of consciousness. No sign of organic etiology was observed, and psychoactive substance use was not suspected. She did not meet the symptomatic criteria for an affective episode.

On antipsychotic treatment she had a complete remission within 3 weeks. Thus, she had an acute and transient psychotic disorder. The symptomatology was not polymorphic but included a schizophrenic first-rank symptom of commenting voices. The subtype, therefore, will be schizophrenia-like disorder. The psychotic disorder followed, within 2 weeks, an event that may be considered stressful to a young female in Halime's cultural setting.

The full diagnosis therefore will be other acute predominantly delusional psychotic disorder, without associated acute stress. (Reprinted with permission from *ICD-10 Casebook.*)

Mr. Dubois is a 43-year-old Frenchman.

Problem Mr. Dubois was convinced that he was being watched and that someone was listening in on his telephone conversations. He was referred for psychiatric consultation by his family physician because he became increasingly anxious and felt that "strange things" were going on around him.

The problems had begun a week earlier, when Mr. Dubois started having doubts about whether his father, who had died more than 5 years before, was really dead or was still alive and being held hostage by the local municipal council, of which he had been a member until shortly before his death. After all, Mr. Dubois thought, his father had been the most honest man in the world, and it was likely that he had vehemently opposed a shady deal that the council had decided to pursue despite his misgivings.

Mr. Dubois had the impression that people looked at him "in a knowing way" or talked or behaved as if they wanted to convey secret messages. On several occasions, when he was alone, he heard voices whispering something he was not able to understand and noticed that normally static objects seemed to move before his eyes.

History Mr. Dubois came from a small industrial town. His father worked in the local steel factory and was very active in the labor union. The son was a bright student. He went to college and trained as a primary school teacher. He took up a teaching position in his home town, got married, had two children, and led a quiet and rather uneventful life.

The patient's father died of a heart attack at the age of 65. Although he had already retired from his job at that time, he had remained active in local politics. He had been a member of the municipal council until a few months before his death and had left the council only because he was compelled to resign as a result of some disagreements with his colleagues. He had felt very bitter about what he considered an unfair ousting, became morose, and hardly went into town afterward. In the view of his family, the forced resignation from the council contributed greatly to his death.

Mr. Dubois's mother was alive and well, and he had a brother who lived abroad. There was no history of mental illness in the family.

The patient felt quite depressed after his father's death but did not have any other psychiatric symptoms before his current

episode. His physical health had always been excellent. He had never smoked, did not take drugs, and drank no alcoholic beverages except for an occasional beer or glass of wine.

Mrs. Dubois described her husband as hard-working, conscientious, and somewhat rigid in his opinions and with a tendency to bear grudges.

Findings On arrival at the psychiatrist's consulting room, Mr. Dubois was anxious, distressed, and bewildered but oriented in time, place, and person. He talked in a coherent way and, although initially suspicious, eventually gave a detailed account of what he had experienced during the previous week. He was convinced that there was a conspiracy against his family and that it had to do with his father's political activities. He remembered his father's funeral, but he was convinced that the coffin must have been empty. In his opinion the conspirators had kidnapped his father and had been holding him as a hostage all these years. Now they had decided to destroy the rest of the family. The patient admitted that he had been under stress for some time, that he had too much work, and that he had let himself get involved in too many activities both at school and outside of school. During the previous week he had not been able to sleep for more than a few hours each night, and he felt exhausted. He did not feel depressed, and in particular he had no feelings of self-reproach or guilt and no thoughts of suicide. He was aware, however, that something was wrong and agreed to stay in the hospital.

The physical examination did not reveal any abnormality. The results of blood tests, including thyroid function, were within normal limits, as were all other special investigations such as an electroencephalogram and brain scan.

Course Mr. Dubois was treated with a haloperidol (30 mg) during the first week, with the dose halved for the second week. After 2 weeks all of the symptoms had disappeared, and Mr. Dubois was discharged on medication. He was seen once a week in the outpatient department for another month, during which the medication was progressively reduced and then stopped completely. Six months after the onset of his delusional episode, the patient continued to be free of symptoms.

Discussion The significant features of Mr. Dubois's disorder were acute delusions, together with occasional auditory hallucinations and disturbance of visual perception. The disorder developed to its peak in a few days and was resolved in a few weeks, with complete recovery occurring within 6 weeks. The patient had no psychiatric history.

The patient was convinced that his father, who had died 5 years before, was in fact alive and held hostage by a group of conspirators. Although extremely improbable, his delusions cannot be considered theoretically and physically completely impossible and thus bizarre (as in a schizophrenia-like disorder).

Mr. Dubois's disorder otherwise meets the general criteria of an acute and transient psychotic disorder. It developed in a few days and could not be attributed to an organic mental disorder or a metabolic disturbance affecting the central nervous system, or to a mood disorder or the use of a psychoactive substance.

The symptoms did not change rapidly in both type and intensity, so they cannot be coded as acute polymorphic disorder. Because Mr. Dubois does not fulfill the symptomatic criteria for schizophrenia, the most probable diagnosis is other acute predominantly delusional psychotic disorder. The onset of the disorder was preceded by a period of overwork, but this did not amount to significant stress.

Other Acute and Transient Psychotic Disorders Other acute psychotic disorders not classifiable under the preceding categories are included in this category provided there is no evidence of an organic cause. Examples include acute psychoses with definite but fleeting delusions or hallucinations, and states of undifferentiated excitement.

Miss Maruyami is Indonesian. She is 30 years old and single and lives with her widowed mother.

Problem Miss Maruyami was brought to the psychiatric hospital by an uncle and two brothers-in-law, who had to hold her tightly to prevent her from running away. They almost had to carry her. She was hissing, spitting, and kicking about with her legs so that she was hardly able to walk.

Four days earlier she had returned from the market in a state of agitation and mild confusion. She claimed that one of the merchants had accused her of shoplifting, and, when she protested, he had further accused her of being an idler and a prostitute who ought to be sent to jail. Since then she had appeared restless, irritable, suspicious, and hardly able to sleep. At night she went about the house checking the locks and peeping through the windows at the neighbor's house in which she could see some shadows and lights move about. She felt that something hostile was going on and that the neighbor was spying on her because he wanted to rape her and kill her. She did not dare leave the house, and she refused to take any food or water; she claimed it had an odd taste because it had been poisoned by the neighbor. She also tried to prevent her mother from eating and drinking, and she threw away the food and vegetables. She became increasingly disturbed, sat staring wildly ahead of her, and hardly responded when her mother talked to her. When a sister and a brother-in-law came to persuade her to see a physician, she recognized them only with difficulty and ran to her room and locked herself up. On the night of her admission to the hospital, she suddenly left the house and attacked a passing neighbor with a large stone, knocking him to the ground. As the man lay there, Miss Maruyami hit him again and would have continued to do so if other neighbors had not restrained her.

History Miss Maruyami grew up in a middle-class neighborhood in Jakarta. She was the youngest of six daughters. At school she was a good student but had only a few friends and usually kept to herself. She did not continue her education after her junior high school year because her parents had financial problems. Since then she had stayed at home and helped her mother look after the house.

Her father, a merchant, died 10 years earlier when he was 60. Her mother is age 65 and is alive and well. Miss Maruyami's sisters are all married, but she is single and lives with her mother in a small house. Her relationship with her parents and sisters was good, although she was not particularly close to them. She was always a quiet person, spending much of her time lost in her thoughts, apparently daydreaming. She seemed shy and self-conscious, especially in public. She was noticeably overweight and often expressed fears that people were staring at her because of her obesity. These fears and suspicions became more marked as she grew older. Physically she was in good health, had never been to the hospital, and received no medication.

Findings On her admission Miss Maruyami was in a state of psychomotor excitement with aggressive and violent outbursts. When left alone she became more quiet and sat staring ahead of her, with sudden startling reactions to minor noises. She did not know the time or the place, but was fairly oriented as to her personal data. Her speech was restricted and somewhat incoherent. She refused to have physical or laboratory examinations, but

accepted an injection of 10 mg of haloperidol and 5 mg of biperiden (Akineton). After this she became quiet and relaxed and finally fell asleep. The following day she seemed considerably improved. She was fully oriented but slightly perplexed, with partial amnesia about the previous few days. She only partly remembered her persecutory delusions. Confronted with the incident at the marketplace, she had a prolonged crying spell; became mildly excited, with fluctuations in attention and awareness of her surroundings; and finally again became herself.

She did not remember having hallucinations or other unusual experiences. She no longer believed that the neighbors wanted to kill her, and she wanted to get back home to her mother. She was discharged after 3 days, during which she continued to be quite natural without further medication.

Physical and neurological examinations, an electroencephalogram, and laboratory tests were all normal.

The neighbor, who had suffered a minor concussion of the head as a result of the attack, was not severely wounded. Being married to a distant relative of Miss Maruyami's mother, he did not want to bring the incident to the attention of the legal authorities.

Discussion Miss Maruyami developed a peracute psychotic disorder with persecutory delusions and possibly also with hallucinations, severe psychomotor excitation with violent behavior, and transient states of confusion. The disorder developed immediately after an event that she experienced as severely traumatic. She recovered with complete remission occurring within 1 week. It is a matter for discussion whether her transient states of confusion actually fulfill the criteria for organically caused clouding of consciousness. Otherwise, no signs of organic disorder were observed. Psychoactive substance abuse was not suspected. Miss Maruyami therefore most probably had an acute and transient psychotic disorder but did not fulfill the symptomatic criteria for an affective episode. The symptomatology was mixed and atypical, not pointing to any specific subtypes of acute psychotic disorders. The most likely diagnosis, therefore, is probably other acute and transient psychotic disorder.

It may further be discussed whether the traumatic event described would be considered as severely stressful to most people in similar circumstances within the same culture. In Miss Maruyami's case, she seems to have been made particularly susceptible by the presence of pronounced personality traits of introversive seclusion and hypersensitive self-consciousness, which with the present information is not sufficient for a subsidiary diagnosis of a personality disorder.

The diagnosis therefore would be other acute and transient psychotic disorder, with associated acute stress.

Acute and Transient Psychotic Disorder, Unspecified The residual category accommodates such concepts as brief reactive psychosis not otherwise specified. ICD-10 also includes another residual category for psychoses that do not meet the criteria for any other ICD-10 psychotic disorder (Table 13.3-2).

DSM-IV

Psychotic Disorder Due to a General Medical Condition The DSM-IV diagnosis of psychotic disorder due to a general medical condition (Table 13.3-3) combines into one diagnosis the two similar diagnostic categories in the revised third edition of DSM (DSM-III-R), organic delusional disorder and organic hallucinosis. The phenomena of the psychotic disorder are defined in DSM-IV by further specifying the predominant symptoms. When the diagnosis is used, both the medical condition and the predominant symptom pattern should be included in the diagnosis (e.g., psychotic disorder due to a brain tumor, with delusions). The DSM-IV criteria further specify that the disorder does not occur exclusively while the patient is delirious or demented and that the symptoms are not better accounted for by another mental disorder.

Table 13.3-2
ICD-10 Diagnostic Criteria for Other Nonorganic Psychotic Disorders

Psychotic disorders that do not meet the criteria for schizophrenia or for psychotic types of mood (affective) disorders, and psychotic disorders that do not meet the symptomatic criteria for persistent delusional disorder should be coded here (persistent hallucinatory disorder is an example). Combinations of symptoms not covered by the previous categories, such as delusions other than those listed as typically schizophrenic under criterion G(1)a or d for schizophrenia (ie, other than completely impossible or culturally inappropriate) plus catatonia, should also be included here.

Table 13.3-3
DSM-IV Diagnostic Criteria for Psychotic Disorder Due to a General Medical Condition

A. Prominent hallucinations or delusions.
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.
D. The disturbance does not occur exclusively during the course of a delirium.

Code based on predominant symptom:
With delusions: if delusions are the predominant symptom
With hallucinations: if hallucinations are the predominant symptom

Coding note: Include the name of the general medical condition on Axis I, eg, psychotic disorder due to malignant lung neoplasm, with delusions; also code the general medical condition on Axis III.

Coding note: If delusions are part of a preexisting dementia, indicate the delusions by coding the appropriate subtype of the dementia if one is available, eg, dementia of the Alzheimer's type, with late onset, with delusions.

Substance-Induced Psychotic Disorder DSM-IV has combined the various DSM-III-R diagnostic categories that relate to psychoactive substance–induced psychotic disorders into a single diagnostic category, substance-induced psychotic disorder (Table 13.3-4). The diagnosis is reserved for persons who have substance-induced psychotic symptoms in the absence of reality testing. Persons who have substance-induced psychotic symptoms (e.g., hallucinations) but who have retained reality testing should be classified as having a substance-related disorder (e.g., phencyclidine intoxication with perceptual disturbances). The intent of including the diagnosis of substance-induced psychotic disorder with the other psychotic

Table 13.3-4
DSM-IV Diagnostic Criteria for Substance-Induced Psychotic Disorder

A. Prominent hallucinations or delusions. **Note:** Do not include hallucinations if the person has insight that they are substance induced.

B. There is evidence from the history, physical examination, or laboratory findings of either (1) or (2):
   (1) the symptoms in criteria 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 psychotic disorder that is not substance induced. Evidence that the symptoms are better accounted for by a psychotic disorder that is not substance induced might include the following: the symptoms precede the onset of the 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 psychotic disorder (e.g., a history of recurrent non-substance-related episodes).

D. The disturbance does not occur exclusively during the course of a delirium.

Note: This diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the 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 psychotic disorder (Alcohol, with delusions; alcohol, with hallucinations; amphetamine [or amphetamine-like substance], with delusions; amphetamine [or amphetamine-like substance] with hallucinations; cannabis, with delusions; cannabis, with hallucinations; cocaine, with delusions; cocaine, with hallucinations; hallucinogen, with delusions; hallucinogen, with hallucinations; inhalant, with delusions; inhalant, with hallucinations; opioid, with delusions; opioid, with hallucinations; phencyclidine [for phencyclidine-like substance], with delusions; phencyclidine [or phencyclidine-like substance], with hallucinations; sedative, hypnotic or anxiolytic, with delusions; sedative, hypnotic or anxiolytic, with hallucinations; other [or unknown] substance, with delusions; other [or unknown] substance, with hallucinations)

Specify if:
With onset during intoxication: if 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

disorder diagnoses is to prompt the clinician to consider the possibility that a substance is causally involved in the production of the psychotic symptoms. The full diagnosis of substance-induced psychotic disorder should include the type of substance involved, the stage of substance use when the disorder began (e.g., during intoxication or withdrawal), and the clinical phenomena (e.g., hallucinations or delusions).

Psychotic Disorder Not Otherwise Specified The psychotic disorder not otherwise specified category is used for patients who have psychotic symptoms (e.g., delusions, hallucinations, and disorganized speech and behavior) but who do not meet the diagnostic criteria for other specifically defined psychotic disorders. In some

Table 13.3-5
DSM-IV Psychotic Disorder Not Otherwise Specified

This category includes psychotic symptomatology (i.e., delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior) about which there is inadequate information to make a specific diagnosis or about which there is contradictory information, or disorders with psychotic symptoms that do not meet the criteria for any specific psychotic disorder.

Examples include:
1. Postpartum psychosis that does not meet criteria for mood disorder with psychotic features, brief psychotic disorder, psychotic disorder due to a general medical condition, or substance-induced psychotic disorder
2. Psychotic symptoms that have lasted for less than 1 month but that have not yet remitted, so that the criteria for brief psychotic disorder are not met
3. Persistent auditory hallucinations in the absence of any other features
4. Persistent nonbizarre delusions with periods of overlapping mood episodes that have been present for a substantial portion of the delusional disturbance
5. Situations in which the clinician has concluded that a psychotic disorder is present, but is unable to determine whether it is primary, due to a general medical condition, or substance induced

cases the diagnosis of psychotic disorder not otherwise specified may be used when not enough information is available to make a specific diagnosis. DSM-IV has listed some examples of the diagnosis to help guide clinicians (Table 13.3-5).

Culture-Bound Syndromes Perhaps the most dramatic example of the difficulties in applying Western-based nosological concepts and criteria cross-culturally can be found in the ongoing controversy surrounding the culture-bound syndromes. As pointed out by the United States National Institute of Mental Health Culture and Diagnosis Group, the term "culture-bound syndrome" denotes recurrent, locality specific patterns of aberrant behavior and troubling experiences that appear to fall outside conventional Western psychiatric categories. These include categories in folk nosological systems (often organized in relation to perceived cause and symptom clusters) as well as idioms of distress or culturally salient expressions for securing social support and communicating symptoms.

A variety of disorders discussed in the cross-cultural psychiatric and anthropological literature do not conform with conventional DSM-IV or ICD-10 diagnostic categories. In previous diagnostic classifications such disorders were often called atypical psychoses or were placed in the category psychotic disorder not otherwise specified. Taken as a whole, however, labeling these seemingly bizarre and culturally different patterns of disorder psychotic is somewhat problematic. The symptoms displayed include many clinical expressions of lesser severity than those of typical psychotic disorders. Frequently the diagnosis of a psychotic disorder is made simply on the basis of category label rather than a close examination of the symptomatic data. Further discussion of these disorders are discussed with a selection of such syndromes in Table 13.3-6.

While all psychiatric diagnoses are influenced by their cultural context, perhaps the most dramatic example of the difficulty in applying Western-based nosological concepts and criteria cross-culturally can be found with respect to the so-called culture-bound syndromes.

Table 13.3-6 Culture-Bound Syndromes

amok A dissociative episode characterized by a period of brooding followed by an outburst of violent, aggressive, or homicidal behavior directed at persons and objects. The episode tends to be precipitated by a perceived slight or insult and seems to be prevalent only among men. The episode is often accompanied by persecutory idea; automatism, amnesia, exhaustion, and a return to premorbid state following the episode. Some instances of amok may occur during a brief psychotic episode or constitute the onset or an exacerbation of a chronic psychotic process. The original reports that used this term were from Malaysia. A similar behavior pattern is found in Laos, Philippines, Polynesia (*cafard* or *cathard*), Papua New Guinea, and Puerto Rico (*mal de pelea*) and among the Navajo *(iich'aa)*.

ataque de nervios An idiom of distress principally reported among Latinos from the Caribbean, but recognized among many Latin American and Latin Mediterranean groups. Commonly reported symptoms include uncontrollable shouting, attacks of crying, trembling, heat in the chest rising into the head, and verbal or physical aggression. Dissociative experiences, seizurelike or fainting episodes, and suicidal gestures are prominent in some attacks but absent in others. A general feature of an *ataque de nervios* is a sense of being out of control. *Ataques de nervios* frequently occur as a direct result of a stressful event relating to the family (e.g., death of a close relative, separation or divorce from a spouse, conflicts with a spouse or children, or witnessing an accident involving a family member). Persons may experience amnesia for what occurred during the *ataque de nervios,* but they otherwise return rapidly to their usual level of functioning. Although descriptions of some *ataques de nervios* most closely fit the DSM-IV description of panic attacks, the association of most *ataques* with a precipitating event and the frequent absence of the hallmark symptoms of acute fear or apprehension distinguish them from panic disorder. *Ataques* span the range from normal expressions of distress not associated with a mental disorder to symptom presentations associated with anxiety, mood, dissociative, or somatoform disorders.

bilis and colera (also referred to as *muina*) The underlying cause is thought to be strongly experienced anger or rage. Anger is viewed among many Latino groups as a particularly powerful emotion that can have direct effects on the body and exacerbate existing symptoms. The major effect of anger is to disturb core body balances (which are understood as a balance between hot and cold valences in the body and between the material and spiritual aspects of the body). Symptoms can include acute nervous tension, headache, trembling, screaming, stomach disturbances, and, in more severe cases, loss of consciousness. Chronic fatigue may result from an acute episode.

bouffée délirante A syndrome observed in West Africa and Haiti. The French term refers to a sudden outburst of agitated and aggressive behavior, marked confusion, and psychomotor excitement. It may sometimes be accompanied by visual and auditory hallucinations or paranoid ideation. The episodes may resemble an episode of brief psychotic disorder.

brain fag A term initially used in West Africa to refer to a condition experienced by high school or university students in response to the challenges of schooling. Symptoms include difficulties in concentrating, remembering, and thinking. Students often state that their brains are "fatigued." Additional somatic symptoms are usually centered around the head and neck and include pain, pressure or tightness, blurring of vision, heat, or burning. "Brain tiredness" or fatigue from "too much thinking" is an idiom of distress in many cultures, and resulting syndromes can resemble certain anxiety, depressive, and somatoform disorders.

dhat A folk diagnostic term used in India to refer to severe anxiety and hypochondriacal concerns associated with the discharge of semen, whitish discoloration of the urine, and feelings of weakness and exhaustion. Similar to *jiryan* (India), *sukra prameha* (Sri Lanka), and *shen-k'uei* (China).

Falling-out or black-out Episodes that occur primarily in southern United States and Caribbean groups. They are characterized by a sudden collapse, which sometimes occurs without warning but is sometimes preceded by feelings of dizziness or "swimming" in the head. The person's eyes are usually open, but the person claims an inability to see. Those affected usually hear and understand what is occurring around them but feel powerless to move. This may correspond to a diagnosis of conversion disorder or a dissociative disorder.

ghost sickness A preoccupation with death and the deceased (sometimes associated with witchcraft), frequently observed among members of many American Indian tribes. Various symptoms can be attributed to ghost sickness, including bad dreams, weakness, feeling of danger, loss of appetite, fainting, dizziness, fear, anxiety, hallucinations, loss of consciousness, confusion, feelings of futility, and a sense of suffocation.

hwa-byung (also known as *wool-hwa-byung*) A Korean folk syndrome literally translated into English as "anger syndrome" and attributed to the suppression of anger. The symptoms include insomnia, fatigue, panic, fear of impending death, dysphoric affect indigestion, anorexia, dyspnea, palpitations, generalized aches and pains, and a feeling of a mass in the epigastrium.

koro A term probably of Malaysian origin, that refers to an episode of sudden and intense anxiety that the penis (or, in women, the vulva and nipples) will recede into the body and possibly cause death. The syndrome is reported in South and East Asia, where it is known by a variety of local terms, such as *shuk yang, shook yong,* and *suo yang* (Chinese): *jinjinia bemar* (Assam); or *rok-joo* (Thailand). It is occasionally found in the West, *Koro* at times occurs in localized epidemic form in East Asian areas. The diagnosis is included in the second edition of *Chinese Classification of Mental Disorders (CCMD-2).*

latah Hypersensitivity to sudden fright, often with echopraxia, echolalia, command obedience, and dissociative or trancelike behavior. The term *latah* is of Malaysian or Indonesian origin, but the syndrome has been found in many parts of the world. Other terms for the condition are *amurakh, irkunil, ikota, olan, myriachit,* and *menkeiti* (Siberian groups); *bah tschi, bah-tsi, baah-ji* (Thailand): *imu* (Ainu, Sakhalin, Japan); and *mali-mali* and *silok* (Philippines). In Malaysia it is more frequent in middle-aged women.

locura A term used by Latinos in the United States and Latin America to refer to a severe form of chronic psychosis. The condition is attributed to an inherited vulnerability, to the effect of multiple life difficulties, or to a combination of both factors. Symptoms exhibited by persons with *locura* include incoherence, agitation, auditory and visual hallucinations, inability to follow rules of social interaction, unpredictability, and possibly violence.

mal de ojo A concept widely found in Mediterranean cultures and elsewhere in the world. *Mal de ojo* is a Spanish phrase translated into English as "evil eye." Children are especially at risk. Symptoms include fitful sleep, crying without apparent cause, diarrhea, vomiting, and fever in a child or infant. Sometimes adults (especially women) have the condition.

nervios A common idiom of distress among Latinos in the United States and Latin America. A number of other ethnic groups have related, though often somewhat distinctive, ideas of nerves (such as *nerva* among Greeks in North America). *Nervios* refers both to a general state of vulnerability to stressful life experiences and to a syndrome brought on by difficult life circumstances. The term *nervios* includes a wide range of symptoms of emotional distress, somatic disturbance, and inability to function. Common symptoms include headaches and brain aches, irritability, stomach disturbances, sleep difficulties, nervousness, easy tearfulness, inability to concentrate, trembling, tingling sensations, and *mareos* (dizziness with occasional vertigo-like exacerbations). *Nervios* tends to be an ongoing problem, although variable in the degree of disability that is manifest. *Nervios* is a very broad syndrome that spans the range from patients free of a mental disorder to presentations resembling adjustment, anxiety, depressive, dissociative, somatoform, or psychotic disorders. Differential diagnosis depends on the constellation of symptoms experienced, the kind of social events that are associated with the onset and progress of *nervios,* and the level of disability experienced.

piblokto An abrupt dissociative episode accompanied by extreme excitement of up to 30 minutes duration and frequently followed by convulsive seizures and coma lasting up to 12 hours. It is observed primarily in Arctic and subarctic Eskimo communities, although regional variations in name exist. The person may be withdrawn or mildly irritable for a period of hours or days before the attack and typically reports complete amnesia for the attack. During the attack persons may tear off their clothing, break furniture, shout obscenities, eat feces, flee from protective shelters, or perform other irrational or dangerous acts.

(continued)

Table 13.3-6 *(continued)*

***qi-gong* psychotic reactions** Acute, time-limited episodes characterized by dissociative, paranoid, or other psychotic or nonpsychotic symptoms that may occur after participation in the Chinese folk health-enhancing practice of *qi-gong* (exercise of vital energy). Especially vulnerable are persons who become overly involved in the practice. This diagnosis included in CCMD-2.

rootwork A set of cultural interpretations that ascribe illness to hexing, witchcraft, sorcery, or evil influence of another person. Symptoms may include generalized anxiety and gastrointestinal complaints (e.g., nausea, vomiting, diarrhea), weakness, dizziness, the fear of being poisoned, and sometimes fear of being killed (voodoo death). Roots, spells, or hexes can be put or placed on other person, causing a variety of emotional and psychological problems. The hexed person may even fear death until the root has been taken off (eliminated), usually through the work of a root doctor (a healer in this tradition), who can also be called on to bewitched an enemy. Rootwork is found in the southern United States among both African-American and European-American populations and in Caribbean societies. It is also known as *mal puesto* or *brujeria* in Latino societies.

sangue dormido ("sleeping blood") A syndrome found among Portuguese Cape Verde Islanders (and immigrants from there to the United States). It includes pain, numbness, tremor, paralysis, convulsions, stroke, blindness, heart attack, infection, and miscarriages.

Shenjing shuariuo ("neurasthenia") In China a condition characterized by physical and mental fatigue, dizziness, headaches, other pains, concentration difficulties, sleep disturbance, and memory loss. Other symptoms include gastrointestinal problems, sexual dysfunction, irritability, excitability, and various signs suggesting disturbance of the autonomic nervous system. In many cases the symptoms would meet the criteria for a DSM-IV mood or anxiety disorder. The diagnosis is included in CCMD-2.

shen-k'uei (Taiwan); *shenkui* (China) A Chinese folk label describing marked anxiety or panic symptoms with accompanying somatic complaints for which no physical cause can be demonstrated. Symptoms include dizziness, backache, fatigability, general weakness, insomnia, frequent dreams, and complaints of sexual dysfunction, such as premature ejaculation and impotence. Symptoms are attributed to excessive semen loss from frequent intercourse, masturbation, nocturnal emission, or passing of white turbid urine believed to contain semen. Excessive semen loss is feared because of the belief that it represents the loss of one's vital essence and can therefore be life threatening.

shin-byung A Korean folk label for a syndrome in which initial phases are characterized by anxiety and somatic complaints (general weakness, dizziness, fear, anorexia, insomnia, gastrointestinal problems), with subsequent dissociation and possession by ancestral spirits.

spell A trance state in which persons "communicate" with deceased relatives or spirits. At times the state is associated with brief periods of personality change. The culture-specific syndrome is seen among African-Americans and European-Americans from the southern United States. Spells are not considered to be medical events in the folk tradition but may be misconstrued as psychotic episodes in clinical settings.

susto (*frigh* or "soul loss") A folk illness prevalent among some Latinos in the United States and among people in Mexico, Central America, and South America. Susto is also referred to as *espanto, pasmo, tripa ida, perdida del alma,* or *chibih. Susto* is an illness attributed to a frightening event that causes the soul to leave the body and results in unhappiness and sickness. Persons with *susto* also experience significant strains in key social roles. Symptoms may appear any time from days to years after the fright is experienced. It is believed that in extreme cases, *susto* may result in death. Typical symptoms include appetite disturbances, inadequate or excessive sleep, troubled sleep or dreams, feelings of sadness, lack of motivation to do anything, and feelings of low self-worth or dirtiness. Somatic symptoms accompanying *susto* include muscle aches and pains, headache, stomachache, and diarrhea. Ritual healings are focused on calling the soul back to the body and cleansing the person to restore bodily and spiritual balance. Different experience of *susto* may be related to major depressive disorder, posttraumatic stress disorders, and somatoform disorders. Similar etiological beliefs and symptom configurations are found in many parts of the world.

taijin kyofu sho A culturally distinctive phobia in Japan, in some ways resembling social phobia in DSM-IV. The syndrome refers to an intense fear that one's body, its parts or its functions, displease, embarrass, or are offensive to other people in appearance, odor, facial expressions, or movements. The syndrome is included in the official Japanese diagnostic system for mental disorders.

zar A general term applied in Ethiopia, Somalia, Egypt, Sudan, Iran, and other North African and Middle Eastern societies to the experience of spirits possessing a person. Persons possessed by a spirit may experience dissociative episodes that may include shouting, laughing, hitting the head against a wall, singing, or weeping. They may show apathy and withdrawal, refusing to eat or carry out daily tasks or may develop a long-term relationship with the possessing spirit. Such behavior is not considered pathological locally.

The controversy arises over the issue of whether the assumptions embedded in Western diagnostic schemes (e.g., DSM or ICD) relating to concepts of normality and the assemblages of symptoms characteristic of a discrete disorder are universally applicable in all cultural settings.

The term "culture-bound syndrome" evolved, in fact, to denote recurrent, locality-specific patterns of aberrant behavior and troubling experiences that appear to fall outside conventional Western psychiatric categories. The descriptive phrases formerly used to refer to such phenomena include "cultural and ethnic psychoses and neuroses" and "atypical and exotic psychotic syndromes." The *culture-bound syndrome* is now generally accepted to refer to culturally based and named patterns of symptoms of mental distress or maladaptive behavior that are prominent in folk belief and practice. Such patterns have etiologies framed by lay cultural assumptions, which in numerous cases are based upon the effects of sorcery, breach of taboo, intrusion of a disease object, intrusion of a disease-causing spirit, or loss of soul. The psychodynamics often represent an exaggerated or pathological reaction to conflicts engendered by central values and behavioral norms in the society. Since they are embedded in the group's ethnomedical practice, institutionalized patterns of diagnoses and societal response typically include treatment by indigenous healers.

Assessment of such syndromes must start with recognition that each human society has an indigenous body of beliefs and practices directed at explaining and treating disease and disorder, and patients internalize that worldview during the process of enculturation. They share their experiences and deal with distress through the currency of commonly understood symbols and meanings. In that light, the diagnostic encounter itself can be used as a point of entry into the patient's world, a "classroom for investigation and discovery." One cannot become an anthropological expert about each and every possible cultural group but one can try to learn by asking patients to share the cultural norms as they understand them.

PATHOLOGY AND LABORATORY EXAMINATIONS

A large number of general medical problems may cause or exacerbate patients' psychotic conditions, often involving confusing and puzzling presentations. They include such conditions as infections (including human immunodeficiency virus [HIV] infection), head

trauma, endocrine disorders (Cushing's and Addison's diseases and disorders of the thyroid and parathyroid glands), autoimmune diseases (systemic lupus erythematosus), vitamin deficiencies, seizure disorder, genetic diseases (Wilson's disease, acute intermittent porphyria), drug and toxin exposures, and the effects of psychoactive drugs. Those conditions are usually included in the differential diagnosis of any psychotic disorder, but they should be given more careful consideration when the patient's symptom profile is polymorphic or inchoate. For such patients laboratory tests should include not only the routine chemistry panels (electrolytes, glucose determination, complete blood counts, renal and liver functions) and urinalysis, but also thyroid function test, syphilis tests, and determination of serum cortisol concentration, vitamin B_{12} and foliate concentrations, and calcium and phosphate concentrations. In addition to a chest X-ray and an electrocardiogram (ECG), an electroencephalogram (EEG) should also be considered. An EEG with sleep deprivation and nasopharyngeal leads also has been recommended. Computerized EEG (brain mapping), magnetic resonance imaging (MRI), single photon emission computered tomography (SPECT), and neuropsychological testing may yield useful information.

Psychosocial assessment should include a careful review of the patient's life history, with special attention to the patient's personality traits and recent stresses. A detailed assessment of family history and dynamics should also be included. Contextual factors, such as psychosocial stressors and supports, should be carefully appraised, along with the ability of the person to perform basic roles (e.g., occupationally, with family and socially).

COURSE AND PROGNOSIS

Patients with an acute and transient psychotic disorder usually experience complete recovery within 1 to 3 months (depending on the specific disorder), often within a few weeks or days, and only a small proportion of patients develop persistently disabling states.

Limited data on the longitudinal course of patients with culture-bound syndromes suggest that some of them eventually develop clinical features compatible with a diagnosis of schizophrenia, bipolar disorder, cognitive disorder, or other psychotic disorders. Thus gathering information from all possible sources is crucial. Since clinical pictures evolve over time, thorough reevaluations should be conducted periodically to refine the diagnosis and improve clinical care.

TREATMENT

The treatment plan for any patient must be individualized, but that principle is particularly important when dealing with cases of acute and transient psychotic disorders and culture-bound psychotic disorders. Because these conditions are intricate and heterogeneous, no standard treatment strategy exists that can be applied to most cases. However, a number of general principles are crucial for the cases of those patients.

Careful evaluation, clinical observation, and comprehensive information gathering are the cornerstones of treatment planning for any psychiatric or general medical disorder. Longitudinal assessments are particularly important in the management of patients who are experiencing acute and transient psychotic disorders and culture-bound disorders. A multiaxial assessment using such schemas as those in ICD-10 and DSM-IV can substantially enhance the validity of diagnosis and the effectiveness of clinical care. A systematic evaluation of the cultural framework of the individual's identity, illness explanations, social context and functioning, and the doctor-patient relationship can be conducted along the lines of DSM-IV.

Because all the disorders discussed in this section share the presence of psychosis, pharmacotherapy frequently involves the use of antipsychotic drugs. Some evidence indicates that the dosage of antipsychotic drugs necessary for acute transient psychotic disorders is significantly lower than that required for other psychotic conditions, especially schizophrenia. It is thus prudent to use the lowest dose that can control the patient's symptoms. Since acute and transient psychotic disorders are often episodic, intermittent use of antipsychotic drugs, guided by the emergence of psychotic symptoms, is worth considering.

Depending on the clinical features of particular patients, many other psychiatric medicines have also been recommended. They include benzodiazepines for controlling agitation, lithium (Eskalith, Lithobid) for modulating mood swings, and antidepressants for ameliorating depressive symptoms. These medicines are often used in conjunction with antipsychotic agents. Anticonvulsants such as carbamazepine (Tegretol) have been reported effective in treating a number of psychotic patients with atypical features.

Limited research has been conducted to date on the efficacy of various psychosocial interventions for managing acute and transient psychotic disorders and culture-bound disorder, but it seems reasonable to consider findings from studies involving other psychotic conditions. These include approaches based on expressed emotion concepts, psychoeducational and skill-competence training, and Thomas McGlashan's phase-specific theory on the need for stimulation in schizophrenic patients (the avoidance of excessive stimuli in the acute phase and the uses of structured activities and stimuli in later phases). It is important to consider involving the family in therapy and to establish a supportive and trusting therapeutic relationship.

The importance of cultural issues in the evaluation and treatment of atypical psychoses can hardly be exaggerated, especially when dealing with patients from non-Western and ethnic minority populations. Cultural information is not only crucial for accurate diagnosis, but also indispensable in the formulation of treatment plans. Treatment approaches that do not take the patient's sociocultural background into account are likely to fail, no matter how well intentioned the therapists may be. For example, in cultures in which family and group harmony and unity are valued over individual independence, the rigid application of Western-based psychotherapeutic techniques may exacerbate, rather than ameliorate, the patient's psychopathological condition. Consideration of the intercultural elements in the clinician-patient relationship is also fundamental for establishment of rapport and effective engagement of the patient and the family in the treatment process.

One promising avenue is collaboration with indigenous healers. Several researchers have reported on their success in the use of indigenous and traditional healers in the treatment of psychiatric patients, especially those whose psychotic conditions are substantially connected to culture-specific beliefs (e.g., fear of voodoo death). Others have mentioned the potential pitfalls and problems in such collaboration. Decisions about involving indigenous healers should be individualized and thoughtfully planned, taking into consideration the setting, the thoughtfulness and flexibility of the available healers, the type of psychopathology, and the patient's characteristics. The World Health Organization (WHO) has long advocated implementation at the local level of a policy of close collaboration between the conventional health system and traditional medicine, particularly between individual health professionals and traditional practitioners.

Wohl has stressed the implications for therapeutic practice of the need to understand the cultural dynamics of a patient's background. While this is important for therapy with any patient, it is particularly necessary in the treatment of a suspected culture-bound syndrome:

Much of the time in the practice of psychotherapy, culture remains silent, part of a non instrusive background, an invisible yet pervasive feature of the context of psychotherapy . . . Psychotherapies differ as the cultures in which they were born and nurtured differ, and each bears the indelible imprint of its culture source. Psychotherapy and the human relationships that comprise both its subject matter and the medium in which it is performed have embedded within them values, rules, assumptions, myths, and rituals of a particular culture. Psychotherapy is thus inescapably bound to a particular cultural framework.

Treatment of a culture-bound syndrome poses several diagnostic challenges, the first of which is determining whether the symptomatology represents a culturally appropriate adaptive response to a situation (although it may be different from the therapist's). What are clinicians to do if confronted with a series of symptoms in a patient that do not fit their conventional diagnostic model? Clinicians are well advised to (1) know or search out the demographics of the local population or catchment area being served; (2) recognize that there is always a local pattern of conceptualization, naming, vocabulary, explanation, and treatment of patterns of distress that afflict a community, including mental disorders; and (3) talk with the family, get instructed in local customs; or search out other modes of documentation.

But while the observed symptom may be familiar in a general sense to the clinician (although pathoplastically different), what separates such an event from conventional understanding is the meaning of the symptom for patients and those who share their cultural background. Determining that meaning and particularly their belief about what has caused the distress, is an important entry point in facilitating therapeutic management and enhancing adherence to the treatment plan. As part of taking the history, ask these patients what they think could have caused the problem, requesting the "patient's explanatory model": (1) What do you think has caused your problem? (2) Why do you think it started when it did? (3) What do you think your sickness does to you? How does it work? (4) How severe is your sickness? Will it have a short or long course? (5) What kind of treatment do you think you should receive?

Such insight into the dynamics of the patient's world facilitates the clinician's efforts to adapt his or her techniques (e.g., general activity level, mode of verbal intervention, content of remarks, tone of voice) to the cultural background of clients; communicate acceptance of and respect for the patients in terms that make sense within their cultural frame of reference; and be open to the possibility of more-direct intervention in the life of the patient than conventional approaches might suggest.

In conclusion, the treatment of patients experiencing acute transient psychotic disorders and culture-bound syndromes, even more than that of patients with other psychiatric disorders, should be personalized and comprehensive, using judiciously all biological, psychological, and social therapies pertinent to the problem at hand and keeping in mind the cultural framework of the patients and their families.

SUGGESTED CROSS-REFERENCES

Culture-bound syndromes are discussed further in Section 4.1 on anthropology and psychiatry. Cultural psychiatry is also discussed in Section 4.4. The influences of culture on the nature of and responses to psychiatric disorders are discussed in Section 4.2 on sociology and psychiatry. Section 4.3, on evolutionary biology and psychiatry, is also relevant. Section 9.2 covers international perspectives on psychiatric diagnosis. Section 13.1 is devoted to other psychotic disorders, including brief psychotic disorder.

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▲ 13.4 Postpartum Psychiatric Syndromes

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During the postpartum period up to 85 percent of women experience some type of mood disturbance (Table 13.4-1). For most women the symptoms are transient and relatively mild; however, some women experience a more disabling and persistent form of mood disturbance. Although postpartum mood disorders are relatively common, depressive symptoms that emerge during the postpartum period are frequently overlooked by patients and their caregivers. Puerperal affective illness places both the mother and infant at risk and has been associated with significant long-term effects on child development and behavior. Therefore, prompt recognition and treatment of puerperal mood disorders are essential.

HISTORY

Although Hippocrates is often acknowledged as the first to have recognized postpartum mental illness, historians have noted that what Hippocrates described as a mania related to lactation was more likely delirium associated with puerperal sepsis, which was relatively common in ancient Greece. There was virtually no mention of puerperal mental illness until the 1700s and 1800s, when case reports of "puerperal insanity" began to appear in the French and German medical literature. In 1818 Jean Esquirol was the first to provide detailed, quantitative data on 92 cases of puerperal psychosis drawn from his studies at the Salpetriere during the Napoleonic Wars. However, it is Victor Louis Marce, a French physician, who is best known for his descriptions of postpartum psychiatric illness. In his famous text published in 1856, *Traite de la Folie des Femmes Enceintes,* he laid the foundation for modern conceptualizations of mental illness related to pregnancy and the postpartum period. He was also the first to suggest that physiological changes associated with the puerperium influence maternal mood.

Although puerperal psychosis was familiar to most clinicians by the late nineteenth century, less attention was given to milder forms of puerperal illness. It was not until the 1960s that B. Pitt first described an "atypical" depression (later called "maternity blues") that affected mothers soon after childbirth and, in contrast to puerperal psychosis, was relatively mild and short-lived. The concept of a more severe form of nonpsychotic depressive illness (i.e., postpartum depression) emerged during the 1970s. Large, population-based studies, which relied upon structured interviews and standardized diagnostic criteria to identify psychiatric illness in new mothers, demonstrated high rates of mild to moderate depression in women during the first 6 months after delivery.

Recent studies have consistently identified the postpartum period as a time of increased risk for the development of psychiatric illness in women. One of the most frequently cited studies on affective illness during the puerperium described a sharp peak in the number of psychiatric admissions during the first 3 months after delivery. Subsequent studies indicate that women who present with significant psychiatric symptoms during the postpartum period suffer most commonly from a mood disorder, either major depressive disorder or a bipolar disorder. During the postpartum period women appear to be at much higher risk for the development of psychiatric illness than at other times in their lives.

Various investigators have argued that postpartum mental illness consists of a group of psychiatric disorders that are specifically related to pregnancy and childbirth and therefore exists as a distinct diagnostic entity. However, recent evidence suggests that affective illness that emerges during the puerperium does not differ significantly from affective illness occurring in women at other times. This opinion is reflected in the fourth edition of *Diagnostic and Statistic Manual of Mental Disorders* (DSM-IV), which includes postpartum psychiatric illness as a subtype of either bipolar disorder or major depressive disorder.

DEFINITION

Postpartum psychiatric illness is typically divided into three categories: (1) postpartum blues, (2) nonpsychotic postpartum depression, and (3) puerperal psychosis (Table 13.4-1). It is helpful to conceptualize these disorders as existing along a continuum, as there may be significant overlap between these three diagnostic subtypes. Although these subtypes vary in severity, it is not clear if they actually represent three distinct disorders.

ETIOLOGY

The puerperium is a period during which significant physiological and psychosocial changes occur. The extent to which a rapidly chang-

Table 13.4-1
Classification of Postpartum Mood Disorders

Disorders	Prevalence	Onset	Characteristic Symptoms
Postpartum blues	30 to 85 percent	Within first week	Mood lability, tearfulness, insomnia, anxiety
Postpartum depression	10 to 15 percent	Usually insidious, within first 2 to 3 months	Depressed mood, excessive anxiety, insomnia
Puerperal psychosis	0.1 to 0.2 percent	Usually within first 2 to 4 weeks	Agitation and irritability, depressed mood or euphoria, delusions, depersonalization, disorganized behavior

ing hormonal environment influences the emergence of mood illness has been considered by many. In fact, it was Victor Louis Marce who first suggested, long before the emergence of the modern field of endocrinology, that a physiological transition occurring after delivery may play an important role in the pathogenesis of puerperal illness. Other investigators have emphasized the importance of biological vulnerability to psychiatric illness during the puerperium and have suggested that some individuals may be more susceptible to the physiological changes characteristics of the postpartum period. However, the impact of psychosocial factors in the development of mood disorder during the postpartum period cannot be underestimated. Given the multiplicity of these factors and the complexity of their interactions, it has been extremely difficult to identify risk factors for puerperal psychiatric illness and to reliably predict who will experience postpartum mood disturbance.

Demographic Variables Many groups have investigated the relationship between risk for postpartum blues and depression and various demographic variables including age, marital status, parity, education level, and socioeconomic status; however, there is little consistent evidence to suggest that any particular demographic factor places a woman at increased risk for puerperal affective illness. Although most studies do not find a strong relationship between age and risk for puerperal illness, there is at least one report of high rates (26 percent) of postpartum depression in adolescent mothers.

It has been significantly more difficult to identify risk factors for puerperal psychosis, given the low prevalence of this subtype of postpartum illness. Some reports suggest that primiparous women are more vulnerable to postpartum psychosis than multiparous women. Other studies suggest that various obstetrical complications (e.g., prolonged labor, caesarean section, stillbirth) may increase the likelihood of postpartum psychosis.

Psychosocial Factors Psychosocial variables appear to play an important role in determining vulnerability to affective illness during the postpartum period. Many studies have sought to link certain personality traits and coping styles with risk for postpartum illness but have yielded inconsistent findings. In contrast, several groups have demonstrated that stressful life events during pregnancy or near the time of delivery appear to increase the likelihood of postpartum depressive illness. One of the most consistent findings is that among women who report marital dissatisfaction or inadequate social supports, postpartum depressive illness is more common.

History of Psychiatric Illness Although it has been difficult to identify specific demographic and psychosocial variables that consistently predict risk for postpartum illness, there is a well-defined association between all types of postpartum psychiatric illness and a personal history of mood disorder (Table 13.4-2). At highest risk are women with a history of postpartum psychosis; up to 70 percent of women who have had one episode of puerperal psychosis will experience another episode following a subsequent pregnancy. Similarly, women with histories of postpartum depression are at significant risk, with rates of postpartum recurrence as high as 50 percent. Women with bipolar disorders also appear to be particularly vulnerable during the postpartum period, with rates of postpartum relapse ranging from 20 to 50 percent.

The extent to which a history of major depressive disorder influences risk for postpartum illness is less clear. As compared to women who have experienced only nonpuerperal depressive episodes, women with histories of postpartum depression are clearly at greater risk. Women with histories of mild to moderate affective illness who remain euthymic during pregnancy are probably at lower risk for postpartum depression than women with severe, recurrent depression. For all women (with or without histories of major depression), the emergence of depressive symptoms during pregnancy increases the likelihood of postpartum depression.

Table 13.4-2
History of Psychiatric Illness and Risk for Puerperal Relapse

Disorders	Risk of Relapse at Future Pregnancy
Postpartum Psychosis	70%
Postpartum Depression	50%
Bipolar I Disorder	20–50%
Major Depressive disorder	30%

Hormonal Factors The postpartum period is characterized by a rapid shift in the hormonal environment. Within the first 48 hours after delivery, estrogen and progesterone concentrations fall dramatically; similarly, cortisol concentrations drop after delivery. As these steroid hormones have been implicated in the pathogenesis of nonpuerperal mood disorders, many investigators have proposed a role for these hormones in the emergence of a mood disorder during the postpartum period.

Progesterone Several anecdotal reports have suggested that mood disturbance during the puerperium may be related to declining concentrations of progesterone and have suggested a beneficial effect of progesterone hormone replacement in the treatment of postpartum psychiatric illness. However, several studies have found no consistent differences in postpartum progesterone concentrations between depressed and nondepressed women.

Estrogen Several studies have explored the relationship between postpartum estrogen levels and risk for postpartum blues and depression and have suggested that postpartum estrogen deficiency may result in postpartum mood disturbance. Although some studies have observed lower estrogen levels in women who developed postpartum blues and depression, most of the studies have yielded negative findings.

Cortisol Concentrations of cortisol, which are high late in pregnancy, peak during labor and delivery. Cortisol concentrations drop rapidly after delivery and then return to baseline levels gradually over the next month. While disturbances in the hypothalamic-pituitary-adrenal axis may play an important role in at least some cases of nonpuerperal major depression, recent studies do not consistently support a relationship between cortisol levels and postpartum blues or depression. The dexamethasone (Dexacidin) suppression test does not appear to distinguish between depressed and nondepressed women during the acute puerperium.

Thyroid Hormones Thyroxine concentrations are high during pregnancy and fall during the postpartum period. Abnormalities in thyroid function tests are relatively common findings during the postpartum period, and clinical hypothyroidism is present in up to 10 percent of women after childbirth. Although thyroid dysfunction, particularly hypothyroidism, may produce psychiatric symptoms, no studies have consistently reported an association between postpartum depression or blues and thyroid dysfunction (either hypothyroidism or hyperthyroidism).

DIAGNOSIS AND CLINICAL FEATURES

Postpartum psychiatric disorders have not been listed separately in recent revisions of the DSM, and no specific criteria for the diagnosis of postpartum psychiatric illness have been provided. According to DSM-IV, postpartum psychiatric illnesses may be indicated with a postpartum onset specifier. The specifier with postpartum onset may be used to describe a major depressive, manic, or mixed episode (in major depressive disorder or bipolar I or II disorder) or brief psychotic disorder, when the episode occurs within the first 4 weeks after delivery (Table 13.4-3). In contrast, the Marce Society, an international scientific organization dedicated to the study of postpartum psychiatric disorders, defines postpartum psychiatric illness as any episode occurring within the first year after childbirth.

Given the prevalence of mood disturbance during the puerperium, it is most striking that diagnoses of postpartum mood disorders are so commonly missed. The emergence of mood disorder during the puerperium is often overlooked or ignored by both patients and their caregivers. Some studies report that less than one-third of women with postpartum illness seek professional help. It is common for women to report the persistence of depressive symptoms for many months before the initiation of treatment. Although the symptoms of depression may remit spontaneously, many women are still depressed at 1 year after childbirth. The reasons for this delay in treatment are not well understood. What is clear, however, is the significant impact of untreated depression on both mother and infant. Untreated depression may contribute to the development of a more chronic and refractory mood disorder in the mother. There are also significant data that demonstrate the adverse effects of maternal depression on the cognitive, emotional, and social development of the child. Given these significant risks, prompt recognition and treatment of postpartum mood disorders are essential.

Postpartum Blues Many women experience mild depressive symptoms during the first week after delivery, which are commonly known as postpartum blues or "baby blues." Depending on the criteria used to diagnose the blues, prevalence estimates range from 30 to 85 percent. Women with postpartum blues report a variety of symptoms, including dysphoria, mood lability, irritability, tearfulness, anxiety, and insomnia. These symptoms typically peak on the fourth or fifth day after delivery and remit spontaneously by the tenth postpartum day. Postpartum blues are relatively benign and are, by definition, time-limited. While the occurrence of postpartum blues does not necessarily reflect psychopathology in the mother, some women with blues will go on to develop postpartum depression. Women with histories of mood disorder require close monitoring, as some data suggest that blues may herald the development of major depressive disorder in women who have had previous episodes of affective illness. Symptoms of the blues that persist beyond the second postpartum week require further evaluation to rule out the evolution of a more serious affective illness.

Table 13.4-3
DSM-IV Criteria for Postpartum Onset Specifier

Specify if:
With postpartum onset (can be applied to the current or most recent major depressive, manic, or mixed episode in major depressive disorder, bipolar I disorder, or bipolar II disorder, or to brief psychotic disorder)
Onset of episode within 4 weeks postpartum.

Postpartum Depression Major depressive disorder is relatively common during the postpartum period. Both retrospective and prospective community-based studies have revealed rates of postpartum minor and major depression in the range of 10 to 15 percent. These rates of depression reported in puerperal cohorts are similar to those observed in nonpuerperal populations of women.

While some women report the acute onset of symptoms shortly after delivery, depression more commonly develops insidiously over the first 6 postpartum months. A significant proportion of women actually experience the onset of depressive symptoms during pregnancy. The signs and symptoms of postpartum depression are generally indistinguishable from those characteristic of nonpsychotic major depressive disorder that occurs in women at other times. Dysphoric mood, irritability, anhedonia, insomnia, and fatigue are frequently reported; somatic complaints are also common. Ambivalent or negative feelings toward the infant are often reported, and it is common for a woman with postpartum depression to express doubts or concerns about her ability to care for her child. In its most severe form, postpartum depression may result in profound dysfunction. Suicidal ideation is frequently reported; however, suicide rates appear to be relatively low in women who become depressed during the postpartum period.

Although few studies have evaluated the prevalence of comorbid psychiatric illness in this population, severe anxiety and obsessionality are prominent in women with puerperal illness. Symptoms of generalized anxiety, panic disorder, and obsessive-compulsive disorder are often observed in women with postpartum depression.

Puerperal Psychosis Puerperal psychosis is the most severe form of postpartum psychiatric illness. In contrast to postpartum blues and depression, puerperal psychosis is a rare event that occurs in approximately 1 to 2 per 1000 women after childbirth. Its presentation is often dramatic, with onset of psychosis as early as the first 48 to 72 hours postpartum. Most women with puerperal psychosis develop symptoms within the first 2 to 4 weeks after delivery.

In women with this disorder, psychotic symptoms and disorganized behavior are prominent and cause significant dysfunction. Puerperal psychosis resembles a rapidly evolving affective psychosis with manic, depressive, or mixed features. The earliest signs are typically restlessness, irritability, and insomnia. Women with this disorder typically exhibit a rapidly shifting depressed or elated mood, disorientation or depersonalization, and disorganized behavior. Delusional beliefs often center on the infant and include delusions that the child may be defective or dying, that the infant has special powers, or that the child is either Satan or God. Auditory hallucinations that instruct the mother to harm or kill herself or her infant are sometimes reported. Although most believe that this illness is indistinguishable from an affective (or manic) psychosis, some have argued that puerperal psychosis may be clinically distinct in that it is more commonly associated with confusion and delirium than nonpuerperal psychotic mood disorder.

Screening Severe postpartum depression and psychosis are easily recognized; however, milder or more insidious forms of depressive illness are frequently missed. Even severe depressive symptoms that arise during the puerperium may be dismissed by both patients and caregivers as normal or natural consequences of childbirth. Since it is difficult to reliably predict which women in the

general population are likely to develop puerperal illness, it is advisable to screen all women for depression during the postpartum period. The greatest obstacle to the diagnosis of postpartum depression is the extent to which clinicians fail to inquire about affective symptoms in women during the postpartum period.

The standard postpartum obstetrical visit at 6 weeks and subsequent pediatric appointments are ideal times to screen for postpartum depressive illness. Screening for mood disorders during the postpartum period may, however, be more difficult than at other times. Many of the neurovegetative signs and symptoms characteristic of major depression (e.g., sleep and appetite disturbance, diminished libido, low energy) are also observed in nondepressed women during the acute puerperium. Various rating scales that have been used to facilitate the diagnosis of depression in nonpuerperal cohorts (e.g., Beck Depression Inventory) have not been validated in puerperal populations. In contrast, the Edinburgh Postnatal Depression Scale (EPDS) is a 10-item, self-rated questionnaire (Table 13.4-4) that has been used extensively for the detection of postpartum depression and has demonstrated satisfactory sensitivity and specificity in women during the postpartum period. Although not commonly employed, the EPDS could easily be integrated into the routine evaluation of women in both obstetrical and pediatric settings and would alert the physician to those women who are in need of a more thorough psychiatric evaluation.

DIFFERENTIAL DIAGNOSIS

Various medical illnesses may mimic psychiatric illness during the postpartum period. Hypothyroidism is relatively common in women after delivery and may cause a constellation of symptoms resembling major depressive disorder. Women with a preexisting psychiatric illness may experience exacerbation of symptoms during the puerperium. Furthermore, any psychiatric illnesses may emerge for the first time during the postpartum period. Schizophrenia or schizoaffective disorder, particularly when characterized by prominent positive symptomatology, may be difficult to distinguish from puerperal psychosis. Whereas mood disorders are the most common type of postpartum psychiatric illness, anxiety symptoms are common during the postpartum period and many present either with or without a coexisting mood disorder. The postpartum period may represent a time of increased risk for the development of panic disorder and obsessive-compulsive disorder.

COURSE AND PROGNOSIS

The duration of postpartum illness appears to be variable. Puerperal episodes are often relatively short-lived and last no more than 3 months. Many women, however, have a more prolonged illness, and several studies suggest that depressive episodes tend to be longer and more severe in those with histories of major depressive disorder; some reports suggest that duration may be related to the severity of illness.

In general, women with postpartum mood disorders have a good prognosis. In about half of the cases, puerperal depression or psychosis represents the first onset of psychiatric illness. Although there appears to be a subpopulation of women who have only puerperal episodes of psychiatric illness, the majority of women with a postpartum mood disorder will go on to have nonpuerperal episodes of psychiatric illness. Rates of recurrence appear to be particularly high in women with bipolar disorders.

Postpartum mood disorders are associated with recurrent psychiatric illness in the mother. The failure to treat may contribute to the emergence of a long-term and more treatment refractory mood disorder. There is data to suggest that the outcome is better in those that receive treatment early during the course of illness.

There is a growing body of literature that demonstrates the detrimental effect of maternal depression on child development. Attachment difficulties are common in new mothers and may be quite severe in women with postpartum depression or psychosis. Long-term follow-up studies have shown that behavioral difficulties were more common in the children of mothers who suffered from postpartum depression. These children also performed worse on structured tests of cognitive ability than children who had mothers who were not depressed. One of the most disastrous outcomes involves harm to the infant. Child abuse and neglect are more common among women who suffer from postpartum psychiatric illness. Infanticide is relatively uncommon; however, it is more likely to occur in women who present with psychotic symptoms.

TREATMENT

Like nonpuerperal depressive illness, postpartum mood disorders present along a continuum. Patients may experience mild or moderate symptoms, or they may present with a more severe depression, characterized by prominent neurovegetative symptoms and marked impairment of functioning. A clinician's approach to the patient should be guided by the type and severity of the symptoms and the degree of functional impairment. However, before initiating psychiatric treatment, medical causes for mood disturbance (e.g., thyroid dysfunction, Sheehan's syndrome) must be excluded. Initial evaluation should include a thorough history, physical examination, and routine laboratory tests.

Postpartum Blues As postpartum blues are usually mild in severity and resolve spontaneously, no specific treatment other than support and reassurance is indicated. Although the symptoms may be distressing, they typically do not affect the mother's ability to function and to care for her infant. Psychiatric consultation is generally not required; however, the patient should be instructed to contact her obstetrician or primary care provider if the symptoms persist longer than two weeks to ensure the early identification of a more severe affective illness. Women with histories of psychiatric illness, particularly postpartum depression, should be monitored more closely, as they are at higher risk for significant puerperal illness.

Postpartum Depression Although postpartum depression is relatively common, few studies have systematically assessed the efficacy of nonpharmacological and pharmacological therapies in the treatment of this disorder. However, there are no data that suggest that postpartum depression should be managed differently than nonpuerperal major depressive disorder. There is, nonetheless, an apparent tendency to treat women with postpartum depression with less urgency than nonpuerperal patients, which places both the mother and infant at risk. In the absence of systematically derived data, depression that emerges during the postpartum period demands the same intensity of treatment as depression that occurs at other times; the earlier the treatment is initiated, the better the prognosis.

Nonpharmacological Therapy Nonpharmacological therapies are frequently employed in the treatment of postpartum depression; however, there are limited data to support the efficacy of these interventions. Although studies that have assessed the use of insight-oriented psychotherapy in the treatment of postpartum depression

Table 13.4-4
Edinburgh Postnatal Depression Scale (EPDS)

The Edinburgh Postnatal Depression Scale (EPDS) has been developed to assist primary care health professionals to detect mothers suffering from postnatal depression; a distressing disorder more prolonged than the "blues" (which occur in the first week after delivery) but less severe than puerperal psychosis.

Previous studies have shown that postnatal depression affects at least 10 percent of women and that many depressed mothers remain untreated. These mothers may cope with their babies and with household tasks, but their enjoyment of life is seriously affected and it is possible that there are long-term effects on the family.

The EPDS was developed at health centers in Livingston and Edinburgh. It consists of ten short statements. The mother underlines which of the four possible responses is closest to how she has been feeling during the past week. Most mothers complete the scale without difficulty in less than 5 minutes.

The validation study showed that mothers who scored above a threshold 12/13 were likely to be suffering from a depressive illness of varying severity. Nevertheless the EPDS score should *not* override clinical judgment. A careful clinical assessment should be carried out to confirm the diagnosis. The scale indicates how the mother has felt *during the previous week,* and in doubtful cases it may be usefully repeated after 2 weeks. The scale will not detect mothers with anxiety neuroses, phobias or personality disorders.

Instructions for users

1. The mother is asked to underline the response which comes closest to how she has been feeling in the previous 7 days.
2. All ten items must be completed.
3. Care should be taken to avoid the possibility of the mother discussing her answers with others.
4. The mother should complete the scale herself, unless she has limited English or has difficulty with reading.
5. The EPDS may be used at 6–8 weeks to screen postnatal women. The child health clinic, postnatal check-up or a home visit may provide suitable opportunities for its completion.

EDINBURGH POSTNATAL DEPRESSION SCALE (EPDS)

J. L. Cox, J. M. Holden, R. Sagovsky
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Name:

Address:

Baby's age:

As you have recently had a baby, we would like to know how you are feeling. Please UNDERLINE the answer which comes closest to how you have felt IN THE PAST 7 DAYS, not just how you feel today.

Here is an example, already completed.

I have felt happy:
Yes, all the time
Yes, most of the time
No, not very often
No, not at all

This would mean: "I have felt happy most of the time" during the past week. Please complete the other questions in the same way.

In the past 7 days:

1. I have been able to laugh and see the funny side of things
   As much as I always could
   Not quite so much now
   Definitely not so much now
   Not at all
2. I have looked forward with enjoyment to things
   As much as I ever did
   Rather less than I used to
   Definitely less than I used to
   Hardly at all
3. I have blamed myself unnecessarily when things went wrong
   Yes, most of the time
   Yes, some of the time
   Not very often
   No, never
4. I have been anxious or worried for no good reason
   No, not at all
   Hardly ever
   Yes, sometimes
   Yes, very often
5. I have felt scared or panicky for no very good reason
   Yes, quite a lot
   Yes, sometimes
   No, not much
   No, not at all
6. Things have been getting on top of me
   Yes, most of the time I haven't been able to cope at all
   Yes, sometimes I haven't been coping as well as usual
   No, most of the time I have coped quite well
   No, I have been coping as well as ever
7. I have been so unhappy that I have had difficulty sleeping
   Yes, most of the time
   Yes, sometimes
   Not very often
   No, not at all
8. I have felt sad or miserable
   Yes, most of the time
   Yes, quite often
   Not very often
   No, not at all
9. I have been so unhappy that I have been crying
   Yes, most of the time
   Yes, quite often
   Only occasionally
   No, never
10. The thought of harming myself has occurred to me
    Yes, quite often
    Sometimes
    Hardly ever
    Never

Response categories are scored 0, 1, 2, and 3 according to increased severity of the symptom.

Items marked with an asterisk are reverse scored (i.e., 3, 2, 1 and 0). The total score is calculated by adding together the scores for each of the ten items. Users may reproduce the scale without further permission providing they respect copyright (which remains with the *British Journal of Psychiatry*) by quoting the names of the authors, the title and the source of the paper in all reproduced copies.

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have yielded inconsistent findings, more structured types of individual psychotherapy have shown promise.

Interpersonal therapy is a time-limited and interpersonally oriented psychotherapy that has been used successfully (in nonpuerperal cohorts) to treat acute episodes of depression. This modality of therapy focuses primarily on interpersonal relationships and has been adapted for the treatment of postpartum depression. In this setting, interpersonal therapy may be used to address the following issues: role transition, disruption of relationships with the spouse and other social supports, and interaction with the infant. In a recent pilot study, interpersonal therapy was shown to be effective for the treatment of women with mild to moderate postpartum major depressive disorder.

Cognitive-behavioral therapy may also be useful in this setting. A recent randomized, placebo-controlled treatment trial demonstrated that short-term cognitive behavioral therapy was as effective as treatment with fluoxetine (Prozac) in women with postpartum depression. Sessions were structured to focus on issues specific to new mothers with postpartum depression: inability to cope with the demands of caring for a child, perceived lack of support, absence of enjoyable activities. A significant reduction in depressive symptoms was observed in women after six sessions of cognitive-behavioral therapy delivered over a 12-week period.

These nonpharmacological interventions may be particularly useful for those patients who are reluctant to use psychiatric medications or for patients with milder forms of depressive illness. These interventions would ideally be performed in the home by a visiting nurse or another trained individual. Further investigation is required to determine the efficacy of this modality in women who suffer from more severe forms of postpartum mood disturbance.

Pharmacological Therapy To date, few studies have assessed the efficacy of antidepressant medications in the treatment of postpartum mood disturbance. The majority of these studies have been open trials, although more recent investigations have employed a double-blind design. Several studies have demonstrated the efficacy of antidepressant medications (e.g., fluoxetine, sertraline [Zoloft] venlafaxine [Effexor]) in the treatment of postpartum major depressive disorder. In all of these studies, standard antidepressant doses were effective and well tolerated.

The choice of an antidepressant drug should be guided by the patient's prior response to antidepressant medication and a given medication's adverse effect profile. Fluoxetine and the other selective serotonin reuptake inhibitors (SSRIs) are ideal first-line agents because they are anxiolytic, generally nonsedating, and well tolerated. Tricyclic drugs are frequently used and, because they tend to be more sedating, may be more appropriate for women who present with sleep disturbance. Given the severity of anxiety symptoms in women with postpartum depression, the adjunctive use of a benzodiazepine (e.g., clonazepam [Klonopin], lorazepam [Ativan]) may be very helpful.

Women who plan to breastfeed must be informed that all psychiatric medications, including antidepressant drugs, are secreted into the breast milk. Concentrations in the breast milk appear to vary widely; however, there is no data to suggest that one antidepressant agent is safer than another for women who are nursing. Available data on the use of tricyclic drugs, fluoxetine, and sertraline during breastfeeding suggest that severe complications related to neonatal exposure to psychotropic medications in breast milk appear to be rare; however, the long-term effects of even trace amounts of medication on the developing brain are not known.

Inpatient Hospitalization In cases of severe postpartum depression, inpatient hospitalization may be required, particularly for patients who are at risk for suicide. In the United Kingdom innovative treatment programs involving joint hospitalization of the mother and baby have been successful; however, mother-infant units are much less common in the United States. In women with severe postpartum illness, electroconvulsive therapy (ECT) should be considered early because it is safe and highly effective. In choosing a treatment strategy, it is important to consider the impact of prolonged hospitalization of the mother on infant development and attachment.

Hormonal Therapy The postpartum period is associated with rapid shifts in the reproductive hormonal environment, most notably a dramatic fall in estrogen and progesterone levels. With increasing evidence to suggest that gonadal steroids modulate neurotransmitter systems involved in the pathogenesis of mood illness, many have proposed a role for hormonal manipulation in the treatment of postpartum mood disturbance. Some authors have suggested that progesterone is helpful in the management of postpartum depression; however, systematically derived data do not demonstrate its usefulness in this setting. A.J. Gregoire and colleagues described a beneficial effect of exogenous estrogen therapy in women with postpartum depression. Although this study was small and was confounded by the inclusion of patients treated with antidepressant medication prior to receiving hormonal therapy, it is the first study to demonstrate that estrogen alone (or possibly when used as an adjunct to an antidepressant agent) may be useful in the treatment of postpartum depression. At this point it is unclear which patients are likely to respond to this type of hormonal therapy. In cases of moderate to severe depression, first-line pharmacological treatment should be an antidepressant medication.

Puerperal Psychosis Puerperal psychosis is a psychiatric emergency that typically requires inpatient treatment; however, systematically derived guidelines for the treatment of this disorder are lacking. Given the well-established relationship between puerperal psychosis and bipolar disorders, some have argued that postpartum psychosis is indistinguishable from a manic psychosis and should be treated similarly. Short-term treatment with an antipsychotic medication as well as a mood stabilizer is appropriate. Most groups have used lithium in the treatment of postpartum psychosis; the efficacy of other mood stabilizers (i.e., valproic acid [Depakene], carbamazepine [Tegretol]) in this setting is not known. Breastfeeding is typically avoided in women treated with lithium, as it is secreted at high levels into the breast milk and may cause neonatal toxicity. ECT (often bilateral) is well tolerated and rapidly effective. Failure to treat puerperal psychosis aggressively places both the mother and infant at increased risk for harm. Rates of infanticide associated with untreated puerperal psychosis have been estimated to be as high as 4 percent; the risk for suicide in this population is also extremely high.

Although some authors recommend the discontinuation of psychotropic medications soon after the psychosis clears, others suggest a longer duration of treatment, arguing that women are at risk for psychiatric illness for up to 1 year after childbirth. Prolonged exposure to conventional antipsychotic agents should be minimized, given the risk of tardive dyskinesia. When neuroleptic medications are discontinued, they should be tapered slowly and with close observation for early signs of recurrence. Treatment with a mood stabilizer should be maintained beyond the resolution of active symptoms to reduce risk for relapse. The appropriate duration of treatment with a mood stabilizer has not been well established. Whether all patients

with puerperal psychosis should subsequently receive maintenance treatment with a mood stabilizer for an indefinite period of time is controversial, although several studies suggest that recurrent mood illness (most commonly bipolar disorder) is the rule following an episode of puerperal psychosis.

Prevention It is not possible to reliably predict which women in the general population will experience postpartum mood disturbance. The identification of women at greatest risk for puerperal illness improves the likelihood of early diagnosis and treatment and provides an opportunity to limit morbidity in the mother and her infant. It is possible to identify certain subgroups of women who are more vulnerable to postpartum mood disorder. Women with histories of affective illness are at particular risk for puerperal worsening of mood. Risk for puerperal relapse as a function of subtype is summarized in Table 13.4-2.

As it is possible to identify certain subgroups of women who are at risk for postpartum illness, many investigators have explored the appropriateness of prophylactic intervention. Several studies have demonstrated that women with histories of bipolar disorders or puerperal psychosis benefit from prophylactic lithium therapy instituted just prior to delivery (at 36 weeks gestation) or no later than the first 48 hours postpartum. Prophylactic lithium appears to significantly reduce relapse rates, as well as to diminish the severity and duration of puerperal illness.

Yet to be adequately investigated is the extent to which other populations of women may also benefit from pharmacological prophylaxis. A pilot study described a beneficial effect of prophylactic antidepressants administered to women with histories of postpartum depression. The efficacy of prophylactic antidepressants in women with recurrent, nonpuerperal depression is currently under investigation.

Psychosocial interventions, such as psychoeducational and supportive groups, are frequently included in the care of women during the postpartum period. The extent to which these interventions are effective in preventing postpartum mood disturbance has not been systematically studied. Several investigators have explored the use of psychoeducational groups during pregnancy and the postpartum period and have demonstrated a significant reduction in the incidence of postpartum depression in women who received this intervention, as compared to untreated controls.

Interpersonal therapy has been used successfully in nonpuerperal cohorts with major depressive disorder to prevent recurrence. Although not yet studied in puerperal populations, IPT and similar techniques may be performed prophylactically during the postpartum period and may be of some value. Those providers who routinely participate in acute and short-term postpartum care (e.g., visiting nurses) may be ideally suited to screen for and intervene in cases of postpartum distress or mood disturbance.

In summary, prophylaxis against postpartum depressive illness may be conceptualized along a continuum where some women are at low risk for puerperal illness whereas others appear to be at high risk for puerperal decompensation. This spectrum of patients at risk for puerperal mood disturbance and the potential role of pharmacological and nonpharmacological prophylaxis is outlined in Table 13.4-5. While a less aggressive "wait-and-see" approach is appropriate for women with postpartum blues or women without histories of psychiatric illness, women at high risk, particularly those with histories of postpartum illness, deserve close monitoring as well as specific prophylactic measures. Further characterization of these subgroups of women and the prophylactic treatments suited to each is clearly warranted.

Table 13.4-5
Risk Factors and Treatment Options for Postpartum Mood Disturbance

Diagnosis	Risk	Treatment Options
No history of psychiatric illness	LOW	Observation
Postpartum blues		Observation and support
History of major depressive disorder (euthymic without medication)		Observation Consider interpersonal therapy prophylaxis
History of postpartum depression	MODERATE	Close observation Consider prophylaxis with antidepressant medication
History of cyclothymic disorder		Close observation Consider lithium prophylaxis
History of severe recurrent major depressive disorder (euthymic without medication)		Close observation Consider prophylaxis with antidepressant medication
History of postpartum depression and recurrent major depressive disorder	HIGH	Consider prophylaxis with antidepressant medication
History of severe recurrent major depressive disorder (euthymic on medication during pregnancy)		Continue antidepressant medication
Depression during pregnancy	HIGHEST	Treatment with antidepressant medication
History of bipolar I or II disorder		Lithium prophylaxis
History of puerperal psychosis		Lithium prophylaxis

SUGGESTED CROSS-REFERENCES

Further information on the reproductive endocrinology of pregnancy and the postpartum period and guidelines for the use of psychotropics during pregnancy and lactation can be found in Section 28.2 on psychiatry and reproductive medicine. Mood disorders are discussed at length in Chapter 14, and brief psychotic disorder is discussed in Section 13.1. Psychopharmacology is covered in Chapter 31.

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14 Mood Disorders

▲ 14.1 Mood Disorders: Introduction and Overview

HAGOP S. AKISKAL, M.D.

For nearly 2500 years mood disorders have been described as the most common diseases of mankind, but only recently have they commanded major public health interest. The World Health Organization has ranked depression fourth in a list of the most urgent health problems worldwide. The U.S. Agency for Health Care Policy and Research, a federal agency concerned with medical practice from a public health perspective, devoted 2 volumes to depression among the first 10 it has published on such topics as pain, hypertension, diabetes mellitus, and coronary artery disease. A University of California psychiatrist, Kenneth Wells, demonstrated that the disability induced by depression compares with and often exceeds those of such diseases. Depressive disorders afflict at least 20 percent of women and 12 percent of men at some time during their lives. Despite the availability of effective treatments, many persons with mood disorders are disabled, and rates of suicide (which occurs in about 15 percent of depressive disorders) are high in both young and (especially) elderly men. Although depressive disorders are more common in women, more men than women die of suicide.

The suboptimal outcome of mood disorders documented in recent research reports cannot be ascribed to underdiagnosis and undertreatment alone for several reasons. First, Gerald Klerman and colleagues have suggested that the incidence of mood disorders may be increasing in younger age groups, especially in cohorts born in the 1960s, and may be associated with rising rates of alcohol and substance abuse. Second, mood disorders, once believed to be essentially adult disorders, are increasingly diagnosed in children and adolescents. Third, clinical studies suggest higher rates of chronicity, recurrence, and refractoriness than previously believed. For instance, chronicity, reported by Emil Kraepelin to occur in no more than 5 percent in the early twentieth century in Germany, is now seen in 15 to 20 percent of affectively ill patients in Western countries. Nonetheless, outcome studies coming from university centers tend to overestimate the proportion of cases with less favorable prognosis, and undeniably, many patients seen in private practice experience a favorable outcome. Also, a recent report indicates that depressed patients treated by psychiatrists in private settings receive much better care than those in other settings.

THE SCOPE OF MOOD DISORDERS

In Europe where the concept of mood disorders has historically embraced a broad spectrum of disorders, two British schools of thought have been influential. The Maudsley school—Aubrey Lewis and his followers—has promoted a continuum model, from anxiety disorders to mild neurotic depressions to severe endogenous and psychotic depressions. The Newcastle school, led by Martin Roth, has sharply demarcated those conditions from one another. Although vestiges of both approaches are still influential in clinical and basic research, their significance is presently overshadowed by continental European studies that subdivide mood disorders on the basis of polarity: unipolar (depressive episodes only) and bipolar (depressive episodes plus manic, hypomanic, or mixed episodes). That subdivision, supported by studies in the United States, has served as the basis for much recent research into the classification of mood disorders, as reflected in the fourth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) and the 10th revision of the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10). Despite such official sanction, many authorities today continue to see considerable continuity between recurrent depressive and bipolar disorders.

Emerging data also tend to favor a continuum between juvenile and adult mood disorders. This is based on the pioneering contributions by Elva Poznanski at the University of Michigan, as well as the work of Leon Cytrin and colleagues at the National Institute of Mental Health (NIMH), and Joachim Puig-Antich conducted at Columbia University in New York. Childhood bipolarity, too, is receiving increasing clinical attention, thanks to the seminal work of Elizabeth Weller and colleagues, originally conducted at Ohio State University. Finally, the work of Gabrielle Carlson and Michael Strober (when they collaborated at the University of California at Los Angeles) and clinical observations by this author on the juvenile offspring of adult bipolar disorders patients have led to a greater appreciation of the bipolar nature of complex clinical presentations of affective illness in children.

Current concepts of mood disorders in the United States embrace a wide spectrum, including many conditions previously diagnosed as schizophrenia, personality disorder, or neurosis. The diagnostic shift occurred in part as a result of the U.S.-U.K. Diagnostic Project, which demonstrated that schizophrenia was being diagnosed at the expense of mood disorders (Fig. 14.1-1). Conceptual boundaries were further broadened by the availability of new and effective treatments and by the unacceptable risk for tardive dyskinesia and suicide in persons with misdiagnosed mood disorders. More generally, present research interest in mood disorders in the United States emanated from a landmark 1969 NIMH conference on the psychobiology of affective illnesses: the NIMH Collaborative Depression Study—a long-term prospective project deriving directly from recommendations made at the conference—has legitimatized the broader perspective.

Unfortunately, findings published by Martin Keller and collaborators in the 1980s documenting gross undertreatment of mood disorders continue to describe the current treatment landscape worldwide.

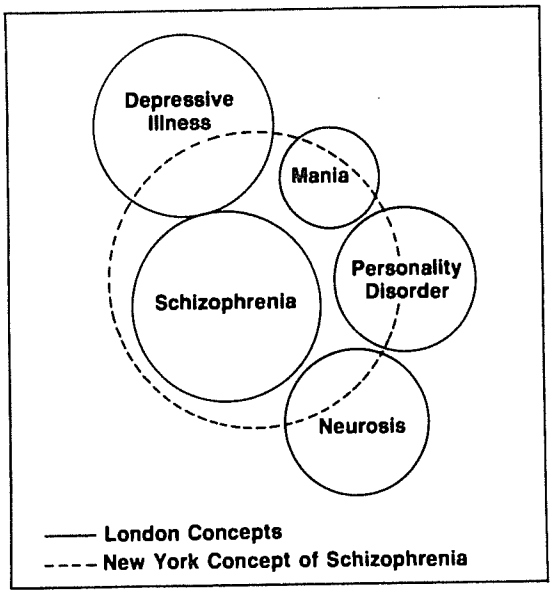

FIGURE 14.1-1 Comparison of British (London) and United States (New York) concepts of schizophrenia. (Reprinted with permission from Cooper JE, Kendell RE, Garland BJ, Sharpe L, Copeland JRM, Simon R: *Psychiatric Diagnosis in New York and London*. Oxford University Press, London, 1972.)

Whatever changes have occurred in diagnostic practice do not appear to have significantly affected the morbidity and mortality of mood disorders. This is all the more scandalous because the 1990s have seen new classes of user-friendly antidepressant and mood-stabilizing agents as well as depression-specific psychotherapies. In the author's opinion, this state of affairs results in part from the fact that both specialized and primary care training in mood disorders have failed to keep pace with recent advances.

The situation is analogous to adult-onset diabetes with approximately 50 percent of cases undetected or inadequately controlled, both of which seem to lag behind the field of hypertension, in which early detection and treatment have significantly reduced complications such as stroke. Efforts by patient advocacy organizations—often in concert with national psychiatric organizations and governmental mental health agencies—appear to be increasing public and government awareness of mood disorders. But ultimately, the challenge is to provide all primary care physicians with the requisite hands-on experience in this prevalent group of disorders.

Since mood disorders underlie 50 to 70 percent of all suicides, effective treatment of these disorders on a national level should, in principle, drastically reduce this major complication of mood disorders. A small-scale Swedish study has yielded promising results in this regard. In addition, clinical findings in recurrent mood disorders have clearly shown the value of lithium prophylaxis in the prevention of suicide as well as overall mortality.

DEFINITIONS

Mood disorders encompass a large group of psychiatric disorders in which pathological moods and related vegetative and psychomotor disturbances dominate the clinical picture. Known in previous editions of DSM as affective disorders, the term *mood disorders* is preferred today because it refers to sustained emotional states, not merely to the external (affective) expression of the present emotional state. Mood disorders are best considered as syndromes (rather than discrete diseases) consisting of a cluster of signs and symptoms sustained over a period of weeks to months, that represent a marked departure from a person's habitual functioning and tend to recur, often in periodic or cyclical fashion.

Major Depressive Disorder and Bipolar Disorder

Major depressive disorder (unipolar depression) is reported to be the most common mood disorder. It may manifest as a single episode or as recurrent episodes. The course may be somewhat protracted—up to 2 years or longer—in those with the single-episode form. Whereas the prognosis for recovery from an acute episode is good for most patients with major depressive disorder, three out of four patients experience recurrences throughout life, with varying degrees of residual symptoms between episodes. Bipolar disorders (previously called *manic-depressive psychosis*) consists of at least one hypomanic, manic, or mixed episode. *Mixed episodes* represent a simultaneous mixture of depressive and manic or hypomanic manifestations. Although a minority of patients experience only manic episodes, most bipolar disorder patients experience episodes of both polarity. Manias predominate in men, depression and mixed states in women. The bipolar disorders were classically described as psychotic mood disorders with both manic and major depressive episodes (now termed bipolar I disorder), but recent clinical studies have shown the existence of a spectrum of ambulatory depressive states that alternate with milder, short-lived periods of hypomania rather than full-blown mania (bipolar II disorder). Bipolar II disorder, which is not always easily discriminable from recurrent major depressive disorder, illustrates the need for more research to elucidate the relation between bipolar disorder and major depressive disorder.

Dysthymia and Cyclothymia Clinically, major depressive episodes often arise from a low-grade, intermittent, and protracted depressive substrate known as dysthymic disorder. Likewise, many instances of bipolar disorders, especially ambulatory forms, represent episodes of mood disorder superimposed on a cyclothymic background, which is a biphasic alternating pattern of numerous brief periods of hypomania and numerous brief periods of depression. Dysthymic and cyclothymic disorders represent the two prevalent subthreshold mood conditions roughly corresponding to the basic temperamental dysregulations described by Kraepelin and Ernst Kretschmer as predisposing to affective illness.

It is not always easy to demarcate full-blown syndromal episodes of depression and mania from their subthreshold counterparts commonly observed during the interepisodic periods. The subthreshold conditions appear to be fertile terrain for interpersonal conflicts and postaffective pathological character developments that may ravage the lives of patients and their families. In North America many such patients end up being labeled with borderline personality disorder, which unfortunately often tends to obscure the affective origin of the presenting psychopathology.

Cyclothymic and dysthymic conditions also exist in the community without progression to full-blown mood episodes. As such, they are best considered, respectively, as trait bipolar and trait depressive conditions. Understanding the factors that mediate transition from trait to clinical state is important for preventing manic and major depressive episodes.

Other Subthreshold Mood States Epidemiological studies both in Europe and North America have also revealed other subsyndromal conditions with depressive and hypomanic manifestations

with few symptoms (oligosymptomatic mood states) and of short duration (brief episodes). Variously referred to as "minor," "subsyndromal," "brief," or "intermittent," these descriptions do not merely represent arbitrary lowering of diagnostic thresholds, but herald increasing realization of their importance in early detection of at-risk individuals, as has happened in other medical fields (e.g., diabetes mellitus and essential hypertension). If disabling mood disorders afflict 5 to 8 percent of the general population (Epidemiologic Catchment Area [ECA] study), milder but still clinically significant mood disorders would raise lifetime rates to 17 percent (National Comorbidity Study [NCS]); if subclinical mood states are added, that figure doubles to involve a third of the general population (as reported, for instance, by Kenneth Kendler and colleagues).

Comorbidity Mood disorders overlap considerably with anxiety disorders. As summarized in an NIMH monograph, anxiety disorders can occur during an episode of depression, may be a precursor to the depressive episode, and, less commonly, may occur during the future course of a mood disorder. Those findings suggest that at least some depressive disorders share a common diathesis with certain anxiety disorders. More-recent clinical experience suggests intriguing comorbidity patterns between bipolar II disorder on one hand and panic, obsessive-compulsive, and social phobic states on the other. Furthermore, bipolar I and II disorders are particularly likely to be complicated by use of alcohol, stimulants, or both. In many cases the alcohol or substance abuse represents an attempt at self-treatment of the mood disorder. Finally, physical illness—both systemic and cerebral—occurs in association with depressive disorders with a greater frequency than expected by chance alone. Unless properly treated, such depression negatively impacts on the prognosis of the physical disorder. More provocatively, there is current reawakening in the contribution of cerebral and cardiovascular factors to the origin of late-onset psychotic depressions (previously classified as "involutional melancholia").

An integrated framework of pathogenesis is necessary for understanding psychopharmacological, somatic, and psychotherapeutic approaches in the clinical management of patients with mood disorders. A historical perspective on current developments is also a valuable lesson in the study of mood disorders.

GRECO-ROMAN DESCRIPTIONS OF MELANCHOLIA AND MANIA

Much of what is known today about mood disorders was described by the ancient Greeks and Romans, who coined the terms *melancholia* and *mania* and noted their relation. The ancients also hypothesized a temperamental origin for those disorders. Much of modern thinking about mood disorders (e.g., the work of the French and German schools in the middle and latter part of the nineteenth century, which influenced current British and American concepts) can be traced back to these ancient concepts.

Melancholia Hippocrates (460–357 BC) described melancholia ("black bile") as a state of "aversion to food, despondency, sleeplessness, irritability, and restlessness." Thus, in choosing the name of the condition, Greek physicians (who may have borrowed the concept from ancient Egyptians) postulated the earliest biochemical formulation of any mental disorder. They believed that the illness often arose from the substrate of the somber melancholic temperament which, under the influence of the planet Saturn, made the spleen secrete black bile, ultimately leading to mood darkening through its influence on the brain. Greek descriptions of the clinical manifestations of depression and of the temperament prone to melancholia are reflected in the DSM-IV and in the subdepressive lethargy, self-denigration, and habitual gloom of the person with dysthymic disorder.

One Hippocratic aphorism recognized the close link between anxiety and depressive states: "Patients with fear of long-standing are subject to melancholia." According to Galen (131–201 AD), melancholia manifested in "fear and depression, discontent with life, and hatred of all people." A few hundred years later another Roman, Aurelianus, citing the now lost works of Soranus of Ephesus, amplified the role of aggression in melancholia (and its link to suicide) and described how the illness assumed delusional coloring: "Animosity toward members of the household, sometimes a desire to live and at other times a longing for death, suspicion on the part of the patient that a plot is being hatched against him."

In addition to natural melancholia, which presumably arose from an innate predisposition to overproduce the dark humor and led to a more severe form of the malady, Greco-Roman medicine recognized such environmental contributions to melancholia as immoderate consumption of wine, perturbations of the soul due to the passions (e.g., love), and disturbed sleep cycles. Autumn was considered the season most disposing to melancholy.

Mania A state of raving madness with exalted mood was noted by the ancient Greeks, although it referred to a somewhat broader group of excited psychoses than in modern nosology. Its relation to melancholia was probably noted as early as the first century BC, but according to Aurelianus, Soranus discounted it. Nonetheless, Soranus had observed the coexistence of manic and melancholic features during the same episode, consisting of continual wakefulness and fluctuating states of anger and merriment, sometimes of sadness and futility. Soranus thus seemed to have described what today are called mixed episodes in DSM-IV and ICD-10. Natural melancholy was generally considered a chronic disorder, but Soranus noted the tendency for attacks to alternate with periods of remission.

Although others prior to him hinted at it, Aretaeus of Cappadocia (ca. 150 AD) is generally credited with making the connection between the two major mood states: "It appears to me that melancholy is the commencement and a part of mania." He described the cardinal manifestations of mania as it is known today:

> There are infinite forms of mania but the disease is one. If mania is associated with joy, the patient may laugh, play, dance night and day, and go to the market crowned as if victor in some contest of skill. The ideas the patients have are infinite. They believe they are experts in astronomy, philosophy, or poetry.

Aretaeus described the extreme psychotic excitement that could complicate the foregoing clinical picture of mania:

> The patient may become excitable, suspicious, and irritable; hearing may become sharp... get noises and buzzing in the ears; or may have visual hallucinations; bad dreams and his sexual desires may get uncontrollable; aroused to anger, he may become wholly mad and run unrestrainedly, roar aloud; kill his keepers, and lay violent hands upon himself.

Noting the fluctuating nature of symptoms in the affectively ill, Aretaeus commented

> They are prone to change their mind readily; to become base, mean-spirited, illiberal, and in a little time extravagant, munificent, not from any virtue of the soul, but from the changeableness of the disease.

Aretaeus was thus keenly aware of the characterological distortions so commonly manifested during the different phases of cyclical mood disorders.

Finally, consolidating the knowledge of several centuries, Aretaeus described mania as a disease of adolescent and young men given intermittently to "active habits, drunkenness, lechery" and an immoderate lifestyle (what today might be called cyclothymic disorder). Exacerbations were most likely to occur in the spring.

Affective Temperaments The concept of health and disease in Greco-Roman medicine was based on harmony and balance of the four humors, of which sanguine humor was deemed the healthiest. But even a desirable humor like blood, which made people habitually active, amiable, and prone to jest, could in excess lead to the pathological state of mania. The melancholic temperament, dominated by black bile and predisposed to pathological melancholia, was described as lethargic, sullen, and given to brooding or contemplation; its modern counterparts are depressive personality disorder (now in a DSM-IV appendix) and its clinical expression as dysthymic disorder (included in both ICD-10 and DSM-IV). A long tradition dating back to Aristotle (384–322 BC) attributed creative qualities to the otherwise tortured melancholic temperament in such fields as philosophy, the arts, poetry, and politics. The remaining two temperaments, choleric and phlegmatic, were less desirable, as yellow bile made people choleric (irritable, hostile, and given to rage) and phlegm made them phlegmatic (indolent, irresolute, and timid). The choleric and phlegmatic temperaments would probably be recognized today as borderline personality disorder and avoidant or schizoid personality disorder, respectively.

Many of the original Greek texts on melancholia were transmitted to posterity through medieval Arabic texts such as those of Ishaq Ibn Imran and Avicenna (and their Latin rendition by Constantinus Africanus). In describing different affective states, Avicenna developed the theory of the temperaments to its fullest. He speculated that a special form of melancholia supervened "if black bile be mixed with phlegm" when the illness was "coupled with inertia, lack of movement, and quiet." Further, mania was not necessarily linked to the sanguine (what today is termed "hyperthymic") temperament, as many forms of excited madness were believed to represent a mixture of black and yellow bile.

Avicenna further observed that the appearance of anger, restlessness, and violence heralded the transition of melancholia to mania. Those elaborations on Galen's tempermental types might be considered the forerunners of current personality dimensions, deriving mood states from various mixtures of neuroticism and introversion-extroversion. (What both ICD-10 and DSM-IV describe as cyclothymic disorder represents the intense mood lability of high neuroticism coupled with cyclic alternation between extroversion and introversion). Speculation on how diverse depressive phenomena could be understood as a mix of humors anticipated modern multiple-transmitter hypotheses of depression. Ishaq Ibn Imran summarized the existing knowledge of melancholia by considering the interaction of genetic factors ("injured prenatally as the result of the father's sperm having been damaged") with a special temperament given to "mental overexertion"—though not necessarily physical overactivity—that in turn was associated with "disruption of the correct rhythms of sleeping and waking." Those views, too, have a very modern ring to them.

MODERN ERA

The first English text (Fig. 14.1-2) entirely devoted to affective illness was Robert Burton's *Anatomy of Melancholy,* published in

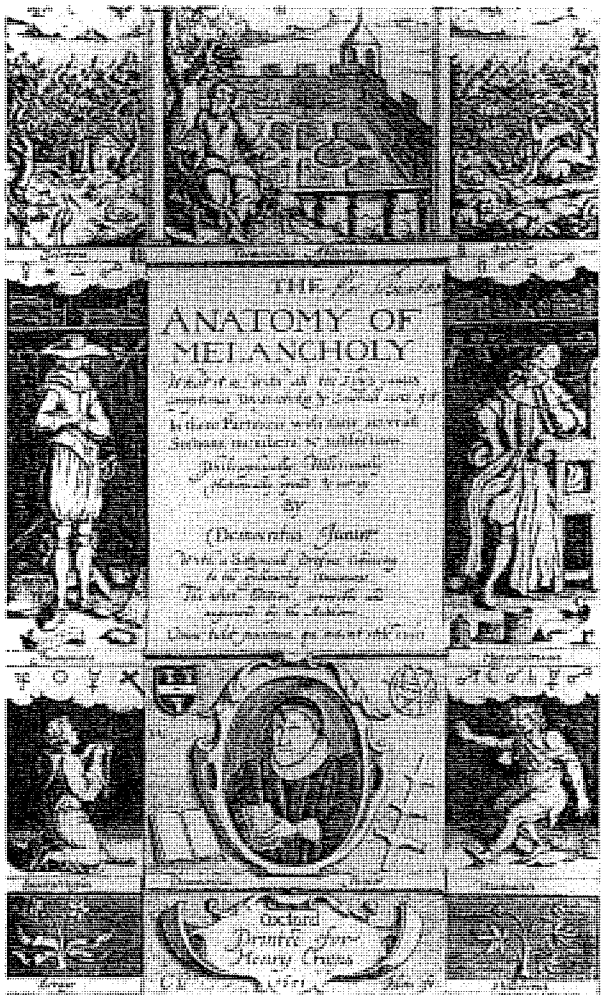

FIGURE 14.1-2 Frontispiece of Robert Burton's *Anatomy of Melancholy* (1621).

1621. A scholarly review of medical and philosophical wisdom accumulated in past centuries, it also anticipated many modern developments. The concept of affective disorder endorsed by Burton was rather broad (as it always has been in the United Kingdom), embracing mood disorders and many disorders today considered somatoform disorders, including hypochondriasis. Although he described "causeless" melancholias, Burton also categorized the various forms of love melancholy and grief. Particularly impressive was his catalogue of causes, culminating in a grand conceptualization:

> Such as have Saturn misaffected in their genitures such as are born of melancholy parents as offend in those six non-natural things, are of a high sanguine complexion are solitary by nature, great students, given to much contemplation, lead a life out of action, are most subject to melancholy. Of sexes both, but men more often. Of seasons of the year, autumn is most melancholy. Jobertus excepts neither young nor old.

Burton's six nonnatural things referred to such environmental factors as diet, alcohol, biological rhythms, and perturbations induced by passions such as intense love. Burton himself did not definitively indicate age prevalences. Like nearly all of his predecessors, he favored male (rather than the currently reported female) preponderance. Finally, Burton considered both the melancholic (contempla-

tive) and the sanguine (hot-blooded) temperaments to be substrates of melancholia. Burton's work thus linked certain forms of depression with the softer expressions of the manic disposition, or bipolar II disorder, from which he himself appears to have suffered.

The eighteenth and nineteenth centuries introduced humane hospital care of the mentally ill, thereby permitting systematic clinical observation of the psychopathology and outcome of mood disorders.

Concept of Affective Disorder Although Celsus (ca. AD 30) had described "forms of madness that go no further than sadness," the French alienist Jean-Philippe Esquirol (1840) may have been the first psychiatrist in modern times to suggest that a primary disturbance of mood might underlie many forms of depression and related paranoid psychoses. Until Esquinol's work, melancholia had been categorized as a form of insanity (i.e., ascribed to deranged reasoning or thought disturbance). Esquirol's observations on melancholic patients led him to postulate that their insanity was partial (dominated by one delusion, a monomania) and that "the symptoms were the expression of the disorder of the affections. The source of the evil is in the passions." He coined the term "lypemania" (from the Greek, "sorrowful insanity") to give nosological status to a subgroup of melancholic disorders that were affectively based. Esquirol cited Benjamin Rush (1745–1813), the father of American psychiatry, who had earlier described tristimania, a form of melancholia in which sadness predominated.

Esquirol's influence led other European psychiatrists to propose milder states of melancholia without delusions, which were eventually categorized as simple melancholias and ultimately as primary depressions. Such descriptions culminated in the Anglo-Saxon psychiatric term "affective disorder," coined by Henry Maudsley (1835–1918), the renowned British psychiatrist after whom the London hospital is named.

Manic-Depressive Illness and the Question of Psychogenic Depressions Although the connection between mania and depression had been sporadically rediscovered since it was first described 2000 years ago, the clinical work that finally established "circular insanity" (Jean-Pierre Falret's term) as "folie à double forme" (Jules Baillarger's term) was undertaken by these two Esquirol disciples in the 1850s. That accomplishment built on Philippe Pinel's reforms, which championed humane treatment of the mentally ill in Paris around the turn of the eighteenth century and emphasized systematic clinical observations of patients, detailed in case records. French alienists made longitudinal observations on the same patient from one psychotic attack into another. Further, Esquirol had introduced chronicling events in statistical tables. Thus, the Hippocratic approach to defining a particular case by its onset, circumstances, course, and outcome was applied by French alienists in studying the affectively ill. The humanitarian reforms introduced in the nineteenth century ensured that standards of general health and nutrition would improve the outlook for the mentally ill—especially those with potentially reversible disorders such as affective disorders—who could now be discharged from the asylums. The French school then, by segregating the nondeteriorating mood disorders from the dementing types of insanity, paved the way for the Kraepelinian system.

Kraepelin's (1856–1926) unique contribution was not so much grouping together all the forms of melancholia and mania, but his methodology and painstaking longitudinal observations, which established manic-depressive illness as a nosological entity and (he hoped) a disease entity. His rationale was (1) the various forms had a common heredity measured as a function of familial aggregation of homotypic and heterotypic cases; (2) frequent transitions from one form to the other occurred during longitudinal follow-up; (3) a recurrent course with illness-free intervals characterized most cases; (4) the superimposed episodes were commonly opposite to the patient's habitual temperament; that is, mania was superimposed on a depressive temperament and depression was superimposed on a hypomanic temperament; and (5) both depressive and manic features could occur during the same episode (mixed states). Kraepelin's synthesis was developed as early as the sixth (1899) edition of his *Lehrbuch der Psychiatrie* and most explicitly stated in the opening passages of the section on manic-depressive psychosis in the eighth edition (published in four volumes, 1909–1915):

> Manic-depressive insanity includes on the one hand the whole domain of so-called periodic and circular insanity, on the other hand simple mania, the greater part of the morbid states termed melancholia and also a not inconsiderable number of cases of confusional insanity. Lastly, we include here certain slight and slightest colorings of mood, some of them periodic, some of them continuously morbid, which on the one hand are to be regarded as the rudiment of more severe disorders, on the other hand, pass over without boundary into the domain of personal predisposition.

For Kraepelin, the core pathology of clinical depression consisted of lowered mood and slowed (retarded) physical and mental processes. In mania, by contrast, the mood was elated and both physical and mental activity accelerated. His earlier observations on what he termed "involutional melancholia" (referring to 40- to 65-year-old patients with extreme anxiety, irritability, agitation, and delusions) had led him to separate that entity from the broader manic-depressive rubric. But, in the eighth edition of *Lehrbuch der Psychiatrie,* he united melancholia with the manic-depressive group, with the justification that it was a special form of mixed state and that follow-up conducted by his pupil Dreyfus had demonstrated unmistakable excited phases.

The classification of depressive disorders is still evolving. Karl Leonhard in 1957, Jules Angst in 1966, Carlo Perris in 1966, and George Winokur, Paula Clayton, and Theodore Reich in 1969, working independently in four different countries, proposed that depressive disorders without manic or hypomanic episodes (major depressive disorder) that appear in middle age and later are distinct from depressive episodes that begin at earlier ages and alternate with manic or hypomanic episodes (bipolar disorder). The main difference between the two affective subtypes is the greater familial loading for mood disorder—especially for bipolar disorder—among bipolar disorder probands.

Kraepelin had conceded the occurrence of psychogenic states of depression occasioned by situational misfortune. Manic-depressive illness, on the other hand, he believed to be hereditary. Yet he could not document postmortem anatomopathological findings in the brains of manic-depressive patients. Therefore, manic-depression had to be considered a functional mental disorder in which brain disturbances were presumed to lie in altered physiological functions. Such biological factors were deemed absent in the psychogenic depressions. Thus, Kraepelin's classification of mood disorders is both dualistic and unitary. It is dualistic to the extent that he designated them as either psychologically occasioned or somatically caused. It is unitary with respect to disorders in the latter group, which have been termed *endogenous affective disorders* (i.e., due to internal biological causes). In other words, Kraepelin restricted the concept of clinical depression to what DSM-IV terms "major depressive disorder with melancholic features." Moreover, he postulated

a continuum between that condition and what DSM-IV and ICD-10 now term "bipolar disorders."

As summarized in Table 14.1-1, endogenous depressions have been contrasted with those of exogenous cause (i.e., external and, presumably, psychogenic causes). Transitions between the two groups are so frequent, however, that the two-type thesis of depression has been largely abandoned in official classifications in North American psychiatry. In one study conducted by the author's mood clinic team in Memphis during the 1970s, 100 patients with neurotic depression (the prototype of exogenous depression), prospectively followed over 3 to 4 years, developed episodes with endogenous, psychotic, and even bipolar features (Table 14.1-2). Nonetheless, the endogenous-exogenous dichotomous grouping still has some adherents worldwide who continue to research its potential for clinical predictions. Such research generally attempts to validate the various subtypes on the basis of their clinical characteristics rather than presumed cause. Today most mood disorders experts would probably agree that depressive illness has endogenous and exogenous components in most patients presenting clinically. Consensus would be less likely on how to delimit clinical depressive disorder from comorbid disorders such as the various anxiety disorders, substance use disorders, and personality disorders. Clarifying the boundaries between those disorders has emerged as a principal challenge in the classification of mood disorders.

Cartesian thinking in seventeeth-century France conceptually separated mind from body, thereby providing physicians autonomy over the somatic sphere, free from interference by the Church. The dichotomous paradigm ensured that study of the two aspects of the human organism would not be confounded by the complexities of mind-body interactions. That is one reason why Kraepelin's descriptive observations have proved valuable to subsequent generations of clinicians. Further, his approach exemplifies the best tradition of scientific humanism in medicine: description and diagnostic categorization of an individual patient are necessary for the physician to apply the knowledge gained from past observation of similarly described and diagnosed patients. One limitation to the Kraepelinian approach is that because of its biological reductionism, it is not sufficiently articulate to account for mind-body interactions in the genesis of mental disorders.

Table 14.1-1
Overlapping Dichotomies of Affective Disorders That Are Not Necessarily Synonymous

Manic-depressive	Psychogenic
S (somatic) type	J (justified) type
Autonomous	Reactive
Endogenous	Exogenous
Psychotic	Neurotic
Acute	Chronic
Major	Minor
Melancholic	Neurasthenic
Typical	Atypical
Primary	Secondary
Biological	Characterological

Table 14.1-2
Three- to Four-Year Prospective Follow-up in Neurotic Depressions (N = 100)

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

[a] The total exceeds 100 because more than one outcome was possible in each patient.

Reprinted with permission from Akiskal H, Bitar A, Puzantian V, Rosenthal T, Walker P: 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.

Depressions as Psychobiological Affective Reaction Types

Bridging the divide between psyche and soma was the ambition of Swiss-born Adolf Meyer (1866–1950), who dominated psychiatry from his chair at Johns Hopkins University during the first half of the twentieth century. Meyer coined the term "psychobiology" to emphasize that both psychological and biological factors could enter into the causation of depressive and other mental disorders. Because of the nascent state of brain science during Meyer's time, he was more adept at biography than biology and therefore paid greater attention to psychosocial causation. He preferred the term *depression* (pressed down) to *melancholia* because of its lack of biological connotation. He conceived of depressive states in terms of unspecified constitutional or biological factors interacting with a series of life situations beginning at birth or even at conception. From that viewpoint arose the unique importance accorded personal history in depressive reactions to life events.

Meyer's terminological revision left a somewhat confusing legacy in that the term *depression* is now applied to a broad range of affective phenomena ranging from sadness and adjustment disorders to clinical depression and bipolar disorders. Repercussions can be seen in the low threshold for diagnosing major depressive disorder in DSM-IV, which makes it difficult to differentiate major depressive disorder from transient life stresses that produce adjustment disorder with depressed mood. Nosological nuances to which Meyerians paid little attention, such as the difference between melancholic depression and more mundane depressions, are not just a matter of semantics. To the extent that those two forms of depression are seen in different clinical settings, hypotheses based on one population may not apply to the other. For instance, uncontrollable traumatic events may have taught study subjects to feel helpless or to view the world in a negative light, but that does not equate with clinical depression; nor does the process appear to be specific to depression. Failure to make such nosological distinctions further clouds interpretations of the results of trials comparing psychotherapy and pharmacotherapy for depressive disorders.

On the other hand, the Meyerian emphasis on biographical factors for the patient represented a more practical approach to depth psychology. Recent sociological interpretations of depression can also be traced to Meyer's work. But in the final analysis, the Meyerian concern for the uniqueness of the individual has proved heuristically sterile. It deemphasizes what is diagnostically common to different individuals, thereby obscuring the relevance of accrued clinical wisdom for the index patient. For that reason the Meyerian approach, after enjoying clinical popularity for several decades in North America, has given way to neo-Kraepelinian rigor. However, the psychobiological vision of bridging biology and psychology, one of the major preoccupations of psychiatric thought and research today, owes much to Meyer's legacy.

CONTEMPORARY MODELS OF DEPRESSION

From classical times through the early part of the twentieth century, advances in understanding mood disorders involved conceptual shifts from supernatural to naturalistic explanations, from reductionistic, unitarian theories of causation to pluralistic theories, and from dualism to psychobiology. Knowledge of those conceptual developments provides a useful base from which to scrutinize more-recent models and concepts of mood disorder, developed later in the twentieth century. The new approaches, derived from competing theoretical positions, have generated models for understanding various aspects of mood disorders, particularly depressive disorders (Table 14.1-3).

The formative influence of early experience as it is dynamically shaped by emerging mental structures during development is the common denominator for the psychoanalytic concepts of psychopathological phenomena. By contrast, behavioral approaches in their more traditional formulations focus on the pathogenetic impact of proximate contexts. The cognitive approaches, which are akin to the behavioral-pathogenetic tradition, nonetheless concede that negative styles of thinking might mediate between proximate stressors and more remote experiences. All three schools—psychoanalytic, behavioral, and cognitive—emphasize psychological constructs in explaining the origin of mood disorders. The biological models, on the other hand, are concerned with defining the somatic mechanisms that underlie or predispose to morbid affective experiences. The schism between psychological and biological conceptualizations is an instance of the mind-body dichotomy that has characterized the Western intellectual tradition since Descartes. After all, psychological and somatic approaches represent merely convenient investigational strategies that attempt to bypass the methodological gulf between mental and neural structures. The ultimate aim is to understand how mood disorders develop within the psychoneural framework of a given person.

Aggression-Turned-Inward Model Sigmund Freud was initially interested in a psychoneural project for all mental phenomena. Limitations of the brain sciences of the day led him to adopt instead a model that relied on a concept of mental function borrowed

Table 14.1-3
Contemporary Major Models of Depression

Proponents (Year)*	Model	Mechanism	Scientific and Clinical Implications
Karl Abraham (1911)	Aggression turned inward	Transduction of aggressive instinct into depressive affect	Hydraulic mind closed to external influences; nontestable
Sigmund Freud (1917) John Bowlby (1960)	Object loss	Disruption of an attachment bond	Ego-psychological; open system; testable
Edward Bibring (1953)	Self-esteem	Helplessness in attaining goals of ego ideal	Ego-psychological; open system; social and cultural ramifications
Aaron Beck (1967)	Cognitive	Negative cognitive schemata as intermediary between remote and proximate causes	Ego-psychological; open system; testable; predicts phenomenology; suggests treatment
Martin Seligman (1975)	Learned helplessness	Belief that one's responses will not bring relief from undesirable events	Testable; predicts phenomenology; predicts treatment
Peter Lewinsohn (1974)	Reinforcement	Low rate of reinforcement, or reinforcement presented noncontingently; social deficits might preclude responding to potentially rewarding events	Testable; predicts phenomenology; predicts treatment
Joseph Schildkraut (1965) William Bunney and John Davis (1965) Alec Coppen (1968) I.P. Lapin and G.F. Oxenkrug (1969) David Janowsky et al. (1972) Arthur Prange et al. (1974) Larry Siever and Kenneth Davis (1985)	Biogenic amine (neurochemical)	Impairment or dysregulation of aminergic transmission	Testable; reductionistic; explains phenomenology and opposite episodes; suggests treatment
Alec Coppen and D.M. Shaw (1963) Peter Whybrow and Joseph Mendels (1968) Robert Post (1990)	Neurophysiological	Electrophysiological disturbances leading to neuronal hyperexcitability and kindling	Testable; reductionistic; explains phenomenology and recurrence; suggests treatment
Hagop Akiskal and William McKinney (1973) Frederick Goodwin and Kay Jamison (1990)	Final common pathway	Stress-diathesis interaction converging on midbrain mechanisms of reward and biological rhythms	Testable; integrative, psychobiological; pluralistic; explains phenomenology; suggests treatment

*Dates provided for the models refer to the original paper or work in which they first appeared. In some instances, the bibliography at the end of the section provides references reflecting more updated thinking by those authors.

Adapted from Akiskal H, McKinney W: Overview of recent research in depression: Integration of 10 conceptual models into a comprehensive clinical frame. Arch Gen Psychiatry *32*:285, 1975.

from physics. The notion that depressed affect is derived from retroflexion of aggressive impulses directed against an ambivalently loved internalized object was actually formulated by his Berlin disciple Karl Abraham and later elaborated by Freud. Abraham and Freud hypothesized that turned-in anger was intended as punishment for the love object that had thwarted the depressed patient's need for dependency and love. Because, in an attempt to prevent the traumatic loss, the object had already been internalized, the patient now became the target of his or her own thanatotic impulses. A central element in those psychic operations was the depressed patient's ambivalence toward the object, which was perceived as a frustrating parent. Aggression directed at a loved object (parent) was therefore attended by considerable guilt. In the extreme such ambivalence, guilt, and retroflexed anger could lead to suicidal behavior.

According to that model, depression was an epiphenomenon of the transduction of thanatotic energy, a reaction that took place in the closed hydraulic space of the mind. Freud's earlier writings had similarly portrayed anxiety as derived from the transformation of dammed-up sexual libido. Although Freud envisioned that psychoanalytic constructs would one day be localized neuroanatomically, the hydraulic mind is a metaphor that does not refer to actual physiochemical space in the brain.

The conceptualization of emotional behavior as an arena of incompatible forces confined to a psyche that is relatively impervious to current influences outside the organism is the major liability of the aggression-turned-inward model and perhaps of orthodox psychoanalysis itself. Although the sexual energy transduction hypothesis of anxiety has been discarded in modern psychoanalytic thought, in modified version the aggression-turned-inward model continues to be used in clinical conceptualization today. The lingering popularity of the model may be due in part to its compatibility with the clinical observation that many depressed patients suffer from lack of assertion and outwardly directed aggressiveness. Yet a substantial number of hostile depressed patients are also encountered in clinical practice (indeed "depression with anger attacks" has been recently described), and clinical improvement in most patients typically leads to decreased, not increased, hostility. Those observations shed doubt on the aggression-turned-inward mechanism as a universal explanation for depressive behavior. Finally, little evidence exists to support the contention that outward expression of anger has therapeutic value in clinical depression.

Outwardly directed hostility in depression is not a new clinical observation: Greco-Roman physicians had noted it. Hostility is best considered a manifestation rather than a cause of depressive disorder, especially when the disorder is attended by mixed bipolar features. The hostility of the depressed patient can also be understood as an exaggerated reaction to frustrating love objects, as secondary to self-referential attribution, or simply as nonspecific irritability of an ego in affective turmoil; this could in part be a function of a concurrent personality disorder from the erratic cluster. Such common-sense explanations that do not invoke unobservable hydraulic transmutations have greater appeal from heuristic and clinical perspectives.

Object Loss and Depression Object loss refers to traumatic separation from significant objects of attachment. Ego-psychological reformulations of the Abraham-Freud conceptualization of depression have paid greater attention to the impact of such losses on the ego, deemphasizing the id-libidinal and related hydraulic aspects. The depressant impact of separation events often resides in their symbolic meaning for a person rather than in any arbitrary objective weight that the event may have for clinical raters. However, love loss, bereavement, and other exits from the social scene, as defined by the London psychiatrist Eugene Paykel, are presently the concepts most commonly used in practice and research.

Although love melancholy had been described since antiquity, the two affective states were systematically compared for the first time in Freud's 1917 paper on mourning and melancholia. According to current data, the transition from grief to pathological depression occurs in no more than 10 percent of adults and 20 percent of children. These figures suggest that such transition occurs largely in persons predisposed to mood disorders.

John Bowlby of the Tavistock Clinic, London, did a comprehensive clinical investigation of the attachment that the child establishes with the mother or mother substitutes during development, a bond considered the prototype for all subsequent bonds with other objects. Like many psychoanalytic explanations of adult symptom-formation, the object loss model is formulated as a two-step hypothesis, consisting of early breaks in affectional bonds, which provide the behavioral predisposition to depression, and adult losses, which are said to revive the traumatic childhood loss and so precipitate depressive episodes. However, the role of proximate separations in provoking depressive reactions rests on more solid clinical evidence than the hypothesized sensitization resulting from developmental object loss. That realization has led Bowlby to regard childhood sensitization resulting from early deprivation as a generic characterological vulnerability to a host of adult psychopathological conditions.

Compared with aggression turned inward, object loss is more directly relevant to clinical depression; yet it is still pertinent to question whether it is an etiological factor. Studies at the Wisconsin Primate Center have indicated that optimal homeostasis with the environment is most readily achieved when the individual is securely attached to significant others, and the dissolution of such ties appears relevant to the emergence of a broad range of psychopathological disturbances rather than depression per se. A related methodological question is whether object loss operates independently of other etiological factors. For instance, a history of early breaks in attachment may reflect the fact that one or both of the patient's parents had mood disorder, with resultant separation, divorce, suicide, and so forth.

On balance, the ego-psychological object loss model is conceptually superior to its id-psychological counterpart. In postulating an open system of exchange between a person and the environment, the model permits consideration of etiological factors other than separation, such as heredity, character structure, and adequacy of social support—all of which might modulate the depressant impact of adult separation events. Conceptualizing the origin of depression along those lines is in the mainstream of current ideas of adaptation, homeostasis, and disease. An important treatment implication is the value of social support in preventing relapse and mitigating chronicity of depression. That is indeed an ingredient in the interpersonal psychotherapy of depression, which can be conceptualized as a form of brief, focused, and practical psychodynamic therapy.

Loss of Self-Esteem and Depression Reformulation of the dynamics of depression in terms of the ego suffering a collapse of self-esteem represents a further conceptual break with the original id-psychological formulation; depression is said to originate from the ego's inability to give up unattainable goals and ideals. The model further posits that the narcissistic injury that crushes the depressed patient's self-esteem is imposed by the internalized values of the ego rather than the hydraulic pressure of retroflected thanatotic energy deriving from the id. Because the construct of the ego is rooted in social and cultural reality, loss of self-esteem may result from symbolic losses involving power, status, roles, identity, values, and pur-

pose for existence. Thus, the existential and sociocultural implications of depression conceived as a derivative ego state provide the clinician with a far more flexible and pragmatic tool for understanding depressed persons than the archaic hydraulic metaphors related to libidinal vicissitudes. That model represents one of the first attempts to formulate depression in terms that subsequent psychological theory and research could operationalize in more testable form.

Self-esteem is part of the habitual core of the individual and hence is integral to the personality structure. Indeed, low self-esteem conceived as a trait is a major defining attribute of the depressive (melancholic) personality. While it is understandable how such individuals can easily sink into melancholia in the face of environmental adversity, it is not obvious why persons with apparently high self-esteem (e.g., those with hypomanic and narcissistic personalities) also succumb to melancholy with relative ease. To explain such cases, one must invoke an underlying instability in the system of self-esteem that renders it vulnerable to depression. The opposite is also known to occur; that is, manic episodes may develop from a baseline of low self-esteem, as in the case of bipolar disorder patients with antecedent traits of shyness, insecurity, and dysthymia.

The foregoing considerations suggest that the vicissitudes of self-esteem deemed central to the model of depression as loss of self-esteem are manifestations of a more fundamental mood dysregulation. In classical psychoanalysis, such dysregulation is considered of constitutional origin. In general, attempts by psychoanalytic writers to account for bipolar oscillations have not progressed beyond metapsychological jargon, with the possible exception of denial of painful affects as a mechanism in the phenomenology of mania.

Cognitive Model The cognitive model, developed by Aaron Beck at the University of Pennsylvania, hypothesizes that thinking along negative lines (e.g., thinking that one is helpless, unworthy, or useless) is the hallmark of clinical depression. In effect, depression is redefined in terms of a cognitive triad, according to which patients think of themselves as helpless, interpret most events unfavorably vis-à-vis the self, and believe the future to be hopeless. In more recent formulations in academic psychology, these cognitions are said to be characterized by a negative attributional style that is global, internal, and stable and to exist in the form of latent mental schemata that generate biased interpretations of life events.

Because the cognitive model is based on retrospective observations of already depressed persons, it is virtually impossible to prove that causal attributions such as negative mental schemata precede and hence predispose to clinical depression; they can just as readily be regarded as subclinical manifestations of depression. The theoretical importance of the cognitive model lies in the conceptual bridge it provides between ego-psychological and behavioral models of depression. It has also led to a new and widely accepted system of psychotherapy that attempts to alter the negative attributional style, to alleviate the depressive state, and, ultimately, to fortify the patient against future lapses into negative thinking, despair, and depression.

The cognitive model, therefore, has the cardinal virtue of focusing on key reversible clinical dimensions of depressive illness, such as helplessness, hopelessness, and suicidal ideation, while providing a testable and practical psychotherapeutic approach. That approach, however, is less likely to succeed in patients with the full-blown melancholic manifestations of a depressive disorder. It is doubtful that negative cognitions alone could account for the profound disturbances in sleep, appetite, and autonomic and psychomotor functions encountered in melancholic depressions. Further, conceptualizing a multifaceted malady such as depression largely or solely as a function of distorted cognitive processes is reminiscent of pre-Esquirolian notions that emphasized impaired reasoning in the development of depression.

Learned Helplessness Model The learned helplessness model is in some ways an experimental analogue of the cognitive model. The model proposes that the depressive posture is learned from past situations in which the person was unable to terminate undesirable contingencies. The model is based on experiments in dogs that were prevented from taking adaptive action to avoid unpleasant electrical shock and subsequently showed no motivation to escape such aversive stimuli, even when escape avenues were readily available. Armed with evidence from many such experiments, a University of Pennsylvania psychologist, Martin Seligman, postulated a trait of learned helplessness (a belief that it is futile to initiate personal action to reverse aversive circumstances) formed from the cumulation of past episodes of uncontrollable helplessness.

The learned helplessness paradigm is a general one and refers to a broader mental disposition than depression. Thus, it is potentially useful in understanding such diverse conditions as social powerlessness, defeat in sporting events, and posttraumatic stress disorder. In addition, past events might shape a characterological cluster, consisting of passivity, lack of hostility, and self-blame, relevant to certain depressive phenomena. The low hostility observed in some patients during clinical depression could, for instance, be ascribed to the operation of such factors. Learned helplessness could thereby provide plausible links between aspects of personal biography and clinical phenomenology in depressive disorders. Therapeutic predictions for alleviating depression and related psychopathological states capitalize on new cognitive strategies geared to modifying expectations of uncontrollability and the negative attributional style. This illustrates how insights gained from experimental paradigms can be fruitfully combined to address clinical disorders.

Nonetheless, the clinician should be wary of unwarranted clinical extrapolations. For instance, some therapists have argued that the depressed patient's passivity is manipulative, serving to obtain interpersonal rewards. It has also been claimed that such factors have a formative influence on the development of the depressive character. That interpretation appears more relevant to selected aspects of depression than to the totality of the disorder. Depressive behavior and verbalizations clearly have a powerful interpersonal impact, but casting depression as merely a masochistic lifestyle developed to secure interpersonal advantages represents a mechanistic circular argument that could be viewed as disrespectful of the clinical agony of patients with mood disorders. Finally, although most formulations focusing on helplessness have emphasized acquisition through learning, recent experimental research in animals tends to implicate genetic factors in the vulnerability to learning to behave helplessly. The value of the helplessness paradigm may reside in its utility to predict a variety of subthreshold affective disturbances generic to civilian reactions to adversity and trauma.

Depression and Reinforcement Other behavioral investigators, notably Oregon psychologist Peter Lewinsohn, have developed clinical formulations of depression that hinge on certain deficits in reinforcement mechanisms. According to the reinforcement model, depressive behavior is associated with lack of appropriate rewards and, more specifically, with receipt of noncontingent rewards. The model identifies several contributory mechanisms. Some environments may consistently deprive persons of rewarding opportunities, thereby placing them in a chronic state of boredom, pleasurelessness, and, ultimately, despair. That reasoning, however, may

offer more insight into social misery than clinical depression. A more plausible postulated mechanism is the provision of rewards that are not in response to the recipient's actions; in other words, the gratis provision of what a person considers undeserved rewards may lead to lowering of self-esteem. Predisposition to depression is formulated in terms of deficient social skills, which are hypothesized to decrease a person's chances of responding to potentially rewarding contingencies in any environment. Indeed, recent research on the relation between personality and depression suggests that such deficits might underlie certain depressive states. Therefore, psychotherapeutic approaches designed to enlarge a patient's repertoire of social skills may prove valuable in preventing some types of depression.

The concepts of depression that have been derived from behavioral methodology and developed in the past several decades are scientifically articulate and therefore testable approaches to clinical depression. Yet, the important distinction between depression on self-report inventories and clinical depression is sometimes overlooked. Further, the behavioral model does not address the distinct possibility that reinforcement deficits may in part represent the psychomotor deficits of depressive illness. Nevertheless, by focusing on reward mechanisms, the behavioral model provides a conceptual bridge between purely psychological and emerging biological conceptualizations of depression.

Biogenic Amine Imbalance Formulation of sophisticated biological explanations of mood disorders had to await development of neurobiological techniques that could probe parts of the brain involved in emotions. Although the complex physiology of the limbic-diencephalic centers of emotional behavior generally cannot be directly observed in humans, much has been learned from animal work. The limbic cortex is linked with both the neocortex, which subserves higher symbolic functions, and the midbrain and lower brain centers, which are involved in autonomic control, hormonal production, and sleep and wakefulness. Norepinephrine-containing neurons are involved in many functions that are profoundly disturbed in melancholia, including mood, arousal, appetite, reward, and drives. Other biogenic amine neurotransmitters that mediate such functions are the catecholamine dopamine, especially important for pleasure, sex, and psychomotor activity, and the indoleamine serotonin, involved in the regulatory control of affects, aggression, sleep, and appetite, among others. Cholinergic neurons, secreting acetylcholine at their dendritic terminals, are generally antagonistic in function to catecholaminergic neurons.

Although the opioid system might, on experimental and theoretical grounds, also serve as one of the neurochemical substrates for mood regulation, in the author's opinion no cogent model of mood disorders involving that system has appeared to date. Likewise, biochemical formulations of mood disorders have paid relatively little attention to the major excitatory brain neurotransmitter glutamate and the inhibitory neurotransmitter γ-aminobutyric acid (GABA).

Biogenic Amine Hypotheses Joseph Schildkraut at Harvard University and William Bunney and John Davis at NIMH published the first formal hypothesis connecting depletion or imbalance of biogenic amines (specifically norepinephrine) and clinical depression. The serotonin counterpart of the model was emphasized in the models proposed by Alec Coppen in England and I. P. Lapin and G. F. Oxenkrug in Russia. Both catecholamine and indoleamine hypotheses were essentially based on two sets of pharmacological observations. First, reserpine (which decreases blood pressure by depleting biogenic amine stores) precipitates clinical depression in some patients. Second, antidepressant medications (which alleviate clinical depression) raise the functional capacity of the biogenic amines in the brain. This style of thinking is known as the pharmacological bridge, extrapolating from evidence on mechanism of drug action to the neurotransmitter pathologies presumed to underlie a given psychiatric disorder. Such pharmacological strategies have been of heuristic value in developing research methods for investigation of mood disorders and schizophrenia. Indeed, the research methodology developed by the relatively few investigators working in the area in the past three decades is among the most elegant in the history of psychiatry.

Variations of the biogenic amine model assign somewhat different relative weights to the biogenic amines norepinephrine and serotonin in the development of pathological mood states. Arthur Prange and colleagues at the University of North Carolina formulated a permissive biogenic amine hypothesis in which serotonin deficits permit expression of catecholamine-mediated depressive or manic states. That hypothesis was supported by subsequent animal research showing that an intact serotonin system is necessary for optimal functioning of noradrenergic neurons. Omission of tryptophan from the diet of antidepressant-responsive depressed patients may annul the efficacy of the antidepressant; among healthy volunteers, that special diet also induces sleep electroencephalographic characteristics of clinical depression. Although such findings are provocative, the precursor-loading strategy to increase the brain stores of serotonin (e.g., with L-tryptophan) has not been unequivocally successful in reversing clinical depression. Dietary loading with catecholamine precursors has fared even worse than serotonin-precursor loading in the treatment of depression.

The cholinergic-noradrenergic imbalance hypothesis proposed by David Janowsky and colleagues represents yet another attempt to elucidate the roles of biogenic amines. This hypothesis, along with the related cholinergic supersensitivity hypothesis developed by J. Christian Gillin, has been tested extensively at the University of California at San Diego. Subsequent formulations by Larry Siever and Kenneth Davis at the Mount Sinai Hospital in New York have refocused on noradrenergic dysregulation. The model envisions oscillation from one output mode to the other at different phases of depressive illness. In a provocative extrapolation from that model, bipolar depression would have low noradrenergic output, but many instances of major depressive disorder, just like some anxiety disorders, could be biochemically conceptualized as high-output conditions.

Despite more than three decades of extensive research and indirect evidence, however, no deficiency or excess of biogenic amines in specific brain structures has been shown to be necessary or sufficient for the occurrence of mood disorders. It has been possible neither to confirm the putative role of central norepinephrine in depression nor to discard it altogether. The role of dopamine as formulated by the Italian pharmacologist Gian Luigi Cessa, though studied less extensively than that of norepinephrine, deserves greater recognition: it might have relevance to atypical and bipolar depression as well as mania.

Except for preliminary data from a small brain imaging study showing blunted serotonin responsivity in prefrontal and temporoparietal areas in unmedicated major depressive disorder patients, the evidence for serotonergic disturbance in depression is based on indirect evidence. Moreover, the putative permissive role of serotonin is better documented for aggressive suicide attempts. Serotonergic dysfunction might subserve other conditions characterized by lack of inhibitory control, among them obsessive-compulsive disorder, panic disorders, bulimia nervosa, certain forms of insomnia, alcohol-

ism (alcohol abuse or dependence), and a host of impulse-ridden personality disorders. Such considerations have led Dutch psychiatrist Herman van Praag and his colleagues to postulate a dimensional neurochemical disturbance generic to a large group of disorders within the traditional nosology. This hypothesis might be variously regarded as a challenge to psychiatric nosology or as a statement of the need to supplement clinical classification with biochemical parameters.

It is implied that the foregoing biochemical faults are genetically determined. Although biogenic amine models of mood disorders were developed retrospectively from the pharmacologic action of antidepressant and thymoleptic agents, they have stimulated development of new classes of antidepressants with more selective action on specific neurotransmitter receptors. Their introduction has virtually revolutionized the treatment of depression. Yet the fundamental biochemistry of mood disorders is still far from being understood. Curiously, though selective in action, the new compounds working on the serotonin system have broad effectiveness in a variety of mood-related conditions such as dysthymic disorder, obsessive-compulsive disorder, panic disorder, social phobia, borderline personality disorder, and bulimia nervosa. Such data indirectly favor the hypothesis of an underlying biological commonality to several of these disorders. New antidepressants with dual action on both serotonergic and noradrenergic receptors and emerging data on their possible greater efficacy in melancholic depressions do suggest that the biochemistry of mood disorders involves more-complex dysregulation than is implied in single-neurotransmitter hypotheses. The work of George Henninger and colleagues at Yale University further suggests that monoamines better explain how antidepressants facilitate recovery from depression than the fundamental causes of depression.

Emerging biochemical paradigms are moving away from distal biochemical lesions to focus on molecular perturbations closest to the putative genetic underpinnings of mood disorders. Originally tied to the mechanism of action of mood stabilizers in bipolar disorder, such work is exploring second messenger systems, phosphorylation G proteins, signal transduction, deoxyribonucleic acid (DNA) transcription, and messenger ribonucleic acid (RNA) translation. Again, the search for biochemical mechanisms is inseparable from the putative mechanism of action of thymoleptic agents.

Neuroendocrine Links Functionally inadequate mobilization of neurotransmitters in the face of continued or repeated stress, as indirectly reflected in pathological modification of noradrenergic and serotonergic receptor function, could represent neurochemical final common pathways of homeostatic failure. Such mechanisms could also provide links with psychoendocrine dysfunction; the hypothesized neurotransmitter deficits may underlie the disinhibition of the hypothalamic-pituitary-adrenal axis, characterized by steroidal overproduction, the most widely studied endocrine disturbance in depressive illness. When challenged with dexamethasone (Decadron), the altered axis resists suppression, thereby offering Bernard Carroll's team (then at the University of Michigan) the possibility of developing the dexamethasone suppression test (DST) for melancholia (subsequently shown to have uncertain specificity for melancholia). That line of research has culminated in the demonstration by the Emory University's Charles Nemeroff of increased concentrations of corticotropin-releasing factor (CRF) in the cerebrospinal fluid of patients with major depressive disorder. CRF also appears relevant to the pathophysiology of anxiety disorders, such as panic disorder.

Another neuroendocrine index of noradrenergic dysregulation, blunted growth hormone response to the α_2-adrenergic receptor agonist clonidine, likewise points to limbic-diencephalic disturbance. However, studies performed in the United States suggest that it is positive in both endogenous depression and severe anxiety disorder (panic disorder). Thyroid-stimulating hormone (TSH) blunting upon thyrotropin stimulation, another common neuroendocrine disturbance in depression, also shows limited specificity.

What is remarkable, however, is that the DST, clonidine (Catapres), and thyrotropin challenge data in aggregate identify most persons with clinical depression. Such evidence of midbrain disturbance argues for considering clinical depression to be a legitimate disease. The disease concept of depression is further buttressed by computed tomography scans showing enlarged pituitary and adrenal glands.

Stress and Depression The concept of a pharmacological bridge implies two-way traffic. The hypothesized chemical aberrations may be primary or biologically induced. Provision should also be made, however, for the likelihood that psychological events that precipitate clinical depression might induce or initiate neurochemical imbalance in vulnerable subjects. That suggestion is supported by studies in animals, in which separation and inescapable frustration effect profound alterations in the turnover of biogenic amines and in postsynaptic receptor sensitivity. Thus, in genetically predisposed persons, environmental stressors might more easily lead to perturbations of limbic-diencephalic neurotransmitter balance. Finally, in vulnerable individuals, especially during the formative years of childhood, psychological mechanisms might more easily perturb midbrain neurochemistry. Traumatic experiences appear particularly potent in this regard.

Neurophysiological Approaches

Neuronal Hyperexcitability Lithium is known to replace intracellular sodium and hyperpolarize the neuronal membrane, thereby decreasing neuronal excitability. Abnormalities in neuronal electrolyte balance (an excess of residual sodium, defined by radioisotope techniques) and hypothesized secondary neurophysiological disturbances were the focus of British investigations by Alec Coppen and colleagues in the early 1960s. The existing data appear compatible with the hypothesized movement of excess sodium into the neuron during an episode of mood disorder and redistribution toward the pre-illness electrolyte balance across the neuronal membrane during recovery. Intraneuronal sodium leakage is postulated in both depressive and manic disorders but deemed more extreme in the latter. Because the harmonious activity of the neuronal cell and, by implication, that of a group of neurons depends on the electrical gradient maintained across its membrane by differential distribution of sodium, abnormalities in sodium concentrations and transport are hypothetically relevant to the production of an unstable state of neurophysiological hyperexcitability. In formulating their thesis of neurophysiologic arousal in melancholic states, Joseph Mendels and Peter Whybrow (both of whom at various times worked at the University of Pennsylvania) have capitalized on the foregoing electrolyte disturbances. The view that mania represents a more extreme electrophysiological dysfunction in the same direction as depression violates the common-sense notion of symptomatological opposition between the two kinds of disorder, yet it may in part account for the existence of mixed states in which symptoms of depression and mania coexist. The NIMH team led by Frederick Goodwin first showed that a substantial minority of depressed patients with a bipolar substrate respond to lithium salts, which further supports the concept of a neurophysiological common denominator to mania and

depression. Perturbations of calcium metabolism also appear limited to bipolar patients. Therapeutic implications of this observation (e.g., the use of calcium channel inhibitors in bipolar I disorder) have not yielded consistent results. Finally, rubidium, another alkali metal, has been explored in the depressive phase of bipolar disorders, again with inconclusive results.

Rhythmopathy European studies have shown that depressed patients are phase advanced in many biological rhythms, including the latency to the first rapid eye movement (REM) in sleep. Shortened REM latency, which has been extensively studied by David Kupfer and colleagues at the University of Pittsburgh, has been proposed as another laboratory test for depressive disorder. Formulations of circadian rhythms by Thomas Wehr and Norman Rosenthal, working at NIMH, have focused on abnormalities on brain regulation temperature, activity, and sleep cycles. Others have investigated the role of the pineal hormone melatonin. These neurophysiologic considerations have paved the way for new therapeutic opportunities.

Sleep deprivation and exposure to bright white light can correct phase disturbances and thereby terminate depressive episodes, especially in patients with periodic and seasonal depressions. Daniel Kripke, working at the University of California at San Diego, has shown that the average citizen is light deprived and that phototherapy can benefit many forms of depression. Although the specificity and efficacy of these neurophysiological indexes and manipulations for clinical depression require more extensive research, cumulatively they point to midbrain dysregulation as the likely common neurophysiological substrate of depressive disorders. The foregoing considerations further suggest that the ancient Greeks, who ascribed melancholia to malignant geophysical influences, did not indulge in mere poetic metaphor. The ancients had observed the disturbed circadian patterns and advocated their readjustment to restore euthymia.

Affective Dysregulation A major challenge for research in mood disorders is to characterize the basic molecular mechanisms that underlie the neurophysiological rhythmopathies, which in turn might account for the recurrent nature of the affective pathology as envisioned by Kraepelin. This means that in the most typical recurrent forms of the disorders, the constitutional foundations (manifested as cyclothymic and dysthymic traits) are so unstable that the illness may run its entire course more or less autonomously, with the environment largely serving to turn on and off the more florid phases (episodes). The Parisian psychiatrist Jean Delay, a pioneer in psychopharmacology in the 1950s, has also emphasized affective dysregulation as the fundamental pathology in the spectrum of mood disorders. Robert Post (at NIMH) has hypothesized that the electrophysiological substrates could be so kindled that an oligoepisodic disorder initially triggered by environmental stressors could assume an autonomous and polyepisodic course. He hypothesizes that this phenomenon might occur because neuronal perturbations brought about by stressors in the early course of mood disorders get incorporated into the DNA. This fascinating kindling hypothesis, however, does not seem to pertain to common mood disorders, but those with extreme cyclicity. The monograph on manic-depressive illness by Goodwin and Kay Jamison presents in-depth arguments for this cyclical paradigm of thymopathy.

THEORETICAL SYNTHESIS

Pathophysiological Understanding Modern psychobiology attempts to link experience and behavior to the central nervous system. Building conceptual bridges between the psychological and biological approaches to mood disorders requires sophisticated strategies that go beyond the Cartesian notion of limited mind-body interactions through the pineal gland and the generalizations of the Meyerian school.

In collaboration with William McKinney in 1973, the author developed the conceptual framework that considers the affective syndromes as the final common pathway of various psychological and biological processes. The overarching hypothesis is that psychological and biological etiological factors converge in reversible deficits in the diencephalic substrates of pleasure and reward. Those areas of the brain subserve the functions that are disturbed in melancholia and mania. The integrative model links the central chemistry and physiology of reward mechanisms with the object loss and behavioral models of depression, both of which give singular importance to the depressant role of loss of rewarding interpersonal bonds. A key element of the model is the circadian disturbances observed since ancient times in both depressive and manic syndromes. Both syndromes are conceptualized as clinical manifestations of a disordered limbic system with its subcortical and prefrontal extensions. Brain-imaging studies in melancholic patients by Wayne Drevets at Washington University have tentatively visualized limbic disturbances extending into subcortical structures and occurring primarily in those with a familial diathesis for depression. The amygdala plays a key role in this model. Clinical experience and research data suggest that multiple factors described below converge to produce dysregulation leading to the final common pathway of clinical depression and mania.

Heredity Current evidence indicates a significant genetic role in the causation of bipolar and recurrent major depressive disorders. Although it is not known exactly what is inherited, recent research suggests that heritability involves a broad spectrum of disorders, including milder depressive states. Genetic heterogeneity is likely, and may involve inheritance of a single dominant gene with variable penetrance or in greater likelihood, polygenic inheritance. Different genetic mechanisms will probably involve more than one disorder (e.g., depression and generalized anxiety; bipolar I disorder, stimulant abuse, and alcohol dependence; bipolar II disorder, mood disorder with seasonal patern, bulimia nervosa, and borderline personality).

Developmental Predisposition Parents with mood disorders are often in conflict, which may lead to separation, divorce, and suicide. It can be said that heredity often determines the type of environment into which the child predisposed to mood disorder is born. Developmental object loss, although not specifically involved in causing mood disorder, might modify the expression of the illness, possibly by leading to earlier onset, more-severe episodes, and an increased likelihood of personality disorder and suicide attempts.

Temperament Since ancient times, persons prone to mania and melancholia have been described as possessing certain temperamental attributes, representing variations on the theme of what today is subsumed under cyclothymic, dysthymic, and anxious-inhibited temperaments. Many monozygotic twins discordant for full-blown mood disorders studied by Aksel Bertelsen's Danish research team exhibited affective instability with temperamental moodiness, which strongly suggests that such attributes are genetically determined. Research conducted by Kendler's team at the Medical College of Virginia further suggests that several of the temperamental attributes

might be transmitted as part of the genetic liability to mood disorders. The author's research has identified such temperaments in the prepubertal offspring of parents with bipolar I disorders, suggesting that they precede by years to decades the overt onset of major mood disorder episodes. The high expressed emotion atmosphere and the negative critical remarks by relatives and affectively unstable patients documented in the recent psychological literature on mood disorders often reflect the interpersonal clashes between patients and their temperamentally intense relatives. Thus, temperaments appear intimately involved in generating much interpersonal friction, emotional arousal, and sleep loss (just to cite common perturbations) thereby eliciting many of the life stressors that precipitate affective episodes. The use of stimulant drugs either to self-treat lethargy or enhance hypomanic traits could further contribute to episode precipitation.

Life Events Most individuals do not develop clinical depression when exposed to environmental adversity. Such adversity seems to play a pathogenic role primarily in those with an affective diathesis. Actually, the work of Kenneth Kendler at the Medical College of Virginia indicates that genetic factors might underlie the depressive disorder patients' susceptibility to life events. Furthermore, current data suggest that social stressors in the onset of depression are more relevant to the first few episodes of the illness. The evidence linking such events to mania is less robust. At any rate, stressful events often appear to be triggered by the temperamental instability that precedes clinical episodes. Interpersonal losses are common events in the lives of individuals with intense temperaments.

Indeed, a recent study by Peter McGuffin's team at the Institute of Psychiatry, London, raised the possibility that one mechanism by which heredity produces depression is by creating environmental adversities in the lives of individuals predisposed to this illness. This work is now replicated by independent groups of investigators. Whatever the origin of environmental adversity, it is common clinical experience that loss represents an important, perhaps even central, theme in clinical depression. Variables that seem to modulate the impact of adult losses include concurrent life events, resultant changes in lifestyle, lack of interpersonal support, deficient social skills, and the symbolic meaning of the putative loss. The research program of George Brown and his followers in London capitalizes on the foregoing considerations, particularly the importance of early and proximate losses in socioeconomically disadvantaged women who lack supportive relationships. However, that conceptualization downplays the degree to which the social context of the depression reflects the dysthymic temperamental liabilities of those depressed women. Recent research indicates that even social support is determined to a considerable degree by the genetic mechanisms that underlie mood disorders.

Biological Stressors Many physical diseases and pharmacological agents are known to precede the onset of both depressive and manic episodes. Like psychosocial stressors, however, they do not generally seem to cause de novo episodes but mobilize them in persons with a personal and family history of mood disorders. Thyroid disturbances have an important role in practice, because they seem to underlie some cases with rapid cycling in bipolar females.

Sex Clinical and epidemiological studies concur in suggesting that women are at higher risk for mood disorders, with the risk highest for depression. This now appears in part a function of anxious-depressive traits represented by neuroticism. These traits have strong genetic determinants. Women have higher concentrations of monamine oxidase (the enzyme that breaks down monamine transmitters) in the brain and more precarious thyroid status. In addition, low estrogen and high progesterone concentrations have been postulated as possible mediating factors in postpartum depressions, premenstrual accentuation of affective instability, and women's vulnerability to the depressant effect of steroidal contraceptives. Personality factors might also be relevant to the sex differences in depression. In recent collaborative work with University of Pisa psychiatrist Giulio Perugi, the author has proposed the hypothesis that female sex might favor greater expression of dysthymic attributes, whereas hyperthymic traits appear favored by male sex. Those considerations tend to parallel, respectively, the "ruminative" and "active" cognitive response styles reported by Stanford's Susan Nolen-Hoeksema to distinguish the sexes. What specific sex-related biographical factors might interact with sex-related biological factors to produce such trait differences is presently largely unknown. An intriguing possibility is that women, because of their temperamental inclination to depressive cognitions, might more adversely respond to childhood adversities, as well as being more specifically vulnerable to adult stressors related to bonding with men and child rearing. Research by Mark George and colleagues has raised the provocative possibility that women overrespond to sad circumstances over a lifetime, thereby permanently altering anterior limbic and prefrontal brain function in a depressive direction.

The integrative model presented here (Fig. 14.1-3) goes beyond the general provisions of the unified approach developed a quarter century earlier. It is submitted that at least in the highly recurrent forms of the malady, affective temperaments represent the intermediary stage between remote (hereditary) and proximate (stressful) factors and that limbic-diencephalic dysfunction is best characterized as the biological concomitant of the clinical manifestations of the affective syndromes. Like the temperamental dysregulations, these biological disturbances represent a putative stage in the pathogenetic chain. They emerge as temperamental instabilities that react to, provoke, or invite life events, substance use, and alterations in circadian rhythms, which in turn appear to usher in the behavioral, emotional, and cognitive manifestations of the illness.

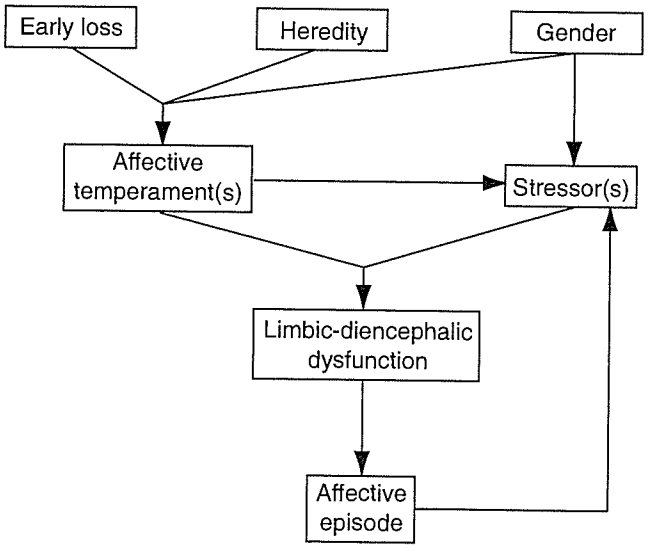

FIGURE 14.1-3 An integrative pathogenetic model of mood disorders.

THERAPEUTIC PERSPECTIVES The foregoing integrative model envisions the joint use of somatic-pharmacological and psychosocial interventions. Although the milder forms of mood disorders can be managed with psychotherapy, somatic treatments are usually required to reverse the biological disturbances in melancholia before the patient can respond to interpersonal feedback. Depressive disorders with psychotic features often necessitate more definitive somatic interventions such as electroconvulsive therapy. Continued psychopharmacological treatment is also effective in decreasing rates of relapse and future recurrence in most.

Psychosocial therapy by skilled clinicians can provide support, combat demoralization, change maladaptive self-attributions, and improve conjugal and vocational functioning. Whether such therapy can also modify personality traits to fortify the patient against new episodes is a future research challenge. In the author's view, it may prove more profitable to attempt to help patients explore professional and object choices that match their temperamental proclivities and assets, which in turn might provide them greater harmony and adaptation in life. Although much needs to be learned about the indications for medication and psychotherapy in different subtypes of mood disorders, research to date not only does not support a negative interaction between the two forms of treatment but on selected parameters suggests additive and even synergistic interaction. There is a great need for patients, their families, and clinicians to understand how a biologically driven illness like depression should be approached from a pragmatic psychotherapeutic perspective.

The challenge for psychiatric research in the decade ahead is to elucidate the basic mechanisms whereby the predisposing, precipitating, and mediating variables reviewed here and others yet to be identified interact to produce the final common path of decompensation in melancholia. Because of the heterogeneity of depressive conditions presenting as a psychobiological final common clinical syndrome and because antidepressant agents, irrespective of specificity to one or another biogenic amine, are about equally effective in two-thirds of those with depressive disorders, the antidepressant agents may be acting not on the primary lesions of these disorders but on a neurochemical substrate distal to the underlying biological faults. The choice of antidepressants is still highly determined by the side effect profile least objectionable to a given patient's physical status, temperament and lifestyle. That so many different classes of antidepressants—with different mechanisms of action—have been marketed in the 1990s represents indirect evidence for heterogeneity of biochemical lesions. The investigation of central neurotransmitter receptor function continues to occupy much current effort to delineate the putative mechanism of antidepressant action and side effects of classic agents as well as the new compounds which have made the treatment of depression "clinician and patient friendly." Whether study of specific recepters will unravel the molecular mystery of depression remains to be seen. During the past decade, studies have begun on antidepressant and mood-stabilizing effects on molecular mechanisms believed to be closer to the "genetic underpinnings" of mood disorders. Herein is the promise of the future, a new generation of psychiatrists conversant with both clinical phenomenology and molecular biology. Data suggest that the biological specificity of genetic factors in mood disorders might be translated into distinct temperamental dysregulations, which in turn might predispose to different affective subtypes.

Returning to the therapeutic arena, mounting evidence indicates that in depressed patients with bipolar disorder, antidepressants might provoke mixed episodes, hypomanic episodes, or both, and possibly increase later cycling. The kindling-sensitization model suggests the utility of anticonvulsant medication on episode escalation and might represent yet another example of pathophysiological intervention. Whatever the merit of this model, the last decade has witnessed intense clinical and research interest and Food and Drug Administration approval of clinical introduction of divalproex (Depakene) for bipolar I disorder, and many other promising anticonvulsants are being developed for that disorder. Anticonvulsant mood stabilizers appear to possess a broad spectrum of activity on bipolar disorders, including mixed dysphoric and rapid-cycling forms. Lithium, by contrast, seems more specific to euphoric mania.

Psychoeducational interventions geared to disturbed rhythms of the disorder represent another example of rational therapeutics. Mood clinics should help patients and their significant others to dampen stimulation so that it is kept at an optimal level for depressed patients with cyclothymic traits. All offending drugs (e.g., cocaine, caffeine, and sedative-hypnotic agents) should gradually be eliminated, and circadian disruptions and sleep loss minimized. The greater challenge is learning how to curb the ill-advised actions of patients with cyclical depressions. Psychoeducation and psychotherapy have the task of ameliorating the resulting social problems. Compliance with mood-stabilizer regimens that for many would attenuate episodes and prevent such sequelae is difficult to achieve. Research on compliance-enhancing techniques is needed for the more efficient use of mood stabilizers.

It is tempting to suggest that biogenic amines, the "humors" of modern psychobiology, play the same heuristic role as the ancient humors did for many centuries. The black humor, appropriately evoked in the construct of melancholia in DSM-IV, may not have the same claim for etiological relevance to depressive disorders as norepinephrine and serotonin, but at least has a classical heritage. Dopamine, by contrast, may represent the sanguine humor that drives hypomanic temperaments and manic behavior. When genetic factors contributing to clinical depression and mania are discovered, in all likelihood they will be more linked to temperamental dispositions than to fullblown affective disease phenotypes. The clinician will still need to interpret the myriad of influences that impinge on such inclinations to produce disease in an individual patient. That is, fundamental scientific advances in mood disorders, rather than diminishing the role of practitioners, will actually increase it.

In any discipline, scientific truth is a function of its technology, but understanding the phenomena under consideration is a matter of philosophical temperament that seeks integration and the hope for a unified vision. Research into the causes and treatment of mood disorders has generated abundant recent data suitable for integration into theory and practice, and conceptualizing the origin and treatment of mood disorders can no longer be justified on the grounds of ideological preference alone.

SUGGESTED CROSS-REFERENCES

Anxiety disorders are covered in Chapter 15. The other sections of Chapter 14 cover the various aspects of mood disorders in detail. Epidemiology is the subject of Section 14.2; neurobiologic aspects are the focus of 14.4; Section 14.3 is a discussion of genetic aspects; psychodynamic aspects are the subject of Section 14.5. Clinical features are covered in Section 14.6, somatic treatment in Sections 14.7 and 14.8, and a discussion of psychosocial treatments concludes the chapter in Section 14.9.

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▲ 14.2 Mood Disorders: Epidemiology

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INTRODUCTION

Since the 1980s community-based epidemiologic studies of mood disorders throughout the world have been significantly influenced

Table 14.2-1
Lifetime Prevalence of Some DSM-IV Mood Disorders

Mood Disorder		Lifetime Prevalence
Depressive disorders		
Major depressive disorder (MDD)	Recurrent, with full interepisode recovery, superimposed on dysthymic disorder	10–25% for women; 5–12% for men
		2–3% of persons with MDD
Dysthymic disorder	Recurrent, without full interepisode recovery, superimposed on dysthymic disorder (double depression)	25–30% of persons with MDD
		3–6%
Bipolar disorders		
Bipolar I disorder		0.4–1.6%
Bipolar II disorder		<1%
	Bipolar I disorder or bipolar II disorder, with rapid cycling	5–15% of persons with bipolar disorder
Cyclothymic disorder		0.4–1.0%

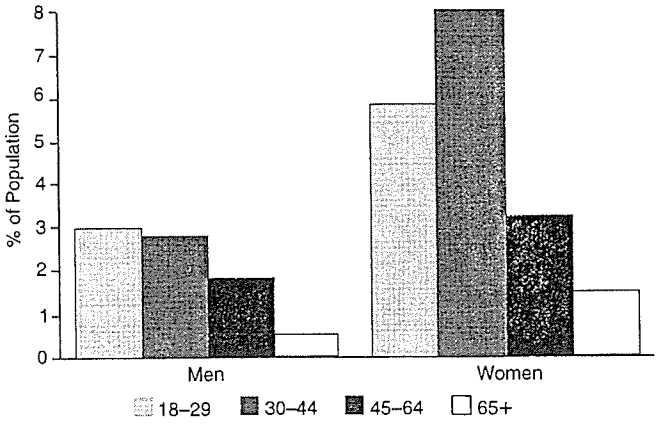

FIGURE 14.2-1 Current prevalence of major depressive disorders by age and gender. (Data derived from the Epidemiologic Catchment Area Study.)

by two large community-based surveys in the United States, the 1981 Epidemiologic Catchment Area Study and the 1991 National Comorbidity Survey. Not only did these surveys provide estimates of the prevalence and distribution of discrete psychiatric disorders (in synchrony with the shifting orientation from symptom burden to operational psychiatric diagnoses reflected in the third edition of *Diagnostic and Statistical Manual of Mental Disorders* (DMS-III) and its successors, they also demonstrated the feasibility of identifying psychiatric patients by use of assessment procedures that could be administered by nonprofessional interviewers. ECA investigators used the Diagnostic Interview Schedule (DIS) and NCS investigators used a modified version of the Composite International Diagnostic Interview (CIDI). These case assessment procedures have now been used in countries throughout the world, including Canada, Finland, Korea, Taiwan, and New Zealand.

Most of the data presented in this chapter derive from community-based estimates of the frequency, distribution, and correlates of depressive symptoms and major depressive disorder as estimated from these studies. Bipolar disorders receive less attention than they do in clinical studies because community-based epidemiological data are sparse. The lifetime prevalence of mood disorders is high in Western society. Estimates of the lifetime prevalence of mood disorders are presented in Table 14.2-1.

CASE IDENTIFICATION

Case identification (i.e., determining who should be diagnosed as experiencing a mood disorder versus who is only expressing a normal fluctuation in mood) has been at the center of debate regarding the true frequency of mood disorders in the community. This debate derived largely from the significant variance in the estimates of the current and lifetime prevalence of major depressive disorder in the ECA and NCS studies, as demonstrated in Figures 14.2-1 through 14.2-4. This debate has relevance to clinicians who treat patients experiencing mood disorders, for they must distinguish normal variations in mood from the mood disorders. The diagnostic criteria for the specific mood disorders in the DSM, which has gone through four editions since its inception, are not easily applied in epidemiological studies. Some diagnostic categories, such as adjustment disorder with depressed mood, cannot be operationalized in standardized interviews because the criteria require a subjective clinical judgment (e.g., the mood disturbance must be related to a specific stressor). Other diagnoses are too inclusive when applied to community samples (e.g., major depressive disorder). Patients identified by current diagnostic criteria are therefore a heterogeneous mix with little clinical relevance beyond symptom severity. In other words, the borderline between clinical depression and normal fluctuation in mood is fuzzy. Even the presence or absence of a symptom may be disputed.

Some persons in community samples may exhibit depressive syndromes that do not fit the DSM diagnostic system (e.g., for major depressive disorder or dysthymic disorder), but they nevertheless suffer disabling depressive symptoms. Much attention has been focused in recent years on so-called minor or subsyndromal depressive disorder, a syndrome defined by symptoms that are less severe than those of major depressive disorder and of shorter duration than those of dysthymic disorder. The frequency of minor depression was estimated to be nearly 4 percent in the ECA study. Minor depression has generally been divided into two categories: less severe episodes that occur in conjunction with major depressive disorder and symptoms that occur spontaneously. Persons identified in community surveys as experiencing minor depressive disorder have been shown in prospective studies to be at greater risk for time lost at work and increased use of general health services than persons without depressive symptoms. In addition, their risk factor profile is similar to that for major depressive disorder.

Another problem that complicates estimation of the frequency of mood disorders in the community is deterioration of memory over time. Recall of past symptoms is only modestly accurate compared with clinical records of previous depressive episodes. The threshold for reporting a symptom of depression may be higher in a community than in a clinical setting because clinicians often probe for evidence of a symptom that the patient initially denies. Most interview instruments used in epidemiological surveys to identify DSM diagnoses, such as the DIS used in the ECA, were developed in clinical settings and were standardized with classic patients who present to psychiatric treatment settings. In contrast, the modified version of the CIDI used in the NCS (see below) was designed to probe for past history of symptoms more thoroughly than the DIS, because the emphasis

of the CIDI was on identifying affected persons in the community who were not experiencing clinically significant depressive symptoms and who had never sought psychiatric treatment. As the threshold for case identification is lower with the CIDI, the estimate of both current and lifetime prevalence of mood disorders is higher. Most persons identified as having mood disorder in the community with the CIDI experience little disruption in function and do not seek psychiatric treatment. Should persons who meet strict fourth edition of DSM (DSM-IV) criteria when interviewed by nonclinicians and asked in detail about past and present symptoms be considered to have true cases of mood disorder, especially major depressive disorder? Therein lies much of the debate.

Comorbidity presents another problem to psychiatric epidemiologists who study mood disorders in community settings. More often than not, symptoms of anxiety and depression overlap. Many subjects receive concurrent diagnoses of major depressive disorder, dysthymic disorder, and generalized anxiety disorder. Most community survey subjects cannot accurately remember whether depression or anxiety was the first syndrome experienced. Do major depressive disorder and generalized anxiety disorder coexist, or is anxiety an epiphenomenon of major depressive disorder? That question remains unanswered.

Nevertheless, development of standardized instruments for case identification in the community, such as the DIS and CIDI, has made it possible to investigate empirically the utility of psychiatric diagnosis. For example, when investigators do not agree upon the frequency of mood disorder with seasonal pattern (i.e., seasonal affective disorder) they can explore their disagreements by using the same criteria and diagnostic instruments for case identification. A recent study demonstrated that though a seasonal pattern of mood swings is common among persons in the community (approximately 8 percent), the frequency of mood disorder with a seasonal pattern, as defined by DSM-IV, is less than 1 percent, even when the most liberal interpretation of the criteria is applied.

DISTRIBUTION OF CASES

Estimates of the prevalence of major depressive disorder by age and gender from the ECA and NCS studies are presented in Figures 14.2-1 and 14.2-2. The DIS was administered for case finding in the ECA study to over 18,000 community and institutionalized subjects (18 + years of age) at five sites throughout the United States—New Haven, East Baltimore, St. Louis, the Piedmont of North Carolina, and Los Angeles. The large numbers of subjects and oversampling of subjects not accurately represented in previous studies, such as African-Americans, Hispanics, and elderly persons, enabled much better estimates of the actual distribution of cases. Over 8000 subjects (15 to 54 years of age) from a nationwide sample were administered a modified version of the CIDI in the NCS study.

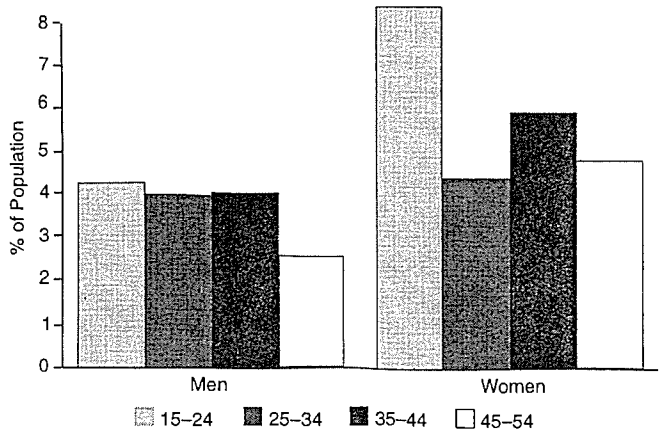

FIGURE 14.2-2 Current prevalence of major depressive disorders by age and gender. (Data derived from the National Comorbidity Survey.)

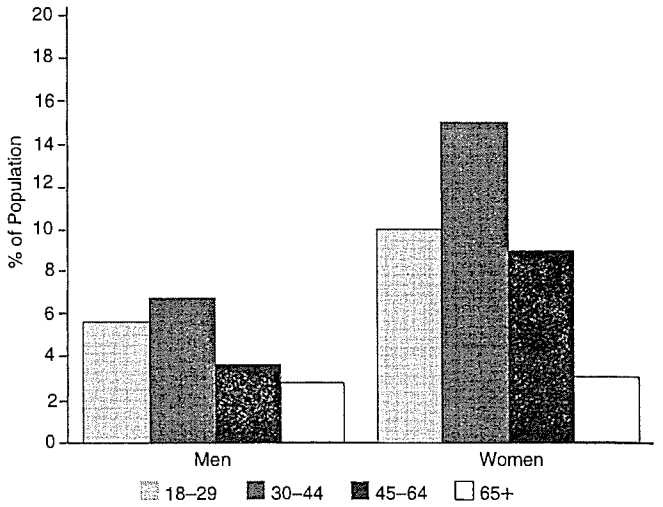

FIGURE 14.2-3 Lifetime prevalence of major depressive disorders by age and gender. (Data derived from the Epidemiologic Catchment Area Study.)

Age, Sex, and Residence The most striking finding from the ECA study was a much higher prevalence of all the mood disorders among persons under the age of 45 than in persons 45 years of age and older. Rates were comparable across ECA sites, except for a lower prevalence in North Carolina. The North Carolina sample was composed of both urban and rural residents. Persons in urban areas were as likely to be diagnosed with a mood disorder in North Carolina as in urban areas at other ECA sites. In contrast, rural subjects in North Carolina had much lower rates of major depressive disorder than rural subjects at other ECA sites. In the NCS study, variance by age and geographic location was much less prominent.

The most consistent finding across epidemiological studies of the mood disorders, confirmed by the ECA and NCS studies, is the relatively higher prevalence of major depressive disorder in women than in men. The sex differences are consistent across the life cycle but are much more prominent in young adult and middle-aged persons than in elderly persons and childhood depressive disorders. Because alcohol abuse and mood disorders are often inherited in the same family and alcohol abuse and dependence is more prevalent in men than in women, some have theorized that depressive disorders and alcohol abuse/dependence are phenotypic variants of the same genotype. Little empirical evidence supports this theory.

Sex differences begin in early adolescence and persist at least until midlife. However, women with a previous history of a depressive episode are no more likely to experience a new episode than men with a previous history of a depressive episode. This suggests that the higher risk in women results from women having a higher risk of experiencing major depressive disorder for the first time.

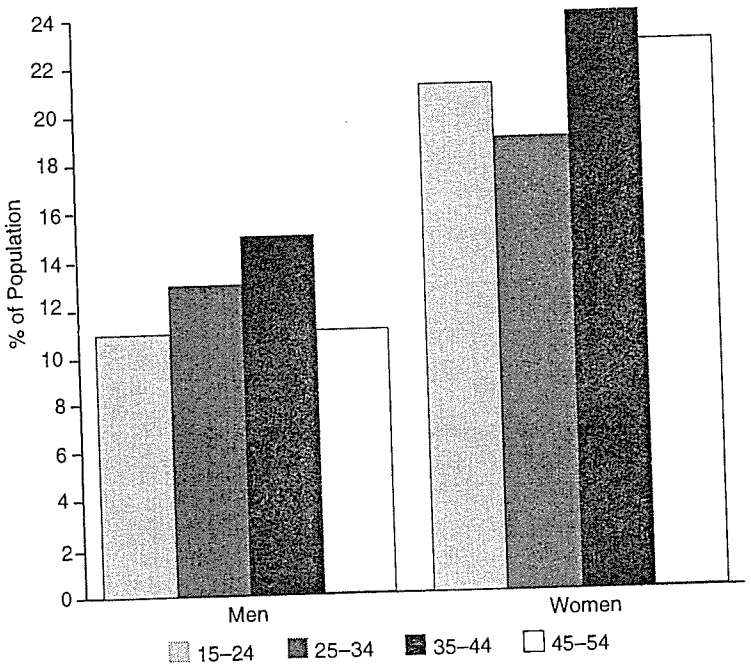

FIGURE 14.2-4 Lifetime prevalence of major depressive disorders by age and gender. (Data derived from the National Comorbidity Survey.)

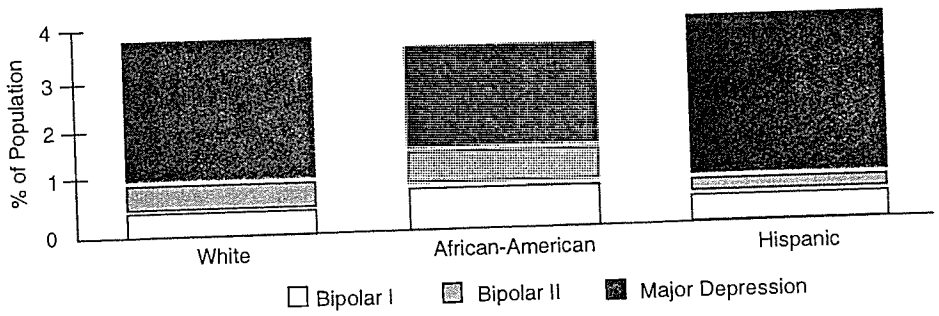

FIGURE 14.2-5 Current (1-year) prevalence of major depressive disorder by race or ethnicity. (Data derived from the Epidemiologic Catchment Area Study.)

Psychosocial explanations for the higher prevalence of major depressive disorder among women are thus considered the most likely explanation of the sex differences. Epidemiologists have identified stressors that may contribute to increased stress experienced by women, such as maintaining multiple roles as homemaker, professional, wife, and mother.

Race and Ethnicity As illustrated in Figure 14.2-5, the prevalence of the mood disorders does not vary significantly by race or ethnicity. In most epidemiological studies of psychiatric disorders, racial differences in the rates can be explained by socioeconomic and educational differences. The ECA was the first study in Western society that permitted direct comparison of whites, African-Americans, and Hispanics. Previous comparisons, which could not control for geographical differences, were subject to significant bias because prevalence estimates clearly vary by place of residence. The NCS results are similar to the ECA results, though as noted, the overall rates are higher.

International Studies Perhaps the most frequently cited epidemiologic study prior to the ECA and NCS studies was the Stirling County Study from Nova Scotia, Canada. The current prevalence of major depression was estimated to be 4.7 percent in men and 6.0 percent in women. Most studies in developed countries estimate the distribution of major depressive disorder to be greater in women than in men, in young adulthood than in midlife and old age, in urban residents than in rural residents, and among single or divorced persons than among married persons. Few studies document a racial difference when social class and education are controlled. In a recent comparison of population-based epidemiologic studies in 10 countries—the United States, Canada, Puerto Rico, France, West Germany, Italy, Lebanon, Taiwan, Korea, and New Zealand—the lifetime prevalence for major depressive disorder ranged from 1.5 percent in Taiwan to 19 percent in Beirut. Current prevalence ranged from 0.8 percent in Taiwan to 5.8 percent in New Zealand. The difference in prevalence estimates across countries suggests that cultural differences or differences in risk factors may influence the expression of major depression.

Depressive Symptoms The differential frequency of clinically significant depressive symptoms parallels that of major depressive disorder, although the age differences are not nearly so great. In most studies, 8 to 20 percent of community-study participants report depressive symptoms at a level above the cutoff used to screen

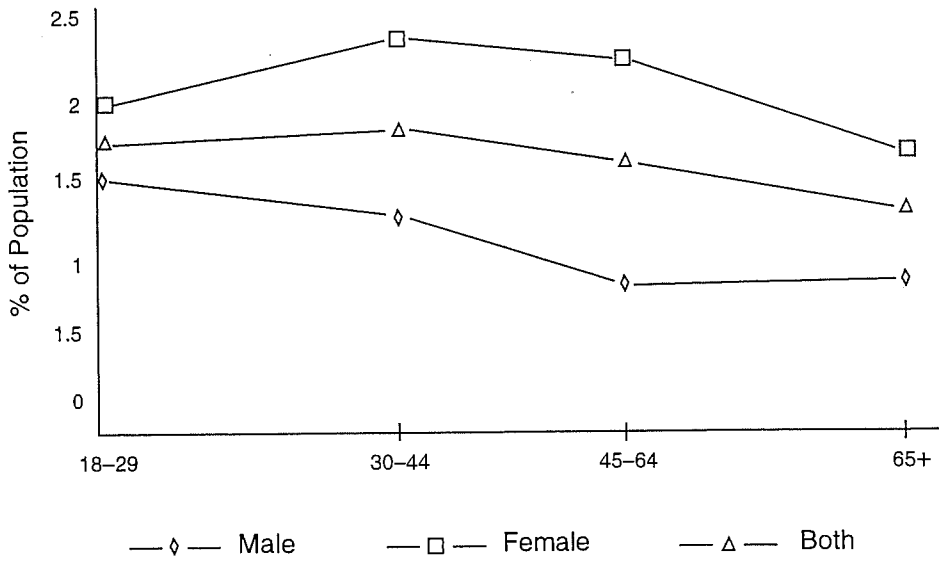

FIGURE 14.2-6 Annual incidence of major depressive disorders by age and gender. (Data derived from the Epidemiologic Catchment Area Study.)

for major depressive disorder, such as 16+ on the Center for Epidemiologic Studies Depression Scale (CES-D). As with all good screening tests, many potential patients are screened out with more-specific case-identification techniques, such as a standardized diagnostic instrument. Therefore, many persons who appear positive on screening do not meet criteria for specific DSM-IV mood disorders. Those who do appear positive on screening for depressive symptoms, however, experience higher mortality rates, higher disability rates, and poor social functioning.

Incidence Because major depressive disorder is common and tends to remit and recur, the incidence is relatively high. The annual incidence of major depressive disorder in the ECA study was 1.59 percent overall. The distribution by age and gender is presented in Figure 14.2-6. A survey in Lundby, Sweden, revealed an annual first incidence of depression (depression in persons who never experienced depression before) of 0.43 percent in men and 0.76 percent in women. Up to the age of 70, the cumulative probability of a first episode of depression was 27 percent in men and 45 percent in women, making depression one of the most important public health problems (Fig. 16.2-7).

Setting The prevalence of major depressive disorder is much higher in treatment settings than in the community at large. Most investigators find that 10 to 15 percent of persons in acute hospital settings and long-term care facilities meet the criteria for the diagnosis of major depressive disorder. An additional 20 to 30 percent of persons in treatment settings report clinically significant subsyndromal depression (minor depression). The similarities between those patients with major depressive disorder to patients found in psychiatric treatment settings has yet to be documented. Although some depressed medically ill patients respond to antidepressant therapy and brief psychotherapy, many have comorbid conditions that render traditional therapies ineffective.

Depression is also more prevalent in primary care settings than in the general population. Using case-identification methods similar to those in the ECA study, the current prevalence of depression is about twice that found in the general population. In most surveys of primary care clinics, over 20 percent of patients report clinically significant depressive symptoms. Major depressive disorder is diagnosed in one-third to one-half of these outpatients. Young women are at greatest risk for depression in primary care, and most persons who report depressive symptoms to a health care professional report them to a primary care physician.

HISTORICAL TRENDS

The higher prevalence of depression in younger age groups than in older ones has led to the hypothesis that birth cohorts born after World War II are at appreciably greater risk for major depressive disorder than older birth cohorts in advanced Western society. The trend has been observed not only in the United States but also in Sweden, Germany, Canada, and New Zealand.

A number of observations made prior to the ECA study suggest that prevalence rates of depressive disorders are changing. Relevant factors include a progressively lower age of onset of depressive disorders reported in community studies, an increase in childhood mood disorders seen by pediatricians and mental health workers, a decrease in deaths from suicide among the elderly (until about 1980), and a lower average age of onset for depressive disorders in clinical samples since World War II. For example, the risk of first-onset depression was higher for younger birth cohorts than for older birth cohorts in Sweden (Fig. 14.2-7). The trends in suicide data parallel the trends in mood disorders (i.e., suicide rates are much higher in younger persons today than they were in younger persons 30 years ago). Suicide rates in older adults have increased by 25 percent since 1980.

Factors That Influence Historical Trends Three factors influenced historical trends in the relative prevalence of mood disorders by age: period effect, age effects, and cohort effects.

Period effects are changes in the prevalence of an illness secondary to environmental stressors on the population or particular age groups within the population at a specific period in history. (For example, the uncertainty of employment among college graduates and the trend among younger persons to delay marriage during the 1990s may place young adults at greater risk for depression and

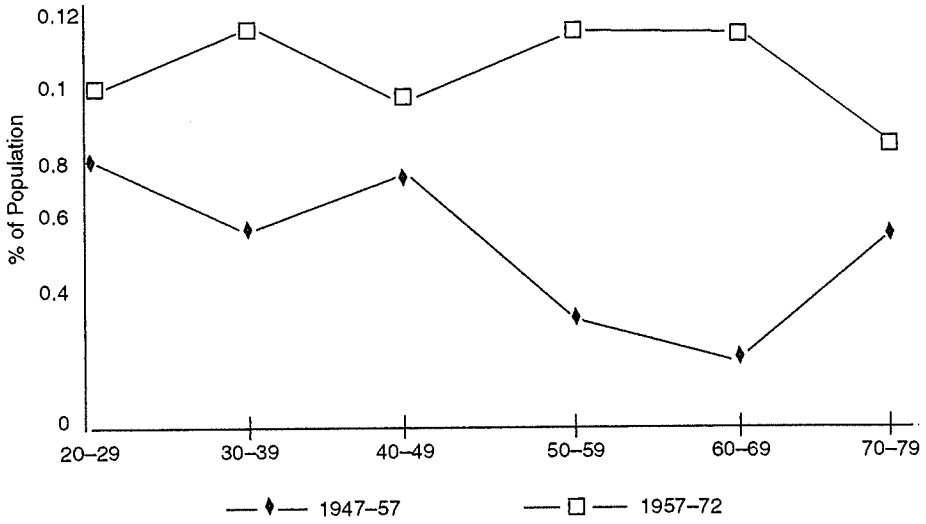

FIGURE 14.2-7 Risk of contracting a first-onset depressive disorder for younger birth cohorts and older birth cohorts in Sweden. (Data derived from Hagnell O, Lanke J, Rorsman B, Ojesjo L: Are we entering an age of melancholy? Depressive illnesses in a prospective study epidemiological study over 25 years: The Lundby Study, Sweden. Psychol Med *12*:279, 1982.)

suicide because of economic impairment and lack of affiliative relations.)

Age effects are the biological and psychosocial factors that predispose an individual to develop a particular disorder during a specific part of the life cycle. (For example, the genetic predisposition to develop major depressive disorder is probably greatest during the 30s, whereas the predisposition to develop a bipolar disorder is greatest during the 20s.) Age-related changes in the brain, such as increased subcortical hyperintensities on brain magnetic resonance imaging, may also be associated with mood disorders. Perhaps the most consistently observed age effect relevant to mood disorders that has been observed during the 20th century is the positive association between age and suicide among white males in the United States.

Cohort effects are the relative differences in rates of illness across different generations. A cohort is usually defined by the year or decade of birth. Persons born in a given year may be at greater risk for an illness, such as major depressive disorder, throughout their lives. Suicide data reveal marked cohort trends throughout the 20th century. (For example, persons currently 75 to 85 years of age [approximately the birth cohorts of 1915 to 1925] have exhibited lower suicide rates at all ages than either the 1900 or the 1940 birth cohorts.)

Considerable statistical and methodological problems confound sorting out the relative contribution of period, age, and cohort effects upon the prevalence and incidence of mood disorders by age. First, these effects undoubtedly interact. Stressors during a particular period interact with age-related vulnerability. (For example, the current high rate of substance abuse among adolescents may reflect both the vulnerability of adolescents to substance abuse, an age effect, and the greater availability of drugs to adolescents, a period effect.) Second, older persons may not recognize major depressive episodes as such and so do not report them, thus setting the threshold for identifying depression among community-dwelling elders higher. Yet age does not appear to affect the rate of hospitalization for mood disorders. The more severe cases of major depressive disorder are hospitalized, regardless of age, and the relative cohort differences persist in hospitalization rates.

Most investigators have explained the current data as reflecting a period effect. They argue that the risk for depressive disorders increased dramatically for all ages from about 1965 to 1975 but has since stabilized at a higher incidence. Young persons are more vulnerable to that period effect, however, and therefore carry the greatest burden of depressive disorders. A young person who experiences a major depressive episode is likely to exhibit ongoing and severe depressive episodes for many years. Therefore, clinicians can expect to see the current cohort of younger persons bear the burden of major depressive disorder for a long time. Despite being the healthiest and most affluent generation of the 20th century, younger persons may be placed at greater risk for major depressive disorder by a number of environmental risk factors, including increased urbanization, increasing social isolation and anomie, changes in occupational roles and career trajectories for both men and women, increased secularization, and increasing geographic mobility.

IDENTIFICATION OF CAUSES

The risk factors for bipolar I disorder and major depressive disorder identified from community- and clinically based epidemiological studies are summarized in Table 14.2-2. Most have been replicated, yet some most interesting hypotheses about risk for mood disorders have failed to hold up with repeated study. For example, an increased risk for major depressive disorder was discovered in an isolated community of Hutterites who live near the border between the United States and Canada, suggesting that the rigid moral control they exert predisposes community members to depression. Most community studies, however, fail to find that identification with or participation in particular religious groups is associated with an increased risk for major depressive disorder. In contrast, virtually every community survey has demonstrated increased risk for major depressive disorder and depressive symptoms in persons who report negative life events.

DEMOGRAPHIC FACTORS

Sex Almost all community-based epidemiological surveys of mood disorders that compare prevalence by sex find that women are twice as likely as men to experience an episode of major depressive disorder. Few investigators discount this finding as an artifact of

Table 14.2-2
Risk Factors for Bipolar I Disorder and Major Depressive Disorder

Risk Factor	Bipolar I Disorder	Major Depressive Disorder
Gender	No effect	Women at greater risk than men
Race/ethnicity	No effect	No effect
Age	Young at greater risk	Young at greater risk
Socioeconomic status (SES)	Higher SES at somewhat greater risk	Lower SES at greater risk
Marital status	Separated and divorced at greater risk	Separated and divorced at greater risk
Family history	Persons with family history at greater risk	Persons with family history at greater risk
Childhood experiences	Bipolar patients may come from families with low perceived prestige in their community	Evidence that early parental death and disruptive childhood environment leads to major depression
Stressful life events	Negative stressful events associated with increased risk	Negative stressful events associated with increased risk
Chronic stress	No known effect	Chronic stress associated with increased risk
Absence of a confidant	No known effect	Absence of confidant leads to increased risk, especially in women
Residence	Greater risk in suburbs than in inner city	Greater risk in urban areas than in rural areas

prejudice in the diagnostic criteria for major depressive disorder or of increased help-seeking behavior among women. Yet female sex has not been demonstrated to be a risk factor per se. The social environment of women and a higher threshold for reporting depressive symptoms in men may account for the increased association. Yet, as discussed above, no mechanism for this apparent increased risk has been established.

Age The average age of onset for both major depressive disorder and bipolar disorders falls between 20 and 40 years. Recent studies also confirm that major depressive disorder can occur in childhood. Bipolar I disorder typically has an earlier age of onset than major depressive disorder, with an average of 30 years. Yet both major depressive disorder and bipolar disorder can first occur at any time during adulthood. Nothing suggests that young age per se places a person at greater risk for the mood disorders (though genetic factors may have their greatest influence at a younger age). Social factors appear to place younger persons at greater risk than elderly persons. Biological predisposition to major depressive disorder may actually increase with age.

Race and Ethnicity Race or ethnicity has not proved to be a significant risk factor for either bipolar I disorder or major depressive disorder. In some community surveys, African-Americans experience a higher prevalence of depressive symptoms. The racial difference usually disappears, however, when other factors, such as socioeconomic status, age, and residence, are controlled. Because treatment for mood disorders is less common for African-Americans than for whites, prevalence studies based on treatment samples usually contain proportionately more whites. Rates for major depression were estimated as higher among Hispanics than among whites and African-Americans in the NCS study in controlled analyses. To date, too few Asians have been included in community-based studies in North America and Europe to permit comparative estimates of risk for Asians. The similarity in overall rates across racial or ethnic groups does not necessarily mean a similarity across all symptoms. For example, older African-Americans have been found more likely to complain of interpersonal problems when depressed and less likely to complain of depressed mood than older whites.

Socioeconomic Status The findings from community-based studies relating to socioeconomic status as a risk factor for-depression are mixed. The overall ECA studies found only a weak correlation between major depressive disorder or bipolar disorders and lower socioeconomic status. The North Carolina ECA study, however, found a consistent relation between socioeconomic status and major depressive disorder, even when multiple potential confounders, such as race and residence, were controlled. In the NCS study, both lower income and education were associated with higher prevalence of major depression. Studies prior to the ECA and NCS found a consistent positive relation between lower socioeconomic status and depression. In one classic study reported by A.B. Hollingshead and Frederick C. Redlich, depressive symptoms were strongly associated with the lower social classes. In a more recent study, working-class women from an eastern suburb of London were much more likely to suffer depressive symptoms than women from higher social classes.

Marital Status Marital status appears to be one of the most consistent risk factors for both depressive symptoms and major depressive disorder. Rates for major depressive disorder are highest among separated and divorced persons and lowest among single and married persons. Recent widowhood is associated with higher rates of major depressive disorder across the life cycle. The risk appears to vary with sex. Single women have lower rates of depression than married women, whereas married men have lower rates than single men. However, the investigator must not confound marital status with the loss of a spouse through death or divorce (a stressful life event). If a woman was widowed during the 6 months prior to the study, then the event not the status is perhaps the causative factor. In addition, cause and effect may be reversed (e.g., depressive illness may place a person at greater risk for divorce). In most studies, however, separated or divorced status places a person at greater risk for depression, even if the marital breakup occurred long before the assessment. The ECA studies, unlike previous studies, also documented a much higher prevalence of bipolar disorders among separated and divorced persons than among those who were single. The highest rates, however, were found among those who were cohabiting, even when adjusting for age, sex, and race or ethnicity. The association of the mood disorders and marital status is also reflected in the association of mood disorders with household size. Major depressive disorder is twice as common among persons living alone than among those who live with others. In persons not living alone household size is not associated with depression.

Marital status may not be the proximal causative factor. The perception of social support and lack of conflict within the social network are critical factors in protecting against mood disorders. Longitudinal studies of the social network and neuroses have shown that

the most important predictors of depression are not the objective characteristics of the network but rather the perception of how adequately the network assisted the person. Large-scale community-based investigations of the risk factors for major depressive disorder cannot disentangle the subtleties of the complex interactions between persons and their social network. (For example, dissolution of a difficult marriage may relieve long-standing depressive symptoms.)

Family History Most epidemiological studies of treatment samples have shown a consistent increase in family history of mood disorders among subjects, especially in first-degree relatives. A family history of suicide and alcoholism has also been repeatedly found to be more common among depressed subjects than among controls. Most experts attribute the increased risk for depression when family history is positive to a genetic predisposition; yet shared family environment may also contribute to the increased risk. Genetic transmission is much more firmly established for bipolar I disorder than for major depressive disorder. In family members of bipolar subjects, both bipolar disorder and major depressive disorder are more prevalent.

Early Childhood Experience Much attention has been directed to the association of early childhood experience with onset of mood disorders later in life. Although the complexities of a psychodynamic investigation of childhood traumas cannot be applied in community-based epidemiological studies, even cursory investigation of childhood experiences has revealed correlates. Parental loss before adolescence is a well-documented risk factor for adult-onset depression. A deprived and disrupted home environment also constitutes a risk. Methodological problems make objective study of childhood trauma and deprivation difficult. Some events (e.g., divorce or separation of parents) can be documented reliably, but others (e.g., parental neglect) are quite subjective. The report of parental neglect by a depressed adult may vary depending on the respondent's emotional state at the time of the interview.

Personality Attributes Personality attributes are closely associated with early childhood experience as a risk for mood disorders in later life. Persons predisposed to develop a depressive disorder lack energy, are more introverted, worry, are more dependent, and are hypersensitive. Major depressive disorder is also frequently comorbid with the Axis II disorders; yet the study of the relation of depression and personality is confounded by the time at which personality is studied. Epidemiologists rarely have the opportunity to assess personality before the onset of the first episode of depression. If personality is assessed during an episode of depression, then the depressive symptoms mask certain personality traits and exaggerate others. When a person has experienced and recovered from a depressive episode, its impact on personality makes accurate assessment of premorbid personality difficult. (For example, the personality characteristics associated with depression are exactly those that might emerge in response to the experience of a serious psychiatric disorder.)

Social Stressors Social stressors have received more attention than other risk factors for major depressive disorder across the life cycle, except sex. Three kinds of social stressors can be distinguished: life events, chronic stress, and daily hassles. Life events are the kind most often explored in epidemiological studies. They are identifiable, discrete changes in life patterns that disrupt the usual behavior and threaten the person's well-being. Bereavement, the reaction to loss of a loved one, is the prototypic stressful life event. Chronic stress includes long-term conditions that challenge the person, including financial deprivation, ongoing interpersonal difficulties (e.g., conflict in the workplace), and persistent threat to security (e.g., living in a dangerous neighborhood). Daily hassles are ordinary but stressful occurrences that are ubiquitous in modern life (e.g., managing household finances and unpleasant interactions with neighbors).

Most epidemiological studies reveal a relation between stressful life events, especially negative events, and the onset and outcome of major depressive disorder. Nevertheless, the use of stressful life event scales such as the Schedule of Recent Events introduces many potential biases into the study of stressors and depression. Such scales usually tally the number of events and weight them according to a predetermined algorithm. Most schedules weight events on the basis of normative data from the population. Because the data usually derive from weightings provided by young adults, they do not necessarily apply across the life cycle. (For example, retirement in late life may be a positive event, whereas premature retirement in midlife may present problems that can precipitate a depressive disorder.)

The perception of the event is probably more important than the event itself. More-sensitive measures of stressful events document not only the event itself but the subject's response to it. Was the event perceived to be positive or negative? Even the death of a spouse may be viewed as a positive event if it occurred after a protracted and disabling illness during which the subject was the caretaker. Was the event perceived to be important or unimportant? For some older persons a move may be extremely traumatic, especially if it is the first move in half a century. For others, a move may be a usual and relatively unimportant event, especially in a society in which mobility is becoming more the norm. Was the event expected or unexpected? If income decreases at retirement at a rate expected by the retiree, then the loss of income is much less stressful than if a person is forced to take an unexpected cut in salary while still in the workforce.

The accumulation of stressful negative life events does appear to predispose a person to episodes of major depressive disorder. In a study from New Haven, depressed patients had an average increased frequency of eight life events during the 6 months preceding the onset of depressive symptoms. Those events included marital arguments, marital separation, starting a new type of work, change in work conditions, serious personal illness, death of an immediate family member, serious illness of family members, and a family member leaving home. Stressful events are also associated with the persistence of depressive disorders. In a study from England, adverse events during the year following the initial episode of depression were associated with a poorer outcome of the episode. The adverse effects of life events may be offset by neutralizing events. (For example, if a woman loses her job but soon after finds another job with equal pay and benefits, then the adverse event is neutralized.)

In addition, the impact of a stressful life event may vary depending upon when that event occurs in the natural history of a mood disorder. Persons experiencing a recurrent major depressive disorder are less likely to report a stressful event associated with the onset of episodes after the first two episodes of depression. The phenomena of kindling may become the predominant impetus for recurrent depressive episode.

Chronic stress can place a subject at greater risk for major depressive disorder than specific stressful life events. The stress of service in the Persian Gulf War led to increased frequency of major depressive disorder among military personnel. As long as soldiers are de-

ployed, they have difficulty recovering from the major depressive episode. In addition, the long-term effects of being deployed also may increase the risk of depression following military service. Persons usually have more difficulty coping with a chronic stressful situation than with specific events.

Few studies document the association of daily hassles with the onset of major depressive disorder. Yet, impulsive acts such as a suicide attempt may be closely associated with daily hassles to which the subject cannot adapt within the context of a stressful life event or chronic stress. That is, daily hassles may be the straw that breaks the camel's back.

Social Support Factors in the social environment that may modify the effects of social stressors have received increased attention in the epidemiological investigation of both physical and psychiatric disorders. One factor is social support, the provision of meaningful, appropriate, and protective feedback from the social environment that enables a person to negotiate environmental stressors. In theory, social support is an attractive concept, for it is potentially more amenable to intervention than environmental stressors. The roots of the construct social support go back at least to the early twentieth century, when Emile Durkheim proposed that persons who are not integrated into society (the condition called "anomie") are at greater risk for suicide. Social support has four components: the social network, social interaction, perceived social support, and instrumental support. The social network is assessed by identifying those individuals or groups of individuals (e.g., a spouse and children) who are available to the subject. The absence of a spouse is a risk factor for major depressive disorder.

Social interaction is assessed by determining the frequency of interactions between the subject and other network members. A number of studies confirm that social isolation (i.e., a deficit in social interaction) places a subject at greater risk for depression. Yet the quality of the interaction appears to be more important than the frequency of interaction. Perceived social support is assessed by determining the subjective evaluation by the individual of the dependability of the social network, the ease of interaction with the network, the sense of belonging to the network, and the sense of intimacy with network members. The association of major depressive disorder and expressed absence of a confidant exemplifies the relation between perceived inadequate support and depression.

Instrumental support is assessed by determining the concrete and observable services that are provided to the subject by the social network (for example, cooking meals, financial assistance, and nursing services for the physically ill). Although such support is essential to the well-being of the young and the elderly in society, few studies document the association of depression with a deprivation of instrumental support. The physical health of the person is a confounding factor. The need for instrumental support is usually not recognized until the person exhibits an actual need for such services. In addition, the perception of the availability of those services in a time of crisis may not reflect the actual availability.

The construct of social support is strongly influenced by the construct of social integration. An integrated society is a social system that ensures the patterns of interpersonal behavior that are essential to the survival and welfare of its members. Those patterns enable persons to obtain what is needed for subsistence and protection against weather and disease, control hostility and other forms of social disruption, create new members and their education and communication, store information, and permit decision making and united action. Alexander Leighton and his colleagues undertook the most ambitious epidemiological studies of social integration and mental health in a survey of communities in Nova Scotia. Social scientists and anthropologists studied each community to determine its relative integration versus disintegration. At all ages, the rates of depressive disorders (and other psychiatric disorders) were higher in disintegrated communities. Studies of social integration are not as proximal to the individual as studies of social stressors and social support because measures of social integration are not specific to the individual. Studies of integration are ecological, for they document that the overall functioning of the community is associated with the overall level of psychopathology.

Most ecological studies in psychiatric epidemiology have been limited to comparisons of communities by traditional parameters, most commonly, urban versus rural residence. The hypothesis is that rural communities are less stressful than urban communities. In the ECA study of North Carolina, major depressive disorder was twice as common in the urban community, with the largest differences among the young (under 45 years of age) and among women. Those urban-rural differences in prevalence persisted even when the comparison was controlled for race, socioeconomic status, marital status, and age. Nevertheless, most ecological studies fail to demonstrate that after adjusting for other factors, communities determined to be socially integrated protect against mood disorders. The reason, probably, is that investigators are usually studying diverse communities and thus the concept of social integration is probably not relevant in complex societies in which communities are layered upon one another or are patterned together in a mosaic that cannot be easily disaggregated.

Another risk factor for depression is unemployment. At present, most men and women under the age of 65 are in the labor force. Men and women who were unemployed for at least 6 months during the 5 years prior to the ECA survey were more than three times as likely as others to report symptoms of an episode of major depressive disorder during the year prior to the survey. In the NCS study, the rate of major depression was three times higher in persons not working than in those working. Homemakers were nearly three times more likely to experience major depression than the employed as well.

The multiple risk factors for mood disorders form a web of causation. Each factor cannot only affect the subject directly but can interact with other factors. Mathematical models of causative factors are therefore useful for determining the relative importance and complex interaction of those factors. Models include linear and logistic regression analyses.

An example is presented in Table 14.2-3. In this logistic regression analysis, sex, education, income, marital status, employment, and household composition are the control (or adjusted) variables. The net effect of risk factors in the NCS is presented as an odds ratio, an approximation of the relative risk of persons with the characteristic developing a major depressive episode compared with that of persons without the characteristic. For example, the risk for females is 1.36 times greater than that for males.

PROGNOSIS

Two recent studies have concentrated on the public health impact of depressive disorders, because of their chronic and disabling nature. In the first, over 1000 patients in a variety of primary care settings were screened for depression. Patients with either depressive disorder or depressive symptoms (without a diagnosis of a specific mood disorder) tended to have worse physical, social, and role functioning. When their objective health status was controlled, they perceived their current health to be worse than did patients who were not de-

Table 14.2-3
Adjusted Odds Ratios for Prevalence of Current (30-day) Major Depressive Episode, by Selected Demographic Characteristics

Characteristic	Odds Ratio	95% Confidence Level
Sex	1.00	–
Male		
Female	1.36[a]	1.01–1.84
Education (years)		
0–11	1.93[a]	1.14–3.25
12	1.93[a]	1.14–3.25
13–15	1.93[a]	1.14–3.25
16 or more	1.00	–
Marital status		
Married	0.42[a]	0.28–0.61
Separated/widowed/divorced	1.00	–
Never married	0.58[a]	0.38–0.88
Employment		
Working	1.00	–
Student	1.00	–
Homemaker	2.40[a]	1.54–3.75
Other	2.54[a]	1.51–4.28

Adapted from Blazer DG, Kessler RC, McGonagle KA, Swartz MS: The prevalence of major depression in a national community sample: The National Comorbidity Survey. Am J Psychiatry *151:* 979, 1994.
[a] $p < .05$

pressed, and they reported more physical pain. The poor functioning associated with depressive symptoms, with or without a diagnosis of a mood disorder, was comparable to or worse than that in eight major chronic medical conditions. The number of days in bed with depressive symptoms was significantly greater than with hypertension, diabetes, or arthritis.

In the second study, the ECA sample in North Carolina, persons with a diagnosis of major depressive disorder or dysthymic disorder and with symptoms of minor depressive disorder were followed for 1 year. Compared with asymptomatic individuals, persons with major depressive disorder had a fivefold greater risk of disability, and persons with minor depressive disorder had one-and-one-half times the risk. Persons with minor depressive disorder were at greater risk of developing major depressive disorder at 1-year follow-up.

A number of *natural history* studies of mood disorders have been performed on clinical samples. The most extensively studied cohort derives from the Psychobiology of Depression Study and consists of over 500 young adult and middle-aged subjects diagnosed with either bipolar I disorder or major depressive disorder. Following diagnosis about 50 percent of subjects recovered during the first year, but fewer than 30 percent of the others recovered during subsequent years. Comorbid dysthymic disorder with a slow onset accompanying psychotic symptoms was associated with less likelihood for recovery. Relapse rates are high for major depressive disorder immediately following recovery. Superimposed dysthymic disorder and a history of three or more major depressive episodes were associated with relapse. Bipolar I disorder patients with only manic episodes had better outcomes than those with major depressive disorder. However, bipolar I patients with a mixed episode (depression and mania) or with rapid cycling had worse outcomes than those with major depressive disorder.

USE OF HEALTH SERVICES

Health services for mood disorders are provided in general health care settings and in specialty settings. Most mental health visits reported by subjects in the ECA study, regardless of disorder, occurred in primary care settings for older persons and in specialty settings for younger persons. Women use mental health services in both settings about twice as often as men. Visits are about equally distributed between general medical providers and mental health specialists. Persons who were depressed used health services more frequently than those with no psychiatric disorder.

SUGGESTED CROSS-REFERENCES

An overview of epidemiology is given in section 5.1. Social origins of mood disorders are discussed in Section 4.2. Classification of mental disorders is presented in Chapter 9. Specific review of the genetics of mood disorders can be found in Section 14.3. The role of stress in the etiology of psychiatric disorders is discussed in Section 25.9. Suicide is discussed in detail in Section 29.1. The epidemiology of psychiatric disorders in late life is reviewed in Section 51.1b.

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▲ 14.3 Mood Disorders: Genetics

JOHN R. KELSOE, M.D.

The familial nature of mood disorders has been a widely observed phenomenon since antiquity. However, only in the last century have systematic studies been conducted that document the degree and nature of this familiality as well as its genetic determinants. In the past two decades molecular genetic technology has brought a new era in the understanding of a wide range of genetic traits and disorders. The application of this technology promises a new, more fundamental understanding of biological etiology of mood disorders and may also produce revolutions in both diagnosis and treatment. Yet mood disorders and other psychiatric disorders are difficult problems for genetic analysis, and early attempts at such analysis using both epidemiological and molecular tools have yielded sometimes contradictory and confusing results. However, as the volume of data increases and more sophisticated analytical methods are used these large problems should become more tractable so the benefits of this approach can be realized.

GENETIC EPIDEMIOLOGY

By determining the rates of illness in different types of relatives, genetic epidemiological studies can provide much information about the familial and genetic nature of a disorder. The questions that can be addressed include: Are mood disorders familial? Are they genetic? What portion of the etiology is genetic? How are the genes for mood disorder transmitted? How do different forms of mood disorder differ in their genetic transmission? How are different forms of mood disorder related to each other?

Numerous such studies conducted over the last century provide much information about the genetic transmission of mood disorders. However, these studies have various methodological limitations. Foremost among these is the range of diagnostic methods used. Many of these studies were conducted before the distinction between depressive (unipolar) and bipolar disorders, and hence results of these studies pool both illnesses. Similarly, many of these studies preceded the introduction of operationalized diagnostic criteria. Therefore, it may not be clear exactly how the diagnoses were made, making it difficult to compare or pool results across studies. Of the studies that distinguish unipolar and bipolar disorder, bipolar disorder has received more attention because of its greater degree of familiality.

Another methodological issue important to such studies is ascertainment bias. If the results of a study are to be meaningfully generalized to the population, the subjects must be selected in a systematic and nonbiased fashion. For example, if *probands* (the first ill subject identified in a family) are selected on the basis of their strong family history, then the results of a family study may inaccurately indicate a strong familial rate of illness in the population. A similar error will be made if ill family members are preferentially selected for study. Systematic ascertainment methods attempt to avoid such bias by studying all patients who present within a certain environment, such as a mood disorders clinic.

Many of these studies are also limited by use of the family history method. In this approach, the rates of illness in family members of probands are determined by systematically questioning probands about their families. Though several excellent standardized instruments for the family history method exist, this method is inherently less accurate than using direct interviews of each family member to make a diagnosis.

Family Studies Family studies address the question of whether a disorder is familial. More specifically, is the rate of illness in the family members of someone with the disorder greater than that of the general population? Typically, all subjects with the disorder in a given environment or population are identified and questioned about illness in their first-degree relatives. The rates of illness are then compared with either the rates in the general population or the rates in first-degree relatives of control subjects. Rates of illness are typically adjusted for age to indicate the morbid risk (i.e., the risk that an individual will develop an illness at some point of his or her life).

Table 14.3-1 illustrates several such studies of bipolar disorders. They indicate a morbid risk of bipolar disorder in first-degree relatives of bipolar disorder probands that ranges between 3 and 8 percent. Compared with a 1 percent rate in the general population, this reflects a substantial familial increase. Similarly, studies of families of probands with depressive disorder (unipolar) reveal morbid risks for depressive disorders among first-degree relatives which are two to three times those of the general population. These data argue strongly for the familial nature of mood disorders. Furthermore, depressive disorders generally occur at a higher rate in the families of probands with bipolar disorders, and the rate of bipolar disorder is

Table 14.3-1
Selected Family Studies of Bipolar Disorders

Study	Relatives at Risk (*N*)	Morbid Risk (%)	
		Bipolar	Depressive (Unipolar)
Dunner et al, 1980	1199	4.2	8.2
Gershon et al, 1982	598	8.0	14.9
Rice et al, 1987	557	5.7	23.0*
Sadovnick et al, 1994	1102	3.5	5.7

* Observed rates rather than morbid risk.

elevated in the families of probands with depressive disorders. In fact, depressive disorders are typically the most common mood disorder in families of probands with bipolar disorders. This familial overlap suggests some common genetic underpinnings between these two forms of mood disorder.

Twin Studies The family study data clearly indicate that mood disorders are familial. However, such studies cannot distinguish whether genetic or environmental factors mediate the familial transmission. Families might share a variety of different environmental factors that could transmit the illness. Such factors might be behavioral but could also be shared exposure to infectious agents, toxins, or other brain insults. Twin studies provide the most powerful approach to separating genetic from environmental factors, or "nature" from "nurture." Many strategies for twin studies have been used, but most commonly both monozygotic (MZ) and same-sex dizygotic (DZ) twin pairs are identified in which one twin has a mood disorder. The other twins are then examined to determine the proportion of twin pairs in which both twins are affected, termed the *concordance rate*. Typically, twin pairs are selected who have been raised together, so that environmental factors are shared equally. A difference in concordance rate between the MZ and DZ pairs, therefore, reflects the role of heritable genetic factors. An alternative powerful strategy is to study twin pairs raised apart; however, such samples are much more difficult to obtain.

Table 14.3-2 summarizes several twin studies of mood disorders. Considering depressive and bipolar disorders together, these studies find that the concordance rate for mood disorder in the MZ twins is two to four times that in the DZ twins. These are the most compelling data for the role of genetic factors in mood disorders. Further, the concordance rate for MZ twins is not 100 percent. Thus nonheritable environmental factors also play a significant role in mood disorders. In studies that distinguish bipolar from unipolar disorders, the MZ to DZ concordance ratio for bipolar-bipolar pairs is higher than that for unipolar-unipolar pairs, which indicates greater genetic involvement in bipolar disorders than in unipolar depressive disorders. Furthermore, the rate of depressive disorders is elevated in monozygotic cotwins of probands with bipolar disorders, and to a lesser extent, the rate of bipolar disorders is elevated in the cotwins of probands with depressive disorders. This is consistent with the family data, and it argues for a genetic overlap between bipolar and depressive disorders.

Adoption Studies Adoption studies provide an alternative approach to separating genetic and environmental factors in familial transmission. A variety of limitations of twin studies have been raised, including the argument that parents treat monozygotic twins and DZ twins differently, so environment is not equally shared. Adoption studies have been conducted using a variety of experimental designs, but the most common is the adoptee-as-proband strategy. In this approach, probands are identified who have a mood disorder and who were adopted away at birth, thus separating nature and nurture. The rates of psychiatric illness are then determined in both the biological and adoptive parents.

Only a limited number of such studies have been reported, and their results have been mixed. Julien Mendlewicz and John Ranier found a threefold increase in the rate of bipolar disorders in the biological relatives of probands with bipolar disorders. They also observed a twofold increase in the rate of depressive disorders in biological relatives. Similarly, in a Danish sample, Paul Wender and coworkers reported a threefold increase in the rate of unipolar disorder and a sixfold increase in the rate of completed suicide in the biological relatives of mood disorder probands. Other studies, however, have been less convincing. Using affectively ill mothers as probands, Remi Cadoret found a nonsignificant trend toward increased unipolar depressive disorders in the adopted children. In a Swedish sample, Anne-Liis Von Knorring and coworkers found no increase in mood disorders in the biological parents of adoptees with mood disorders. Overall, these results support the role of genetics and are consistent with the twin data. The difficulty of obtaining subjects and the resulting small sample sizes may help explain why these data are weaker than the twin data.

Table 14.3-2
Selected Twin Studies of Mood Disorders

	Monozygotic Twins		Dizygotic Twins	
Study	Twin Pairs (*N*)	Concordance (%)	Twin Pairs (*N*)	Concordance (%)
Rosanoff et al, 1935	23	69.6	67	16.4
Kallman, 1954	27	92.6	55	23.6
Bertelsen, 1979	55	58.3	52	17.3
Kendler et al, 1993	154	69.7	326	34.9

MODE OF TRANSMISSION

If mood disorders are in large part caused by genetic factors, then what is the nature of its genetic transmission? Segregation analysis of the family study data has been used to attempt to answer this question. Are mood disorders the result of one or a few genes transmitted in a mendelian fashion? Or do many genes interact within each individual to predispose to illness? Different modes of transmission result in different patterns of inheritance of illness. By examining these patterns in families, one may attempt to distinguish the different possible modes of transmission. For example, in a simple dominant genetic disorder, one expects to observe that half of the children of an affected parent are also affected. In a recessive disorder, only one-quarter of the children of two nonaffected carriers should be affected. More-complex modes of inheritance involving multiple genes result in other patterns of illness that can be sought in the family data. Typically, in segregation analysis, the predicted patterns of several different models of transmission are tested to see which best fits the observed family data.

The results of such analyses have been mixed. Several such analyses have been inconclusive and excluded all tested models of transmission. Other, more recent analyses using large samples and more-sophisticated genetic models have supported the presence of an autosomal dominant major locus. Most such studies have focused on bipolar disorders because of their greater heritability. However, a recent segregation analysis of early-onset, recurrent depressive disorder has supported the presence of major gene effects with autosomal recessive or codominant modes of transmission. Other studies have supported a multifactorial-threshold model for mood disorders. In these models, the additive effects of multiple genes produce a unitary predisposition common to all mood disorders. Different mood disorders result at different thresholds in this single underlying genetic liability. X-linkage has also been argued based on the observation that female relatives of probands with bipolar disorders have a twofold higher risk for disorders than males. This is also supported by evidence for decreased male to male transmission of bipolar disor-

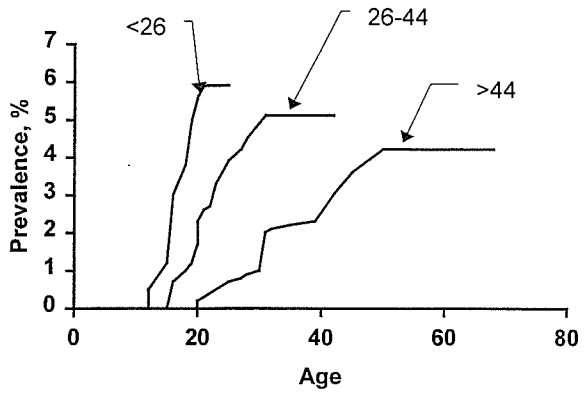

FIGURE 14.3-1 Age-related penetrance curves for bipolar disorder. The risk for bipolar disorder among relatives of bipolar disorder probands is depicted as a function of age. The probability of having bipolar disorder, or penetrance, increases with age. The cohort effect is illustrated by the different age-dependent risk curves for relatives within three different age groups. Relatives born more recently have a higher rate of bipolar disorder and an earlier age of onset. (Reprinted with permission from Rice J, Reich T, Andreasen NC, Endicott J, van Eerdewegh M, Fishman R, Hirshfeld RM, Klerman GL: The familial transmission of bipolar illness. Arch Gen Psychiatry *44*:441, 1987.)

ders. Drawing any definitive conclusions from such complex and inconsistent data is difficult. The complexity likely results from the presence of multiple genes with multiple modes of transmission. In the face of such heterogeneity, the sample sizes and statistical methods used may have limited power to demonstrate a given mode of transmission consistently. The data do suggest that of the many genes probably operating in mood disorders, some have a major effect on predisposition, and in bipolar disorders these major genes are likely to have autosomal dominant or perhaps X-linked inheritance. Consistent with such heterogeneity, recent analyses have argued for more-complex modes of transmission in which multiple genes interact to predispose to illness.

Several other intriguing results emerge from the family study data. Subjects with mood disorders are more likely to marry spouses who also have mood disorders than is expected by chance. This is termed *assortative mating,* and it leads to a higher rate of families in which the illness can be traced to both the mother's and the father's side of the family than would be expected by chance. Such bilineal families may play an important role in the interaction of multiple genes in the population. Family studies have also indicated that the rate of mood disorders is increasing over time in the population, termed the *cohort effect* (Fig. 14.3-1). Among family members of probands with bipolar disorders, those born more recently have a higher risk for bipolar disorders and an earlier age of onset. The cause of the cohort effect is unknown. It has been speculated to be a result of changing environmental stresses in our society, an artifact of recollection, or possibly an indication of a genetic effect termed *anticipation.*

GENETIC RELATIONSHIPS WITHIN THE SPECTRUM OF MOOD DISORDERS

The genetic relation between the various forms of mood disorder has received much study and debate. Bipolar and depressive disorders are widely considered to have some sort of common genetic underpinning, though its exact nature is unclear. The twin and family data reviewed above argue for more depressive disorders occurring in the twins or other relatives of probands with bipolar disorders than is expected by chance. However, it is less clear that bipolar disorders occur in the relatives of probands with depressive disorders at an elevated rate. Twin studies indicate that polarity is usually consistent in MZ twins (i.e., bipolar-bipolar or unipolar-unipolar pairs are much more common than bipolar-unipolar pairs. Yet bipolar-unipolar pairs do occur. These data suggest that bipolar and unipolar disorders are genetically neither completely identical nor completely distinct. Rather, there is a partial genetic similarity. A possible model for the relationship between these genes and disorders is illustrated in Figure 14.3-2. In this model, some or all of the genes for bipolar disorders may also result in depressive disorders. In addition, a larger pool of genes predisposes only to depressive disorders. Therefore, the rate of unipolar disorder would be clearly elevated in families with bipolar disorder. However, because only a minority of cases of unipolar disorder result from bipolar genes, only a small increase in the rate of bipolar disorders would be seen in the relatives of probands with depressive disorders. Such overlapping relationships between genes and disorders may also occur for other forms of mood disorders. A more definitive understanding of these relationships will likely require identification of the specific genes involved.

This model predicts that a portion of those with unipolar disorder carry genes that may also predispose to bipolar disorder. Such patients have been said to have "bipolar III" disorder by some writers and have been the subject of much discussion and investigation. They are presumably identified by a family history of bipolar disorder or a history of developing hypomania or mania only in response to antidepressant treatment. Similarly, Hagop Akiskal and coworkers have described a hypomanic-like personality style termed *hyperthymic temperament.* Depressive disorder patients with hyperthymic temperament likely carry some bipolar disorder genes. Such hyperthymic-depressive patients are more likely to have a family history of bipolar disorder and to develop mania spontaneously. These depressive disorder patients with a bipolar disorder genetic diathesis may also be more likely to respond to lithium augmentation of antidepressant treatment.

Other forms of mood disorders have also been postulated to be at least somewhat genetically distinct. Several studies have reported that though the risk for bipolar I disorder is similar in the relatives of probands with bipolar I or bipolar II disorder, the risk for bipolar

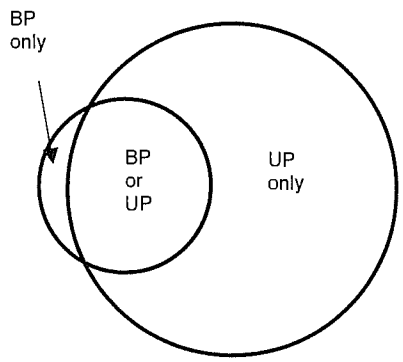

FIGURE 14.3-2 This model of the relation between genes for bipolar and depressive disorders posits that most genes for bipolar disorders can predispose to either bipolar or depressive disorders. A larger set of genes predisposes only to unipolar disorder. Hence, a subset of those with depressive disorders carries genes that may also predispose to bipolar disorders.

II disorder is greater than that for bipolar I disorder in the relatives of probands with bipolar II disorder. This suggests that bipolar II disorder to some extent breeds true and that a subset of the genes for bipolar disorders predispose preferentially to bipolar II disorder. However, studies of patients with rapid-cycling bipolar disorder find that rapid cycling in the proband does not affect the risk for mood disorders or rapid cycling in relatives. This argues that rapid cycling is not a distinct genetic subform of bipolar disorder.

The genetic relation of schizoaffective disorder to mood disorders is a complex question that involves the role of psychosis in the genetics of mood disorders. The genetic nature of schizoaffective disorder also bears on the genetic relation between schizophrenia and mood disorders. Studies examining familial risks in relatives of schizoaffective disorder patients have led to inconsistent results, some finding an increased risk of schizophrenia and some an increased risk of bipolar disorder. A possible explanation is that patients with schizoaffective disorder represent a mixture, some with bipolar and some with schizophrenia diatheses. This notion is supported by data that show an increased rate of bipolar disorders among relatives of probands with the bipolar type of schizoaffective disorder. The rate of schizophrenia has also been reported to be increased among the relatives of probands with the depressive type of schizoaffective disorder. Alternatively, it has been proposed that the Kraepelinian distinction between the disorders is not valid and that schizophrenia and mood disorders lie at the extremes of a spectrum of a common genetic liability. Recent linkage studies (reviewed below) may be beginning to support the existence of some genetic loci common to both schizophrenia and bipolar disorders.

INTERPRETATIONS OF THE GENETIC FEATURES OF MOOD DISORDERS

The above data argue that mood disorders are not simple genetic traits. No one gene consistently causes illness in all cases in a simple and predictable fashion. In genetic terms, there is not a 1 to 1 relation between the expressed trait (phenotype) and genes (genotype) transmitted in a simple mendelian fashion. Therefore, mood disorders are said to be complex genetic disorders rather than simple mendelian traits. What factors contribute to this complexity?

The twin data argue compellingly that genes account for only 50 to 70 percent of the etiology of mood disorders. Environment or other nonheritable factors must explain the remainder. Thus, a predisposition or susceptibility to disease is inherited. The probability that someone will manifest a trait, given that they have a certain genotype, is termed the *penetrance* of the gene. Mood disorders are said to have "reduced penetrance" (less than 100 percent). Furthermore, the penetrance of the mood disorder genes increases from a low risk for illness in childhood to a maximum in adulthood. The cohort effect (Fig. 14.3-1) further complicates the relation of penetrance to age, causing penetrance to vary with the date of birth. Therefore, families of people with mood disorders likely include individuals who have the genes for mood disorder but do not develop the disease. These are termed *nonpenetrant carriers.* The converse of this situation is individuals who have mood disorder but do not have the genes. Individuals with purely environmentally caused disease are termed *phenocopies.* These factors conspire to produce an indirect relationship between genes and disease.

Variable expressivity refers to the phenomenon of the same gene or group of genes resulting in a variety of different forms of illness. The twin data clearly demonstrate this for mood disorders. Monozygotic twins with identical genomes are observed with one twin exhibiting bipolar and the other unipolar disorder. Nonheritable factors must play a role in the specific manifestation of the predisposition to mood disorder. Such variability in expression is not unique to psychiatric disorders. In neurofibromatosis, for example, ill individuals range in manifestations and severity from those with only pigmented retinal lesions to others with multiple large tumors—a range in expression that results from the same disease gene.

Of the various factors complicating the genetic transmission of mood disorders, the most significant and the most challenging for gene mapping efforts is genetic heterogeneity. *Heterogeneity* refers to the likely occurrence of multiple genes in the etiology of illness. Only the identification of multiple disease genes can convincingly demonstrate genetic heterogeneity. However, the segregation analyses described above strongly suggest its presence. There are several critical questions about the nature of heterogeneity in mood disorders. How many genes are involved? How large an effect does each gene have? How do the genes interact to produce illness? These questions suggest a variety of models of heterogeneity, which can be broadly grouped into those in which disease results from a few genes with major effects (major loci) and those in which disease derives from the combined action of many genes with small effects (polygenic or oligogenic). The answers to these questions are not currently known for mood disorders. However, segregation analyses suggest a mixture of genes of both large and small effect, which are transmitted in a variety of ways.

Evidence for several other complex forms of genetic transmission has also been reported for mood disorders. Some studies of bipolar disorder have indicated that the illness is more likely to be transmitted through mothers than through fathers. Such *parent-of-origin effects* imply a genetic phenomenon called *imprinting.* In imprinting, a genetic locus is processed differently in male and female meioses so that different traits result from maternal and paternal transmission. For example Angelman and Prader-Willi syndromes are two different mental retardation syndromes that result from different maternal or paternal imprinting of the same locus on chromosome 15. Rather than yielding different phenotypes, the bipolar data suggest that the penetrance of bipolar genes may be affected by imprinting.

Another nonmendelian genetic phenomenon reported in mood disorders is anticipation. In disorders displaying *anticipation,* the severity of the illness increases and the age of onset decreases with successive generations. Anticipation is generally associated with genetic mutations involving trinucleotide repeat expansions. In such disorders (e.g., Huntington's disease or fragile X mental retardation), the defective gene contains a region of deoxyribonucleic acid (DNA) in which a three-nucleotide sequence is repeated a variable number of times. For reasons currently not well understood, the number of repeats increases in successive generations until the gene's function is disrupted and illness results. Anticipation involving both increasing severity of illness and decreasing age of onset has been reported for bipolar disorder. Indirect evidence for the presence of trinucleotide repeat expansions has also been reported; however, no specific gene manifesting such a mutation has been described.

COMPLEX GENETIC DISORDERS

Simple Mendelian Traits Complex genetic disorders are simply those that are not transmitted in classical mendelian patterns. A review of mendelian transmission thus provides a useful background for understanding complex genetic traits. Simple mendelian traits display genetic homogeneity; one gene transmits the trait with complete penetrance. Figure 14.3-3 illustrates the three primary

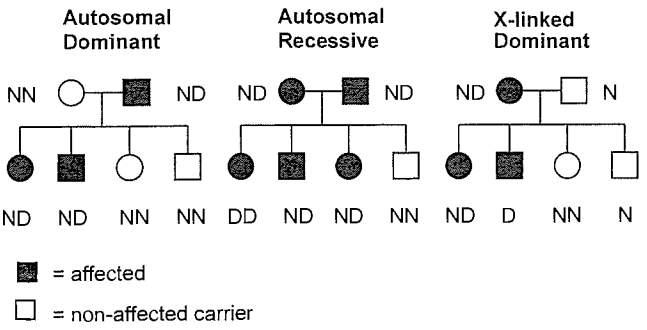

FIGURE 14.3-3 Mendelian transmission. Simple mendelian disorders are transmitted by three different modes. Dominant disorders require only one copy of the disease allele for a family member to be affected. In recessive disorders, both copies of the disease gene must be defective. In X-linked disorders, the disease gene is carried on the X chromosome.

modes of mendelian transmission. In genetic terminology, different forms of a given gene are termed *alleles*. A disease gene may have either a normal, nonmutated allele or a mutated, disease-causing allele. In dominant genetic disorders, only one copy of the disease allele is necessary to cause illness. Dominant illnesses are typically transmitted vertically from grandparent to parent to child. In the simplest case, half of the children of an affected parent will have the disease. In recessive disorders, both copies of the disease gene must be defective for disease to result. Heterozygotes with only one disease allele are nonaffected carriers. Disease typically results from the mating of two nonaffected carriers. One-quarter of the resulting children will be homozygous for the disease allele and hence ill. Recessive illnesses typically appear in a horizontal pattern in families (i.e., in cousins). The nature of the mutation in the gene determines whether it is transmitted in a dominant or recessive fashion. Recessive mutations typically deactivate genes that are expressed in excess. Therefore, an adequate amount of gene product can be produced by only one functioning copy. In dominant disorders, the amount of gene product expressed may be critical. A reduction in gene dosage, resulting from only one functioning copy, leads to illness. Alternatively, a dominant mutation may result in overfunctioning of the gene, which results in illness. In X-linked disorders the disease gene is located on the X chromosome. These may be either dominant or recessive. X-linked dominant disorders are more common in women, while X-linked recessive disorders are more common in men. Father to son transmission is impossible in X-linked disorders, since the father transmits the Y sex chromosome to sons.

Heterogeneity Models Of the various factors that distinguish complex disorders from mendelian ones, the most important is the presence of multiple genes, or genetic heterogeneity. Multiple genes may combine to produce illness in a variety of different ways, as illustrated in Figure 14.3-4. These heterogeneity models fall into two categories based on genetic effect size. In single major locus models, only one disease gene is necessary to produce illness in a given individual. In an interfamilial heterogeneity model, one gene transmits the predisposition to illness in each family. However, there are different predisposing genes in different families. In an intrafamilial heterogeneity model, any one of multiple genes within the same family can transmit the illness.

In oligogenic or polygenic transmission models, multiple genes of smaller effect interact to predispose to illness. In these models, one gene by itself is unlikely to cause illness. Rather, the probability of illness increases with the number of different genes involved. The terms "oligogenic" and "polygenic" are distinguished simply by whether a smaller or larger number of genes, respectively, are involved. In an additive polygenic model, each gene contributes a certain probability (penetrance) of manifesting the disorder. The total genetic liability to illness is then the sum of the probabilities contributed by all the polygenes. In Figure 14.3-4, under the additive model, the disease alleles for genes A and B alone each convey a 40 percent probability of illness. Individuals who carry the disease alleles for both A and B have an 80 percent risk for illness. The total risk is simply the sum of the risks for each individual polygene. In the epistatic model, the disease alleles at genes A and B each convey a relatively small effect alone. However, individuals with the disease alleles for both A and B have a risk for illness that exceeds the sum of risks for A and B. In the example in Figure 14.3-4, A and B each convey a 20 percent risk alone. The affected daughter with the AB genotype, however, has an 80 percent risk for illness. Epistatic interactions have been observed in many organisms and frequently reflect a "two-hit" effect on a biological system. For example, a neurotransmitter system may be able to tolerate a defect in gene A by increasing the activity of gene B. Similarly gene B may be able to compensate for a defect in A, so that individuals with defects in A or B alone may have only a limited risk for illness. However, if both A and B are defective, the system cannot compensate, and the risk for illness escalates.

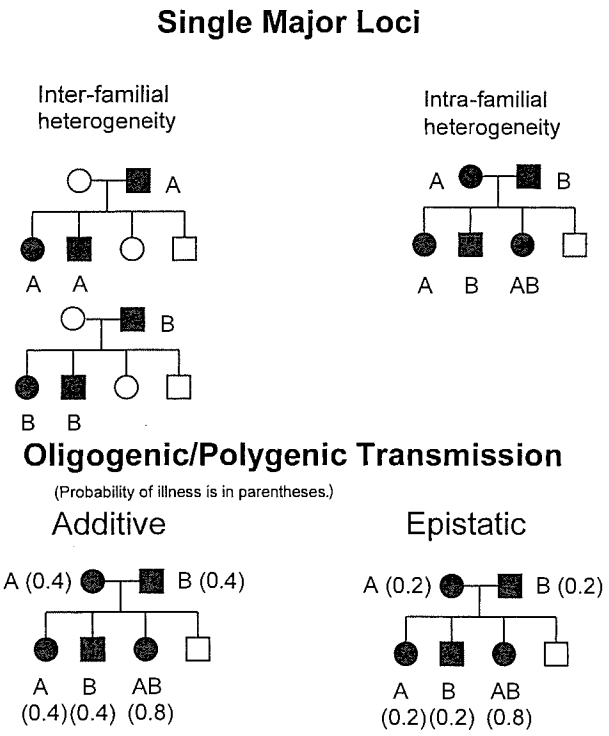

FIGURE 14.3-4 Several different models for the role of multiple genes in genetic disorders. In single major locus heterogeneity models, a single gene is primarily responsible for the predisposition to illness in an individual. However, different single major loci may act in different families or within the same family. In oligogenic models, multiple genes each of smaller effect typically interact to produce the susceptibility to illness. In an additive model, the effects of these genes simply add together. In epistatic models, the overall effect exceeds the sum of each gene acting separately.

Quantitative Traits One of the many difficulties in psychiatric genetics studies is the definition of "affected." Variable expressivity results in a variety of disorders from similar genotypes, and is frequently not clear which of these disorders should be considered "affected" for the purposes of genetic analyses. An alternative to such dichotomous definitions of phenotype is the use of quantitative phenotypes. Many biological variables are obvious quantitative phenotypes (e.g., blood pressure or height). However, it is not immediately obvious which mood disorder is "worse" or "more" than another. Nevertheless, quantitative phenotypes have been applied with some success to mood disorders. An example is the multiple-threshold model. Though quantitative phenotypes can result from single major loci, the concept has evolved historically in connection with polygenic traits. In such models, each polygene contributes in either an additive or epistatic fashion to the value of the quantitative phenotype. Quantitative models offer a useful alternative to the dichotomous approach to phenotype. However, the basic problem is that mood disorder phenotypes are more complex than either the dichotomous or quantitative genetic models.

POSITIONAL CLONING OF COMPLEX DISORDERS

Positional cloning refers to the use of molecular genetic methods to identify disease genes based on their chromosomal location. Such studies, directed at the identification of specific disease genes, are the focus of most recent research on the genetics of mood disorders. The methods and strategies of positional cloning are reviewed in more detail elsewhere in this text, but a brief description here prefaces a review of the problems faced in such studies of mood disorders and some of their potential solutions.

DNA markers are segments of DNA of known chromosomal location that are highly variable among individuals. They are used to track the segregation of specific chromosomal regions within families affected with a disorder. When a marker is identified whose alleles consistently cosegregate with disease in families, it is said to be *genetically linked,* which implies that a gene for the disorder is physically near the marker on a chromosome. The Human Genome Project has provided thousands of such markers and precisely mapped them to chromosomal locations. By using several hundred markers, one can systematically survey the genome in search of markers linked to a disease. In this fashion, novel disease genes can be identified on the basis of their chromosomal location rather than their physiological function. This ability to identify novel genes without relying on knowledge of their function or the pathophysiology of the disorder makes positional cloning a powerful approach. This approach has led to the successful identification of genes for numerous diseases such as Huntington's disease and cystic fibrosis.

The statistics of linkage analysis are either parametric or nonparametric. *Parametric analyses* assume a certain model of inheritance (e.g., dominant or recessive) and then test the marker data for the probability of fitting that assumed model. The statistic typically generated is the LOD score. The *LOD score* is the logarithm of the odds for linkage divided by the odds against linkage. A LOD score of 3 represents odds of 10_3 or 1000 to 1 in favor of linkage. The appropriate threshold for statistical significance of LOD scores varies with the nature of the analysis and is currently under some debate, but is in the range of 3.0 to 3.6. Nonparametric analyses do not require an assumption of model of inheritance. Instead, affected family members are tested for significantly increased sharing of marker alleles. The affected sib pair method and the affected pedigree member method exemplify this approach. Parametric methods generally have greater power to detect linkage if the correct model is used. Nonparametric methods have less power but are not vulnerable to error resulting from the use of an incorrect model of inheritance.

When a chromosomal region is identified by genetic linkage studies in families, the disease gene has typically been localized to a region of between 5 and 30 million base pairs of DNA, which might contain several hundred genes. Genetic association studies are then sometimes used to locate the disease gene more precisely within this region. In these studies, markers are tested for significant differences in the frequencies of their alleles between unrelated groups of affected subjects and control subjects. Such differences may be observed if the DNA-sequence variation at the marker is the disease causing mutation itself. Alternatively, the marker allele may have no functional impact, but be so physically close to the disease causing mutation that they have been propagated together through the population. The marker allele and disease mutation are then said to be in *linkage disequilibrium.* In addition to fine mapping, association is also commonly used to test the role of a candidate gene whose known function suggests its possible involvement in the disorder. Physical mapping methods are also used to identify the exact disease gene. These methods involve cloning large regions of DNA and screening them for the presence of genes and possible disease-causing mutations in those genes.

Difficulties of Mapping Complex Disorders Simple mendelian traits show a 1 to 1 correspondence between genotype and phenotype. Everyone in a family who has the disorder has the gene, and everyone who has the gene has the disorder. This allows extraction of maximal information regarding the possible cosegregation of marker and disorder in linkage studies. However, both reduced penetrance and phenocopies loosen the connection between genotype and phenotype and thus reduce the statistical power of linkage methods to identify genes. In complex disorders, it is neither clear that nonaffected individuals did not receive the disease allele nor that affected ones did. Thus one needs to study larger samples of families.

Variable expressivity and difficulty in diagnosis introduce further uncertainty in modeling genetic transmission. It is not clear which of the spectrum of mood disorders should be considered "affected." If the definition of affected is too narrow, then valuable information from family members with more subtle forms of illness may be lost. However, if the definition of affected is too broad, then error may be introduced by inclusion of too many phenocopies. Most linkage studies currently use a hierarchy of different definitions of illness, ranging from narrow to broad. For example, a narrow model might include as affected only those with bipolar disorder. A broad model would include bipolar disorder and recurrent major depression. The difficulty in making behavioral diagnoses adds further complexities. Psychiatric diagnoses rely on the accuracy of the subject's memories and judgments about behavior that depend on the individual's life and environment.

Other difficulties arise out of the limitations of statistical methods. The most powerful statistical methods currently available are based on mendelian models of transmission. However, it seems clear that mood disorders are not transmitted according to these simple models. Currently most linkage studies are conducted using a variety of genetic models (e.g., dominant and recessive). However, only limited information is available about the robustness of applying these methods to nonmendelian and heterogeneous forms of transmission. Furthermore, recent simulation studies have indicated that even when linkage is established, a much larger chromosomal region is impli-

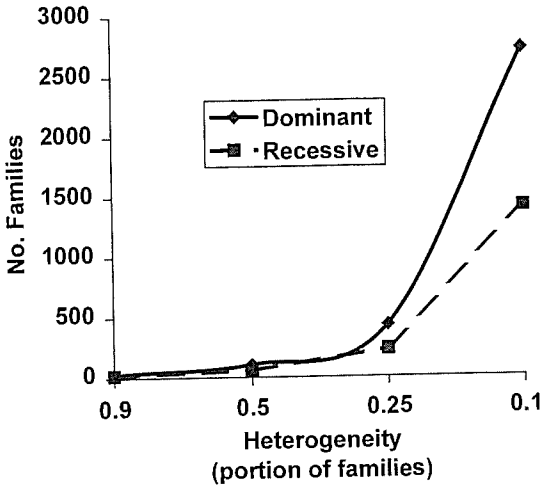

FIGURE 14.3-5 Sample sizes required to detect linkage for different degrees of heterogeneity. The number of families with affected sib pairs required to detect linkage is depicted as a function of the degree of genetic heterogeneity. This power analysis for genetic linkage studies was performed by computer simulation of both an autosomal dominant and a recessive disorder with 50 percent penetrance. If a gene for a disorder occurs in less than 25 percent of families, the number of families required to detect it in a linkage study goes up substantially. (Reprinted with permission from Martinez MM, Goldin LR: The detection of linkage and heterogeneity in nuclear families for complex disorders: One versus two marker loci. Am J Hum Genet *44*:552, 1986.)

cated in complex disorders than in mendelian ones. This makes the job of fine mapping and gene identification substantially larger.

The greatest problem facing positional cloning studies is clearly heterogeneity. If mood disorders result from a relatively small number of genes with large effect, then they will be identified soon. However, if a large number of genes with small effect are involved, identifying them will require large sample sizes or a different approach altogether. Current data suggest that the number of genes probably lies somewhere between these extremes. The cost of heterogeneity in terms of sample size is illustrated in Figure 14.3-5. This simulation study, using affected sib pairs, indicates that if a gene is present in less than 25 percent of families under study, the total number of families required to detect linkage increases significantly.

Solutions for Mapping Complex Disorders Despite these problems, recently developed tools and strategies for linkage studies of complex traits promise to make the challenges of mood disorders more tractable. Many of these new developments involve using more-sophisticated statistical methods. Parametric methods have recently been developed that can model the interaction of two genes simultaneously. In this way, the power of parametric analytical methods can be applied to more-complex modes of inheritance. However, as more genes are included, the number of possible models for their interaction increases. This may make the choice of the correct model both more difficult and more important.

For these reasons, nonparametric methods have recently received increasing attention. Since they do not depend on assumptions about the mode of transmission, they are less vulnerable to error resulting from use of the wrong model. However, they have lower statistical power to detect genes than do parametric methods using the correct model. Much effort has been focused on developing new nonparametric methods with greater statistical power. There is no current agreement on which approach is superior. As a result, many investigators use both approaches.

Various approaches to refining the phenotype may improve the odds of success in linkage studies. Studying subforms of illness, whose genetic distinctness is supported by epidemiological data, may allow investigators to reduce the number of genes under study. For example, bipolar II disorder or lithium-responsive illness may represent distinct subsets of bipolar genes. Such subforms of illness may be easier to map. Intermediate phenotypes may also be useful in this regard. *Intermediate phenotypes* are biologic markers associated with illness that segregate in families. Sleep electroencephalographic (EEG) measures and sensitivity to various pharmacological challenges exemplify such possible markers. Intermediate phenotypes can be used to identify psychiatrically well family members who carry susceptibility genes. In this way, these biological markers display higher penetrance than the psychiatric disorder itself and, therefore, retrieve more genetic information from family members. Furthermore, they may also reflect biologically distinct subforms of illness.

The rapid progress of the Human Genome Project will provide new tools for genetic studies. The quality of markers and maps continues to improve. It is likely that within the next several years, all human genes will be identified and mapped, which will be invaluable for the identification of disease genes. The next wave of the Human Genome Project will develop a dense set of markers that will ultimately enable genome-wide association studies. By studying tens of thousands of markers in thousands of ill and control subjects, genes of small effect may be identified. Until recently, such an approach was not considered feasible; however, now both the dense map of markers and the technology for high-throughput screening seem in sight. Methods are now being developed to array genes or DNA markers on microchips allowing the simultaneous detection of thousands of markers. Ultimately, one can expect that most sequence variation in all human genes will be known. This knowledge combined with large samples for association studies should enable detection of virtually all genes involved in mood disorders, even if current linkage strategies are not successful.

RESULTS OF GENETIC LINKAGE AND ASSOCIATION STUDIES

To date the search for genes for mood disorders has focuse primarily on bipolar disorder because of the stronger evidence fo its genetic basis. In its early years, this search exhibited a series o ups and downs of reported findings and subsequent nonreplication that was likened to the highs and lows of the illness itself. Suc high-profile nonreplications led to frustration among investigator and concern that false-positive linkage results might be commor Many investigators argued for highly conservative thresholds for th statistical significance of linkage results to guard adequately agains such events. However, subsequent experience has indicated tha strongly positive results are relatively uncommon. Furthermor simulation studies indicate that nonreplications should be expecte even for real loci, until enough data are accumulated to demonstra linkage convincingly.

Recently a number of positive results have emerged that are qui encouraging in terms of the ability of linkage analysis to identif genes for bipolar disorder. As more of the genome has been surveye in larger sets of families, several loci have yielded modest evidenc for linkage, which is being independently replicated in multiple dat sets. It seems likely that at least some of these loci reflect the locatio of real susceptibility genes; therefore, it seems appropriate to expe

Table 14.3-3
Summary of Loci Potentially Linked to Bipolar Disorders

Chromosome	Reference	Result
11p15	Egeland et al, 1987; Kelsoe et al, 1989	Original LOD of 4.08 reduced to 1.69 on reexamination of core pedigree
11p15, Tyrosine hydroxylase	Leboyer et al, 1990 Gurling et al, 1995	Positive association LOD 3.58—two-locus analysis with D21S171
Xq28	Baron et al, 1987; Baron et al, 1993	Diminished evidence, LOD 2.09
Xq26	Pekkarinen et al, 1995	LOD 3.1
	Nurnberger et al, 1997	ASP*, $P < .05$
18p	Berrettini et al, 1994	LOD 2.6, sig. APM & ASP*
18p, 18q	Stine et al, 1995	LOD 3.51, in paternal pedigrees
18q22–23	Freimer et al, 1996	LOD 3.7
21q22.3	Straub et al, 1994	LOD 3.4, sig. APM & ASP*
	Gurling et al, 1995	LOD 3.58—two-locus analysis with TH
	Nurnberger et al, 1997	ASP*, $P < .05$
12q23–24 Darier's disease	Dawson et al, 1995 Barden 1998	LOD 1.6 LOD 4.9
22q11	Lachman et al, 1996 Nurnberger et al, 1997	LOD 2.5 LOD 2.46
4p16	Blackwood et al, 1996	LOD 4.1
16p13	Ewald et al, 1995 Nurnberger et al, 1997	LOD 2.65, multipoint ASP*, $P < .01$
5p15, Dopamine transporter	Kelsoe et al, 1996	LOD 2.38
5q35	Coon et al, 1993	LOD 1.1
6pter-p24	Ginns et al, 1996	LOD 2.46
13q13	Ginns et al, 1996	LOD 1.6
15q11-qter	Ginns et al, 1996	LOD 1.7

* APM, affected pedigree member method; ASP, affected sib pair method.

some nonreplications. The road to linkage success may involve neither too-readily dismissing modestly positive results nor too readily accepting strongly positive results but rather seeking independent confirmation. Some of the more prominent of these possible bipolar loci are summarized in Table 14.3-3 and reviewed below. The most notable aspect of the summary in Table 14.3-3 is the number of loci that have support from multiple independent datasets. Only time, further data, and the identification of actual disease genes will determine which of these are real disease loci.

THE HIGHS AND LOWS OF PAST BIPOLAR LINKAGE STUDIES

Chromosomes 11 and X The first molecular genetic linkage study of mood disorder was conducted in the Old Order Amish population of southeastern Pennsylvania. Bipolar disorders are no more common or different in presentation in the Amish than in the general population. The Amish were chosen for study because they were genetically isolated. The current population of approximately 30,000 Amish are descended from about 50 couples who immigrated nearly 300 years ago from Germany and Switzerland. Since that time, for religious reasons, this group has remained isolated from the surrounding population. The primary advantage of studying such a group is the reduced genetic heterogeneity that results from a founder effect with subsequent genetic isolation. Other advantages of studying this group are its large families and the virtual absence of substance abuse. In 1987, Janice Egeland and coworkers reported evidence for linkage of bipolar disorders to markers at the insulin and Harvey *ras* loci on 11p15. Their data yielded an LOD score of nearly 5, or odds of 100,000 to 1 in favor of linkage. However, numerous other studies in different populations failed to replicate this result. Subsequently, reexamination of an updated and expanded version of the same Amish pedigree substantially reduced the evidence for linkage. Recently, however, association and linkage studies of the nearby tyrosine hydroxylase locus have supported the existence of a bipolar disorder locus in this region.

A similar scenario played out in studies of the X chromosome. Much epidemiological data has suggested a possible X-linked locus for bipolar disorder. In 1987, Meron Baron and coworkers examined two nonmolecular X chromosomes markers, color blindness and glucose-6-phosphate dehydrogenase (G6PD), for linkage to bipolar disorder in a set of Israeli families. They found very strong evidence for linkage to these markers on Xq28. However, as with the Amish study, numerous other studies failed to replicate this result in different samples. Subsequently, the evidence for linkage was substantially reduced when several more-informative molecular genetic markers were examined. More recently, however, several studies have implicated a nearby region, Xq26, in studies of American and Finnish families. Therefore, despite their checkered history, evidence remains for both the 11p15 and Xq26–28 regions, but more data will be required to confirm these possible linkages.

Chromosome 18 One of the most intriguing regions for possible bipolar susceptibility loci is on chromosome 18. Currently this region has the strongest data for linkage, because of the number of independent replications. Evidence for linkage to the pericentromeric region of chromosome 18 was first found by Wade Berrettini and coworkers in a series of 21 North American pedigrees. Subsequently, other studies replicated this finding and identified two more-distal regions on 18q. Some of these reports have found that the evidence for linkage was stronger in families with paternal or mixed transmission than in those with only maternal transmission. These data suggest a parent-of-origin effect at this locus. Other studies have argued that the evidence for linkage to chromosome 18 markers is strongest in families with comorbid panic disorder. Such data begin to suggest that different susceptibility loci may predispose to different forms of bipolar disorder with distinct clinical presentations. It is currently unclear whether these three different reported regions reflect three different susceptibility loci or if one or more reflect false-positive results. However, given the amount of independent data implicating this chromosome, it seems very likely that at least one locus for bipolar disorder resides on chromosome 18.

Other Promising Genetic Loci Several other chromosomal regions have been implicated by multiple studies and may harbor bipolar susceptibility loci. Linkage to the marker PFKL on chromosome 21q was first reported by Richard Straub and coworkers, with most of the evidence coming from one extended pedigree.

Subsequently, linkage to this region was replicated in several other studies. A locus for bipolar disorder on chromosome 12 was implicated initially by the serendipitous observation of cosegregation of bipolar disorder and a dermatological disorder, Darier's disease, in a Welsh family. Subsequently, Darier's disease was mapped to chromosome 12. Based on this observation, a set of Welsh families with bipolar disorder and without Darier's disease were studied, and modest evidence for linkage to the same region of chromosome 12 was obtained. Recently, Nicholas Barden and coworkers implicated this same region in a study of a large family from a population isolate in Quebec.

A region on 22q is interesting because it has been implicated in both bipolar disorder and schizophrenia. This region was originally investigated in schizophrenia because of the observation of psychosis in adolescents with the 22q11 deletion syndrome, velocardiofacial syndrome. Several studies have reported evidence of linkage of markers in this region to schizophrenia; other investigators have examined adolescents with velocardiofaciol syndrome and observed rapid-cycling mood disorders. Based on these data, Herbert Lachman and coworkers studied this region in a set of bipolar disorder families and found evidence suggesting linkage. A subsequent study of an expanded version of this family set has further strengthened this result. The National Institute of Mental Health (NIMH) consortium also reported evidence for linkage of bipolar disorders to 22q. Similar to these results on chromosome 22, the same regions on chromosome 13 and 18 have also been implicated in studies of both bipolar disorders and schizophrenia. This raises the intriguing possibility that some genes may play a role in the susceptibility to both disorders. Confirmation of this idea awaits further replication and the definitive identification of disease genes. However, if confirmed, these results may indicate a greater degree of genetic commonality between these two disorders than had been thought.

The dopamine transporter has been implicated in bipolar disorders in a recent linkage study by John Kelsoe and coworkers. Its role as an important regulator of dopamine neurotransmission and the site of action of such stimulants as cocaine and amphetamine, make the dopamine transporter a compelling candidate gene. This gene has also been associated with attention-deficit/hyperactivity disorder in children, which occurs with greater frequency in families with bipolar disorder.

Several complete genome surveys were reported recently that have added substantially to the bipolar linkage data now available. Several additional loci were implicated by these studies including markers on 5q and 4p. A genome survey of the Old Order Amish recently provided data for possible loci on chromosomes 6, 13, and 15. The NIMH Consortium for Linkage Studies of Bipolar Disorder recently reported its initial findings in one of the largest such datasets examined to date, suggesting new loci on chromosomes 1, 6, 7, and 10. Perhaps more importantly, their data support previously reported loci on 16, 21, 22, and X. Such possible replications imply that some genes for mood disorders have relatively large effect and will be detectable by current linkage strategies.

GENETIC COUNSELING

Based on the observation of psychiatric illness in their own families or the increasing public awareness of psychiatric genetics, patients frequently ask clinicians three questions: Are mood disorders genetic? What is the risk to my children or grandchildren? Is there a blood test for the gene? The answer to the last question is the easiest, currently no blood test is available. However, such a test is likely to be available in the future, and it will raise a variety of serious practical and ethical issues. The answer to the first question is also easy: Yes, mood disorders are genetic, a position defended by the large body of epidemiological data summarized in this chapter. However, patients must understand that mood disorders are only partly genetic. The twin studies argue strongly that only 50 to 70 percent of the etiology of mood disorders is genetic. Therefore, a predisposition to illness is inherited that interacts with other, nonheritable factors.

The risk to children and grandchildren is a difficult question that deserves the greatest consideration. The family data indicate that if one parent has a mood disorder, a child's risk for mood disorder is between 10 and 25 percent. If both parents are affected, this risk roughly doubles. A careful family history is needed for more accurate prediction of risk for a specific family. Several factors from the family history should be considered. The more members of the family that are affected, the greater the risk to a child, particularly if the disorder is in both parents' families. The risk is greater if the affected family members are first-degree relatives rather than more distant relatives. A family history of bipolar disorder conveys a greater risk for mood disorders in general and a much greater risk for bipolar disorder specifically. The presence of more-severe illness in the family also probably conveys a greater risk. All these factors should be considered in forming an estimate of risk for the concerned parent.

Equally important to providing the estimate of risk is providing guidance in interpreting and responding to that information. Patients' reactions to risk information vary greatly depending on their own experience with the illness. Some will be relieved to find it so low, others fearful because it is so high. One must emphasize that their child carries a risk or predisposition to illness, not a certainty of illness. One can also describe the range of illness from mild to severe that could result and the availability and efficacy of treatment. Ultimately, the use of such information in family planning is a highly personal decision. Some patients may choose not to have children. For existing children, parents should be told about the typical age of onset, presenting symptoms, and the importance of early recognition and treatment. However, this must be balanced with the goal of not labeling the child or being overly protective.

FUTURE DIRECTIONS

The gradual accumulation of a large body of data led to the successful identification of possible disease loci described above. Therefore, in the near future, gene mapping studies will likely continue to use current strategies. As still more data are accumulated, more reported loci will likely be confirmed, while others will prove false. It currently seems promising that many genes for mood disorders can be identified through such large, though tractable, projects. The development and study of the large samples required will necessitate large collaborative efforts between multiple groups of investigators using common diagnostic and genetic methods. The recent NIMH consortium is a model for such future collaborations.

The variety of methodological advances and alternative approaches detailed above may further advance the project. Larger sets of family and genotypic data will enable application of new, more-sophisticated statistical methods. Larger datasets will also permit the possible subdividing of the disease into subforms based on clinical or biological measures. The rapid advance of the Human Genome Project will greatly facilitate this work by providing a much denser set of markers, a detailed physical map of the genome, and more efficient genotyping and sequencing methods. Ultimately, the identification and mapping of all human genes, the complete sequence of the human genome, and a catalog of human genetic variation will enable development of powerful novel approaches to complex disorders. Such tools and large samples will likely permit identification of most genes for mood disorders in the next several decades.

What will be the implications of this knowledge? The most immediate impact may well be on public opinion. Psychiatrically ill persons have long suffered from the stigma and discrimination that portions of the public impose out of fear and ignorance. Acceptance of major mental illnesses as brain disorders has been slow. The definitive identification of genetic causes may be highly beneficial to public understanding and acceptance.

This knowledge should also have a dramatic impact on our understanding of pathophysiology and approaches to treatment for mood disorders. Most current theories of pathophysiology are based on the mode of action of therapeutic agents, which were for the most part discovered serendipitously. The site of action of therapeutic drugs is not necessarily either the site of the genetic defect or the primary site of the pathophysiology. Identification of disease genes may point to entirely new systems involved in the pathophysiology or components of currently implicated systems that were previously unknown. It is hoped that such an understanding may lead to the rational drug design long sought by patients, clinicians, and pharmaceutical companies. The result may be new drugs that act by completely novel mechanisms, possibly with greater efficacy and specificity. Further down the genetic road lies the prospect of gene therapy for mood disorders. In this approach, DNA is used as a therapeutic agent, delivered to the relevant tissues by engineered viruses or other vectors. Such artificially delivered DNA can provide the correct version of a defective disease gene. Alternatively, a disease process might be ameliorated by changing the expression of other regulatory genes. Such an approach goes straight to the root of biology and pathology and offers the prospect of an extremely powerful and completely new treatment modality. Application to psychiatric disorders faces formidable problems and is likely to occur in the relatively distant future. However, trials of gene therapy for other, simpler disorders are going on today.

The identification of disease genes will probably have a major impact on diagnosis and nosology. Just as the diagnosis of jaundice has given way to a classification scheme based on pathophysiology, in the future, the diagnosis of major mood disorders may be specific to disease mechanism. Mechanism-specific diagnoses may dictate the use of different, more specific and effective treatments. The field of pharmacogenetics promises genetic tests able to predict the best pharmacological treatment for specific patients based on an understanding of genetic differences in drug response. But such knowledge will also carry danger and responsibility. Premorbid DNA testing could become available that would indicate the degree of genetic vulnerability to major mood disorders. Those with psychiatric disorders will then face the same issues of genetic testing currently faced by families with Huntington's disease or breast cancer. Will at-risk family members want such information? How will they use it? How will they cope with it? How can psychiatrists assist them in these decisions? How can patients be protected from discrimination based on such information?

In summary, genetic studies promise a new era of understanding and treatment of mood disorders. Identification of genes will not elucidate pathophysiology. It will merely point the way for the application of modern neuroscience methods in the equally large task of understanding mechanisms. Recent results suggest that such guidance may not be far away.

SUGGESTED CROSS-REFERENCES

A general review of basic molecular genetics is provided in Section 1.10. Principles of population genetics are discussed in Section 1.17. The concepts and methods of linkage analysis and their application to psychiatry are reviewed in 1.18. The epidemiology of mood disorders is discussed in Section 14.2.

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▲ 14.4 Mood Disorders: Neurobiology

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The role of physical or biological factors in the pathogenesis of depression has been suspected since antiquity. However, it has only been in the latter half of the twentieth century that the technology and experimental methodology have been available to study these processes in mood disorder. During the past 40 years knowledge about the biology of the depressive disorders has grown by leaps and bounds as experimental methods have advanced from studies assaying peripheral specimens to investigations employing more direct measurements of cerebral metabolism, receptor function, and gene activity; regarding mania and bipolar disorders, however, there is comparatively less data.

CLINICAL PHENOMENOLOGY AND THE BRAIN

The signs, symptoms, and subjective experiences of depressed people have long suggested dysfunction of core neurobiological processes. At one level depression involves multiple disturbances of information processing. People who are severely depressed automatically interpret experiences negatively and their access to memories is similarly biased. Cognition and problem-solving skills are further compromised by poor concentration, loss of abstraction, and decreased ability to perform effortful mental tasks. The virtual monologue of negative thoughts and images is often difficult to disrupt and, unlike normal sadness, ventilation to a confidante typically has little beneficial effect. In more extreme cases, delusions or hallucinations grossly distort reality testing. Mental life is thus disturbed by simultaneous excesses and deficits of activity in specific cortical regions, including the hippocampus, prefrontal cortex, and other limbic structures.

Many severe depressions are characterized by a loss of mood reactivity. In essence, something that should elicit an uplift in mood does not do so. One correlate of this phenomenon is an apparent loss of reinforcer salience. Hedonic deficits also are apparent in a loss of gusto for food or sex and there can be significant weight loss, especially in the elderly. These disturbances point to abnormalities in neuroregulatory circuits involving the hypothalamus, nucleus accumbens, and thalamus.

Another correlate of decreased mood reactivity is a fixity or slowing of expression, initiation of activity, and spontaneous movement. This loss of animation, called *psychomotor retardation,* is sometimes confounded by a superimposed state of "driven" psychomotor agitation. These stereotypic behaviors characteristically include biting at the nailbeds or lips, a furrowed brow, tugging at one's hair, and purposeless scratching, in addition to the pacing and frequent postural shifts that accompany most states of dysphoric arousal. Like hedonic deficits, psychomotor disturbances are more commonly observed in older people with depression, with agitation typically seen in the most severe or psychotic depressive syndromes. These observable signs point to the probable involvement of circuits joining prefrontal cortex, thalamus, striatum, and basal ganglia.

Almost all depressed people report fatigue and an inability to feel refreshed by sleep. Some, particularly those under age 40, sleep excessively, whereas others, especially those over age 50, cannot maintain sleep or awaken spontaneously 1 to 2 hours earlier than desired. For those with such "terminal" insomnia, the morning hours are typically the worst of the day (i.e., *diurnal mood variation*). Such circadian disturbances strengthen the likelihood of thalamic dysregulation and also suggest abnormalities in the pons and medulla.

These signs and symptoms often coaggregate, which has formed the basis for several of the classical clinical subtypes of depression. Thus, anhedonia and psychomotor disturbances are more commonly associated with weight loss, middle and terminal insomnia, preservative ruminations, and diurnal mood disturbance, a constellation of the syndrome classified as an endogenous, autonomous, biological, psychotic, or vital depressive subtype. The fact that such depressions are slow to remit spontaneously, yet relatively responsive to electroconvulsive therapy (ECT), clearly reinforce perceptions of underlying biological abnormalities. Such depressions often appear to arise without provocation by a significant stressor, hence the presumption of an autonomous or endogenous etiology. The apparent stability of this syndrome over the centuries is recognized explicitly by the contemporary use of the ancient Greek term *melancholia,* even though black bile is no longer considered to be an etiological factor.

The depressions of early adult life tend to be "nonendogenous" and often seem to be imbedded with manifold psychosocial problems. Of course, an early age of onset may distort personality development and shape one's reportoire of coping skills, which increases the probability of handling stressors poorly. Moreover, such patients seem to elicit, provoke, or stumble into a disproportionately greater number of stressors. Historically, the association of an early age of onset with comorbid anxiety generally further solidified impressions of a conflicted or "neurotic depression." The presumed lesser role of biological factors in neurotic depression was further suggested by

less than gratifying responses to ECT and, when available, to tricyclic drugs. In addition to the nonendogenous and neurotic appellations, these early-onset depressions traditionally have been described as reactive, personal, or exogenous disorders. Many of these depressions run a chronic course that fluctuates between major and minor (dysthymic) levels.

Emerging data on the utility of new antidepressant drugs, particularly serotonergic agents, suggests that biological abnormalities of a different kind might be associated with nonendogenous depression.

A subset of nonendogenous depression was further described by "reverse" neurovegetative symptoms, namely, increased appetite, weight gain, and hypersomnolence. Such symptoms were considered uncommon in the late 1950s and 1960s and hence were referred to as *atypical.* However, as the average age of onset of depression declined into the early 20s and both research and practice has shifted to ambulatory settings, these atypical features are now commonplace. Reverse neurovegetative features are common in several forms of recurrent depression, including seasonal type (winter pattern), bipolar disorders, and major depressive disorder. These subtypes are characterized by an early age of onset and relatively poorer responses to tricyclic medications, as compared to monoamine oxidase inhibitors (MAOIs). Such observations suggest that differences in phenomenology could reflect more specific pathophysiological alterations that affect treatment response.

GENETIC FACTORS

Mood disorders clearly run in families and, as a result, both genetic and environmental influences must be considered. At present, it is well established that bipolar I disorder is more heritable than the other mood disorders, that an early age of onset is associated with greater heritability, and that heritable risk decreases in proportion to the amount of genetic material shared by members of a pedigree. Thus, identical twins have greater heritable risk than fraternal twins, who have a risk comparable to siblings and parents. First-degree relatives, in turn, have greater risk than half-siblings, grandparents, or cousins. Research on fraternal and identical twins or use of the adopted-away paradigm further suggests that heritable risk transcends environmental influences. Thus, vulnerability to mood disorders is, in some fashion, encoded in human deoxynucleic acid (DNA). The next generation of molecular genetic studies should help to identify the specific genes and gene products that influence this risk.

Although the significance of inherited vulnerability cannot be disputed, considerable variability exists both within and across groups with comparable risks. For example, in some at-risk pedigrees, alcohol use disorders and sociopathy are more common among male probands than depression. Among women, there is some evidence that environmental experiences may influence whether a generalized anxiety disorder or a depressive disorder is expressed. The late-onset mood disorders (i.e., those beginning past age 60) have relatively low rates of heritability. Even identical twins do not have 100 percent concordance of bipolar I disorder. Genetics therefore constitutes just one pathway of vulnerability or, perhaps more accurately, a foundation upon which other biopsychosocial risk factors may be expressed.

ETIOLOGY OF EMOTIONAL RESPONSES

The mood disorders are conditions in which normal emotional responses are distorted into more extreme and persistent manifestations. Some consider normal sadness to be an analogue of depressed mood, and elation the normal counterpart of manic euphoria. Continuity between normal and pathological mood states is illustrated by grief or bereavement. Grief is a universal experience, yet it can segue almost inexorably into a state that is so extreme and disabling that professional attention is warranted. Although there are less obvious natural parallels to mania, it is not uncommon for hypomania to go unrecognized. For others, the intensity of new romantic love is associated with changes in perception, cognition, behavior, and judgment that border on manic excitement. The euphorogenic effects of cocaine and other psychostimulants amply document that the "hard wiring" for manic states exists and is expressed if the individual is exposed to the right neurochemical milieu.

Predipositions to various emotional states, mood set points, appear to be partly heritable; this background emotional tone is referred to as *temperament.* Of particular importance to our current topic is a temperament characterized by excessive reactivity and behavioral inhibition, which can be recognized in infancy and is associated with enduring vulnerability to both depression, and anxiety, in adolescence and young adulthood. Similarly, onset of dysthymic traits in childhood presages extremely high rates of depressive and bipolar disorders in adolescence and adulthood. Modern theories of temperament and personality converage around several dimensions, including harm avoidance (neuroticism or behavioral inhibition). In bipolar disorders cyclothymic, extraverted, and novelty-seeking traits are more relevant.

There is now considerable evidence that the basic emotions are manifest across human cultures. The capacity to recognize such emotions in others can be observed so early in infancy that innate processes are undoubtedly implicated. Sadness and crying, for example, may be viewed as universal distress signals. Behaviors consistent with basic emotional states can also be observed in other mammals. For example, certain behavioral predispositions towards aggressivity (or passivity) and social dominance (or subordination) appear to extend across vertebrate species. By virtue of the large neocortex, *Homo sapiens* are distinguished by the capacity to integrate, abstract, and synthesize complex symbolic representations of life experiences; to communicate experiences in direct, abstract, and elaborated forms; and to develop and maintain a self-concept that guides behavior in relation to others and an anticipated future. The domains of competence are similarly broader and diverse. Whereas a highly competent primate may earn a position of dominance if placed in a new group, only the human may seek such a position by drafting a curriculum vitae and lobbying vigorously, and only humans can intentionally misrepresent their competence or motivations, or be affected by the larger social network's knowledge of their past performances.

The importance and intensity of human attachment bonds serves to facilitate the protracted task of childrearing and the necessary advantages of kinship. Indeed, for hundreds of thousands of years *Homo sapiens* adapted in a world in which the average life expectancy was less than 40 years and the infant mortality rate approached 50 percent. Although perhaps politically incorrect, it is not simply social Darwinism to suggest that necessary divisions of labor increased the chances of viable offspring and shaped evolution of gender differences in affectivity, affiliative behavior, and nuturance. Humans are also the slowest to mature of the mammals and functionally the most vulnerable and dependent upon caregivers for the longest period of time.

Having evolved over at least 900,000 years, humans must now deal with the massive changes in environment and social structure that have taken place much too rapidly for natural selection to keep pace. In relative terms, the breathtaking sociocultural and technological changes of the twentieth century have occurred in less than one ten-thousandth of human experience! The resulting complexity of human social systems thus often overtaxes the integrative capacities

of the large human neocortex. When such capacities are overwhelmed, humans have to cope and adapt with neural mechanisms that are phylogenetically similar to those of other mammals and vertebrates.

STRESS AND ANIMAL MODELS OF DEPRESSION

Studies of rodents, dogs, cats, and nonhuman primates have confirmed that acute stress responses are characterized by activation of central and peripheral components of two interactive psychoneuroendocrine systems, the cortical-hypothalamic-pituitary-adrenocortical axis and the cortical-sympathomedullary axis. Although such acute stress responses are more akin to fear and anxiety than depression, it is the concepts of uncontrollability and inescapability that link the responses of other mammals to stress to human depression. Whereas stress acutely signals threat, it is loss, the anticipation of loss, or hopelessness that elicits sadness and despair.

Acute stress activates noradrenergic cell bodies in the locus ceruleus, whose axons trigger increased noradrenergic output by the adrenal medulla. At a behavioral level there is heightened arousal, increased perceptual vigilance, and inhibition of consummatory activities such as hunger and sex.

Stress also elicits synthesis and release of corticotropin-releasing hormone from neurons in the hypothalamus and cerebral cortex. This hormone activates the pituitary-adrenocortical components of stress response by causing increased release and synthesis of cortisol, adrenocorticotrophic hormone, and other glucocorticoids, and it synergistically enhances locus ceruleus activity as well.

The acute response to stress is counterbalanced by homeostatic or adaptive mechanisms. These include feedback inhibition by glucocorticoid receptors in the hippocampus and pituitary, down-regulation of postsynaptic noradrenergic receptors, and inhibitory autoreceptors and heteroreceptors on presynaptic norepinephrine neurons. Parallel input from serotoninergic (5-HT) and γ-aminobutyric acid (GABA) neurons also exert dampening or inhibitory effects.

Exposure to prolonged, inescapable stress is associated with numerous adaptations and changes in neurobehavioral responses. Although corticosteroid levels may remain elevated, levels of norepinephrine, serotonin dopamine, and GABA in the brainstem and forebrain eventually decrease. Animals trapped in such a state cease trying to resist or escape, and show decreased grooming and appetitive behavior outside of the experimental situation. There are significant individual differences in development of such learned helplessness, as well as differences across pedigrees, or strains, and species. Nevertheless, antidepressant drugs have been shown to prevent, attenuate, or reverse learned helplessness across species.

Studies of the experiences of primates in the wild are more relevant to the stresses faced by people than a rat's response to inescapable painful electric shock. These naturalistic studies demonstrate that a fall from a dominant role within a primate social hierarchy is associated with increased cortical-hypothalamic-pituitary-adrenocortical activity and decreased 5 serotonin neurotransmission. In the wild, subordinate animals with low concentrations of the serotoninergic metabolites 5-hydroxyinoleacetic acid (5-HIAA) are likely to be more aggressive and less sexually active. Moreover, when social status is manipulated by creating a new group from a cohort of subordinate primates, a dominance hierarchy will emerge and the winner will experience a corresponding increase in serotonergic function. Conversely, during times of adversity such as drought or famine, the socially dominant primate experiences an increase in cortical-hypothalamic-pituitary-adrenocortical activity.

Early Adversity Physical, verbal, and sexual abuse have an indelible effect on the life trajectory. Although maltreatment has been well documented in the pathogenesis of posttraumatic stress disorder and borderline personality disorder, it now appears that such a history is also associated with an increased risk of depression.

Studies of animal models confirm that lasting alterations in neuroendocrine behavioral response can result from severe early stress. More recently this vulnerability has been linked to possible enduring changes in gene expression. Animal studies indicate that even transient periods of maternal deprivation can have a similar effect on subsequent response to stress. Early loss and neglect, a correlate of having been raised by parents with a mood disorder, is not uncommon in the history of mood disorder patients. How to integrate these clinical observations with the data on early stress in animals remains a challenge.

MONOAMINE DISTURBANCES

The area of scientific inquiry chosen is dependent on the knowledge base and experimental paradigms available to the investigator. In the early 1960s it was possible to measure catecholamine metabolites in body fluids and the principal indoleamine metabolite 5-HIAA in cerebrospinal fluid. However, the visualization of the functional brain was essentially impossible because waking electroencephalograms (EEGs) provided little useful information aside from documentation of epilepsy or diffusing slowing associated with delirium.

In addition, there were multiple lines of evidence from pharmacological studies implicating perturbations of monoamine systems in both therapeutic and iatrogenic effects of drugs on mood and behavior. Relevant pharmacotherapies of the time included tricyclic antidepressants, MAOIs, dextroamphetamine (Dexedrine), and the amine-depleting compound reserpine (Serpasil).

Although the early biogenic amine hypotheses have undergone much revision, the critical importance of norepinephrine and 5-HT in the pathophysiology and physiology of mood disorders remains unquestioned. A second important monoamine, dopamine, has received less emphasis and there is also strong evidence of dysfunction in some forms of depressions. Since the mid-1960s there has been a shift in focus away from single neurotransmitters towards neurobehavioral systems, neural circuits, and more intricate regulatory mechanisms. Moreover, postsynaptic receptor families, presynaptic autoreceptors and heteroreceptors, second messengers, and gene transcription factors were not known when the original monoamine hypotheses were formulated.

Noradrenergic Systems Noradrenergic neurons have their cell bodies in the locus ceruleus of the brainstem and project rostrally to the cerebral cortex, limbic system, basal ganglia, hypothalamus, and thalamus (Fig. 14.4-1). This diffuse distribution belies norepinephrine's role in initiating and maintaining limbic and cortical arousal, as well as in modulation of the function of other neurotransmitters. Noradrenergic projections to the hippocampus have recently been implicated in behavioral sensitization to stress, and prolonged activation of the locus cerulus contributes to the state of learned helplessness. The locus ceruleus also is the origin of neurons that project to the adrenal medulla, the principal source of norepinephrine into the peripheral blood circulation.

Novel stimuli increase the activity of the locus ceruleus, which in turn is decreased during vegetative functions, such as eating or sleeping. Cognitive processes can amplify or dampen sympathoadrenal responses to internal or external stimuli. Thus, the perception

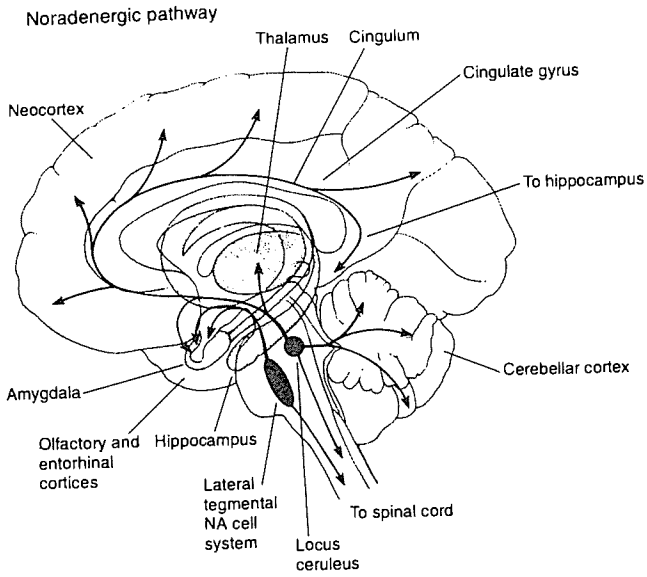

FIGURE 14.4-1 A lateral view of the brain demonstrates the course of the major nonadrenergic pathways emanating from the locus ceruleus and from the lateral brain stem tegmentum. (Reprinted with permission from Kandel ER, Schwartz JH, Jessell TM, editors: *Principles of Neural Science,* ed 3. Appleton & Lange, Stanford, CT, 1991.)

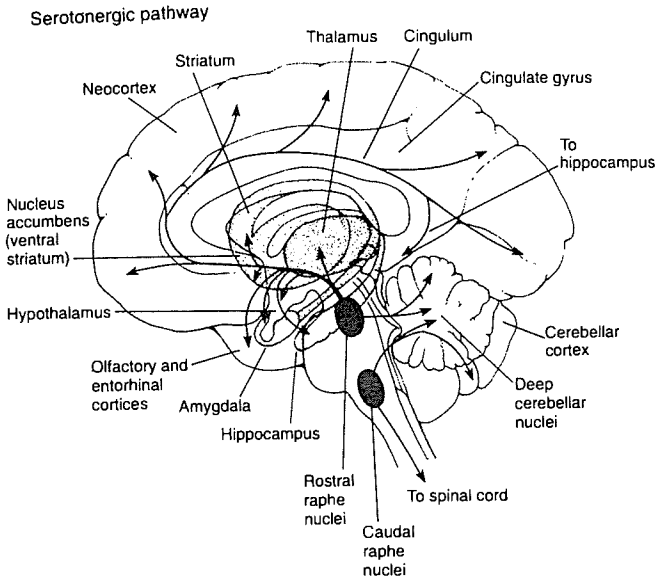

FIGURE 14.4-2 A lateral view of the brain demonstrates the course of the major serotonergic pathways. Although the raphe nuclei form a fairly continuous collection of cell groups throughout the brain stem, they are graphically illustrated here as two groups, one rostral and one caudal. (Reprinted with permission from Kandel ER, Schwartz JH, Jessell TM, editors: *Principles of Neural Science,* ed 3. Appleton & Lange, Stanford, CT, 1991.)

of stress is relayed via the appropriate cortical structures through the thalamus to the locus ceruleus and sympathoadrenal components of the acute stress response.

Stimulation of the medial forebrain bundle, the second major norepinephrine pathway in the brain, elicits increased levels of goal-directed and reward-seeking behavior. Sustained stress also eventually results in decreased levels of norepinephrine in the medial forebrain bundle, which may account for anergia, anhedonia, and diminished libido in depression. Increased noradrenergic output also stimulates inhibitory α_2-adrenergic heteroreceptors on serotonergic neurons.

Serotoninergic Systems Serotoninergic neurons project from the brainstem dorsal raphe nuclei to the cerebral cortex, hypothalamus, thalamus, basal ganglia, septum, and hippocampus (Fig. 14.4-2). Serotonin pathways have both inhibitory and facilitatory functions in the brain. For example, much evidence suggests that 5-HT is an important regulator of sleep, appetite, and libido. Serotonergic neurons projecting to the suprachiasmatic nucleus of the hypothalamus help to regulate circadian rhythms (e.g., sleep-wake cycles, body temperature, and hypothalamic-pituitary-adrenocortical axis function). Serotonin also permits or facilitates goal-directed motor and consummatory behaviors in conjunction with norepinephrine and dopamine. Moreover, serotonin inhibits aggressive behavior across mammalian and reptilian species.

There is some evidence that serotonin neurotransmission is partly under genetic control. Nevertheless, acute stress increases serotonin release transiently, whereas chronic stress eventually will deplete serotonin stores. Chronic stress may also increase synthesis of 5-HT_{1A} autoreceptors in the dorsal raphe nucleus, which further decrease serotonin transmission. Elevated glucocorticoid levels tend to enhance serotonergic functioning and thus may have significant compensatory effects in chronic stress.

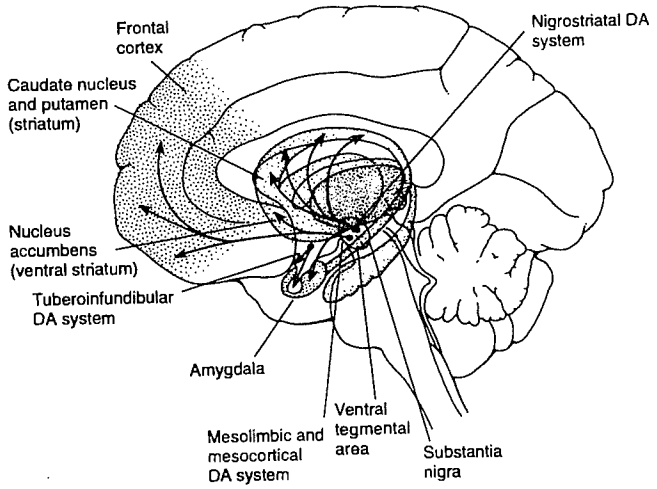

FIGURE 14.4-3 A lateral view of the brain demonstrates the course of the four major dopaminergic tracts. (Reprinted with permission from Kandel ER, Schwartz JH, Jessell TM, editors: *Principles of Neural Science,* ed 3. Appleton & Lange, Stanford, CT, 1991.)

Dopaminergic Systems There are four relatively discrete dopamine pathways in the brain (Fig. 14.4-3). The tuberoinfundibular system projects from cell bodies in the hypothalamus to the pituitary stalk, exerting inhibitory control over prolactin secretion. The nigrostriatal system originates from cell bodies in the substantia nigra and projects to the basal ganglia, regulating involuntary motor activity. The cell bodies of the mesolimbic pathway are located in the ventral tegmentum and project to almost all limbic regions: the nucleus accumbens, amygdala, hippocampus, medial dorsal nucleus of the thalamus, and cingulate gyrus. The mesolimbic dopamine pathway mod-

ulates emotional expression, learning and reinforcement, and hedonic capacity. The fourth dopamine pathway, also originating in the ventral tegmentum's mesocortical pathway, which projects to the orbitofrontal and the prefrontal cortical regions, helping to regulate motivation, concentration, initiation of goal-directed and complex, executive cognitive tasks. Decreases in mesocortical and mesolimbic dopamine activity have obvious implications in the cognitive, motor, and hedonic disturbances associated with depression. Moreover, dopamine activity appears to be potentiated by nicotinic inputs and glucocorticoids, and dopamine concentrations are correlated with brain serotonin activity.

Biogenic Amine Function After nearly 30 years of research it can be concluded that subsets of depressed people manifest one or more abnormalities of monoamine neurotransmission. Decreased central norepinephrine activity can be inferred, in part, from decreased urinary excretion of the metabolite 3-methoxy-4-hydroxyphenylglycol. A partly overlapping subgroup of patients has elevated circulating levels of norepinephrine and its metabolites. This suggests a dissociation of norepinephrine activity in the brain's medial forebrain bundle and the sympathomedullary systems peripheral activities. Increased noradrenergic activity also is reflected by blunted α_1, β, and β-coupled second messenger (i.e., cyclic adenosine monophosphate) responses. Further, an acute response to noradrenergically active antidepressants (i.e., desipramine, nortriptyline, or bupropion) may be transiently reversed by the norepinephrine synthesis inhibitor α-methyl-paratyrosine.

Serotonin dysfunction has been documented in overlapping subgroups of patients using a variety of methods, ranging from low cerebrospinal fluid (CSF) levels of 5-HIAA to decreased cerebral metabolism. Serotonin dysfunction also is reflected by blunted responses to specific serotonin (5-hydroxytryptamine [5-HT]) HT_{1A} subtype 1A ($5\text{-}HT_{1A}$) agonists (e.g., ipsapirone) and nonselective agonists (e.g., L-tryptophan or dex-fenfluramine), decreased neuroendocrine responses, and decreased serotonin uptake sites on blood platelets. Decreased serotonin neurotransmission can be inferred from the findings of cortical-hypothalamic-pituitary-adrenocortical and EEG sleep studies. In functional terms, a state of a relative hypofrontality of cerebral blood flow and glucose metabolism in the brain is fully consistent with decreased neurotransmission by 5-HT neurons projecting from the dorsal raphe nuclei. In support of this observation, dietary depletion of L-tryptophan will induce this abnormality in a subset of vulnerable patients. Tryptophan depletion also reverses acute responses to selective serotonin reuptake inhibitors. Increased sensitivity to dopamine, perhaps mediated by elevated glucocorticoid levels, may contribute to the development of delusions and hallucinations.

Other Neurotransmitters Cholinergic neurons containing acetylcholine are distributed diffusely throughout the cerebral cortex, and have reciprocal or interactive relationships with all three monoamine systems. Abnormal levels of choline, which is a precursor to acetylcholine, are seen in the brains of some depressed patients, perhaps reflecting abnormalities in cell phospholipid composition. Cholinergic agonist and antagonist drugs have differential clinical effects on depression and mania. Agonists can produce lethargy, anergia, and psychomotor retardation in normal subjects; exacerbate symptoms in depression; and reduce symptoms in mania. These effects generally are not sufficiently robust to have clinical applications and adverse effects limit their clinical utility. Via their serotonergic or adrenergic effects, antidepressant drugs may decrease cholinergic function, although direct anticholinergic effects are unrelated to antidepressant activity.

In an animal model of depression, a strain of mice that is supersensitive to cholinergic effects has been found to develop learned helplessness more quickly and cholinergic supersensitivity has been shown to be attenuated by manipulation of adrenergic activity. Conversely, cholinergic agonists can induce changes in cortical-hypothalamic-pituitary-adrenocortical activity and sleep EEG studies that mimic those associated with severe depression. Indeed, some remitted patients with bipolar or depressive disorders, as well as their never-ill first-degree relatives, have a trait-like increased sensitivity to cholinergic agonists.

GABA has an inhibitory effect on ascending monoamine pathways, particularly the mesocortical and mesolimbic systems. Reductions of GABA have been observed in plasma, CSF, and brain GABA concentrations in depression. Animal studies have also found that chronic stress can reduce or deplete GABA levels and, by contrast, GABA receptors can be upregulated by antidepressants.

The amino acids glutamate and glycine appear to be the major excitatory neurotransmitters in the central nervous system. Glutamate and glycine bind to sites associated with the *N*-methyl-D-aspartate (NMDA) receptor and, in excess, can have neurotoxic effects. The hippocampus has a high concentration of NMDA receptors; it is thus possible that glutamate in conjunction with hypercortisolemia mediate the neurocognitive effects of chronic stress. There is emerging evidence that drugs that antagonize NMDA receptors have antidepressant effects.

The binding of a neurotransmitter and postsynaptic receptor triggers a cascade of chemical processes that include the second messenger systems. Receptors interact with the intracellular environment via guanine nucleotide-binding proteins (G proteins). The G proteins, in turn, connect to various intracellular enzymes and effectors (e.g., adenylate cyclase, phospholipase C, and phosphodiesterase) that stimulate the formation of second messengers, such as cyclic nucleotide [e.g., cyclic adenosine monophosphate (cAMP) and cyclic guanine monophosphate (cGMP)], phosphatidylinositols (e.g., inositol triphosphate and diacylglycerol), and calcium-calmodulin. These second messengers regulate the function of neuronal membrane ion channels, neurotransmitter synthesis and release, and protein kinase activity. Protein kinase, for example, catalyzes phosphorylation, an anergy-liberating process involved in synthesis and degradation of neuroreceptors, ion channels, G proteins, and DNA transcription and messenger-RNA translation factors that regulate gene expression. Recent studies have reported abnormalities in platelet adenylate cyclase activity, phosphoinositide hydrolysis, intracellular calcium metabolism, and G-protein function in depressive disorders. Moreover, antidepressant medications may initiate a series of intracellular reactions that "turn down" synthesis of corticotropin-releasing hormone and monoamine receptors and "turn on" peptides such as neuronal growth factors. There is also increasing evidence that mood-stabilizing drugs (e.g., lithium) act upon G proteins or other second messengers.

Alterations of Hormonal Regulation

Cortical-Hypothalamic-Pituitary-Adrenal Cortical Activity Elevated glucocorticoid activity is a hallmark of the mammalian stress response. Evidence of increased cortisol secretion is apparent in 20 to 40 percent of depressed outpatients and 40 to 60 percent of depressed inpatients. Rates are highest among older patients, particularly those with highly recurrent or psychotic depres-

sive disorders. Hypercortisolism is thus one of the most common correlates of melancholic depressions.

A variety of methods can be used to study elevated cortical-hypothalamic-pituitary-adrenal cortical activity: excretion of urinary free cortisol, 24-hour (or shorter time segments) intravenous collections of glucocorticoid plasma cortisol levels, salivary cortisol levels, and tests of the integrity of feedback inhibition. Methods of testing feedback inhibition usually involve administration of the potent synthetic glucocorticoid dexamethasone, which in 0.5-, 1-, or 2-mg doses normally suppresses cortical-hypothalamic-pituitary-adrenal cortical axis activity for 24 hours. Impaired feedback inhibition is reflected by nonsuppression of cortisol secretion at 8 AM the following morning or subsequent escape from suppression at 4 PM or 11 PM. A more recent development is the pairing of dexamethasone suppression with an infusion of corticotropin-releasing hormone. The sensitivity and specificity of these various tests of feedback inhibition are not sufficient for use and adrenocortical hyperactivity is observed in many other psychiatric disorders, albeit usually at a lower prevalence. Nonsuppression usually implicates a premature loss of inhibitory hippocampal glucocorticoid receptors, which also may account for the age dependence of cortisol nonsuppression. Hypercortisolemia associated with early trauma also may permanently decrease synthesis of glucocorticoid receptors or actually lead to atrophy of these vulnerable neurons.

Hypersecretion of cortisol and dexamethasone nonsuppression are imperfectly correlated (about 60 percent concordance). Elevated cortical-hypothalamic-pituitary-adrenal cortical activity in depression is typically not associated with the physical stigmata of Cushing's disease, but it is sufficient to induce a reversible cortical atrophy and is implicated in the genesis of neurocognitive disturbances. Starvation and protracted sleep deprivation also can induce hypercortisolism. Patients with increased cortical-hypothalamic-pituitary-adrenal cortical activity are typically less responsive to attention placebo and psychosocial treatments. However, hypercortisolism does typically resolve with effective treatment and, when persistent, conveys a high risk of relapse. This is presumed to be a consequence of incomplete resolution of the depressive episode at the level of the brain. Dexamethasone and the cortisol synthesis inhibitor ketoconazole (Nizoral ®) are sometimes used to externally suppress the hypothalamic-pituitary-adrenocortical axis of hypercortisolemic patients with more refractory depressive disorders. Beyond failure of feedback inhibition, a deficit of 5-HT activity and an increase in norepinephrine or acetylcholine activity have been shown to increase cortical-hypothalmic-pituitary-adrenal cortical activity.

Thyroid Axis Activity About 5 to 10 percent of people evaluated for depression have previously undetected or subclinical thyroid dysfunction, as reflected by an elevated basal thyroid-stimulating hormone (TSH) concentration or an increased TSH response to a 500-μg infusion of the hypothalamic neuropeptide thyrotropin-releasing hormone (TRH). Such abnormalities are often associated with elevated antithyroid antibody levels and, unless corrected with thyroid hormone replacement therapy, may compromise response to treatment. These findings are especially relevant to women with rapid-cycling bipolar disorder.

More commonly, depressed patients receiving a TRH challenge test show a blunted TSH response. This abnormality, which may be state-independent, has been associated with a heightened relapse risk following pharmacotherapy or ECT. The TSH response may represent pituitary downregulation consequent to a prolonged elevation of TRH secretion. In turn, increased TRH secretion could result from a homeostatic response intended to enhance noradrenergic neurotransmission. Some researchers further speculate that the therapeutic benefit of liothyronine (Cytomel) augmentation therapy is the result of correction of this failed homeostatic response.

Growth Hormone Growth hormone secretion from the anterior pituitary is stimulated by norepinephrine and dopamine and inhibited by CRH and somatostatin, a hypothalamic neuropeptide. Somatostatin also inhibits CRH secretion. Secretion of growth hormone follows a 24-hour circadian rhythm, with a characteristic secretory surge during the first few hours of sleep. The most consistent finding in depression is a blunted growth hormone response to clonidine, an α_2 receptor agonist. The onset of sleep and nonselective adrenergic agonists such as desipramine also elicit a blunted growth hormone response.

Somatostatin Although the hypothalamus has the highest concentrations of somatostatin, significant concentrations are also found in the amygdala, hippocampus, nucleus accumbens, prefrontal cortex, and locus ceruleus. In addition to inhibition of growth hormone and release of corticotropin-releasing hormone, somatostatin inhibits GABA, adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone. Somatostatin levels are lower in the cerebrospinal fluid of people with depression as compared to those with schizophrenia or normals, and increased levels have been observed in mania.

Prolactin Prolactin release from the pituitary is stimulated by serotonin and inhibited by dopamine. Most studies have not found significant abnormalities of basal or circadian prolactin secretion in depression, although a blunted prolactin response to various serotonin agonists has been frequently reported. This response is less likely to be abnormal in premenopausal women, suggesting that estrogen has a moderating effect.

Alterations of Sleep Neurophysiology People prone to depression tend to have a premature loss of deep, slow (delta) wave sleep, and an early onset of the first episode of rapid eye movement (REM) sleep (Fig. 14.4-4). Results of family and twin studies suggest that these related abnormalities are at least partly heritable. Consistent with the expected behavior of a heritable trait, reduced REM latency and deficits of slow-wave sleep typically persist following recovery from a depressive episode. A blunted growth hormone response following sleep onset or administration of adrenergic agonists is correlated with a slow-wave sleep deficit and shows similar state-independent or trait-like behavior.

More severe depressions are associated with age-dependent decreases in sleep maintenance (i.e., the capacity to sleep without awakenings) and an increase in the phasic intensity of REM sleep, particularly during the first several REM periods. These changes correlate with clinical measures of severity of depression and tend to normalize during times of remission. Other state-dependent abnormalities are hypercortisolemia, dexamethasone nonsuppression, and elevated levels of peripheral catecholamine metabolites.

A deficit of slow-wave sleep and reduced REM latency can be induced and may be caused by a decrease in 5-HT neurotransmission or an increase in central cholinergic activity. Serotoninergic neurons from the dorsal raphe-nuclei project to cholinergic cells in the pons to tonically inhibit REM sleep. During non-REM (NREM) sleep,

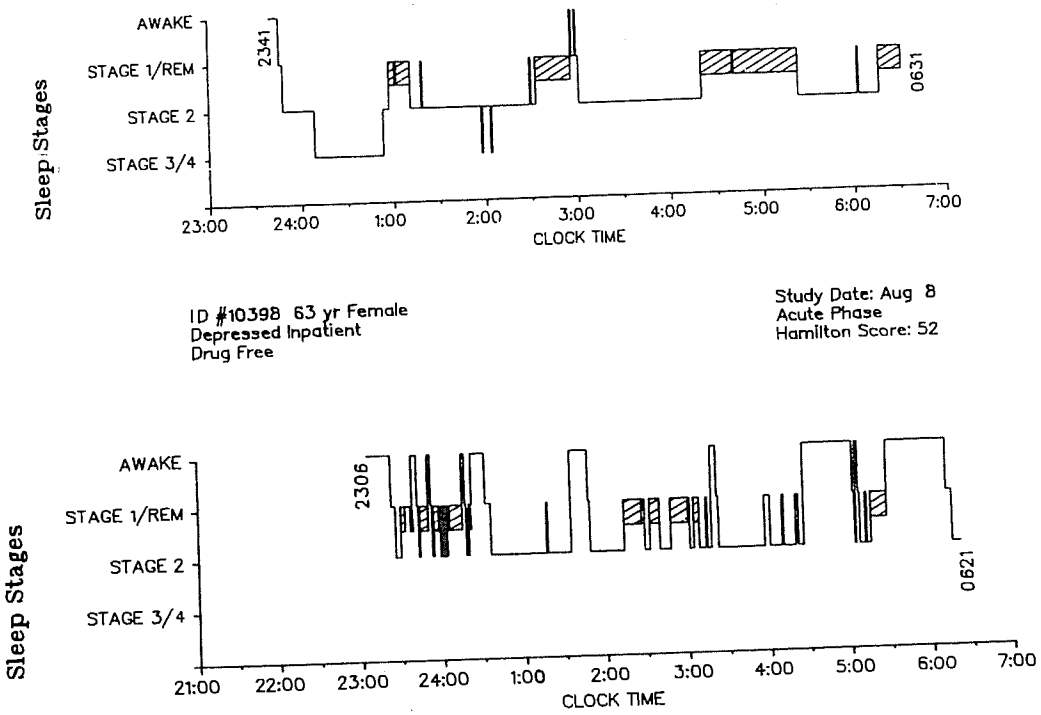

FIGURE 14.4-4 The all night electroencephalographic (EEG) sleep profiles of a healthy young woman and a 63-year-old woman with melancholia. (Reprinted with permission from Thase ME, Howland: Biological Processes in Depression: An Updated Review and Integration. In *Handbook of Depression,* ed 2, EE Beckham, WR Leber, editors. Guilford, New York, 1995.)

these cholinergic neurons are inactive. L-tryptophan depletion results in an increase in REM time and a decrease in REM latency.

Serotoninergic neurons projecting rostrally to the thalamus and prefrontal cortex also mediate slow-wave activity, as do drugs that antagonize 5-HT_2 receptors. Low CSF concentrations of 5-HIAA is correlated with diminished slow-wave sleep, an effect mimicked by acute serotonin depletion.

Prefrontal cortical metabolism is normally decreased during nREM sleep, a time of physical and metabolic rest. By contrast, REM sleep is normally associated with an increase in glucose metabolism in the limbic system. In depression there is relatively increased prefrontal glucose metabolism during nREM sleep, corresponding to the diminution of restorative slow wave sleep. REM sleep is associated with an even greater increase in limbic glucose utilization.

The sleep profiles of younger, hypersomnolent patients can be remarkably normal, particularly if laboratory routines do not permit an extended morning sleep period. Such patients may actually have increased slow-wave sleep and an increase in REM time associated with a greater total sleep time. Reduced REM latency, however, has been reported in juvenile depressives by at least one group of investigators.

The combination of reduced REM latency, increased REM density, and decreased sleep maintenance identifies about 40 percent of depressed outpatients, 80 percent of depressed inpatients, and 10 percent of age-matched normal controls. These sleep abnormalities also have been reported in a subset of dysthymic disorder patients. Sleep studies are too expensive and inconvenient to be used routinely for diagnostic purposes in depression and, like dexamethasone nonsuppression, false-positive cases are common in other psychiatric disorders. Nevertheless, current data indicate that patients manifesting this constellation of disturbances are less responsive to psychotherapies and may benefit preferentially from pharmacotherapy. It remains to be seen if those normal individuals with false-positive studies have an increased vulnerability to future episodes of depression. Successful nonpharmacological treatment of the depressive episode results in normalization of this profile in about 50 percent of cases. Pharmacotherapy with most antidepressant agents has an overcorrective effect characterized by prolongation of REM latency and suppression of REM sleep; such medications have variable effects on sleep maintenance. REM suppression may reflect activation of postsynaptic 5-HT_{1A} receptors or enhanced norepinephrine neurotransmission. Both desipramine (Norpramin) and the SSRIs for example, produce a rapid REM suppression in normal patients as well as in patients with depression. The efficacy of antidepressant medications that do not suppress REM sleep, such as nefazodone (Serzone), and bupropion (Wellbutrin) in patients with pathologically increased REM sleep suggests that these formulations may not apply to all depressions.

Alterations of Circadian Rhythms In addition to sleep disturbances, depressed patients often show a blunting of circadian rhythms of cortisol secretion, growth hormone secretion, and body temperature. These changes were originally thought to represent a phase advance of the sleep-wake cycle, although stronger evidence now suggests that circadian rhythms may be disorganized by heightened nocturnal arousal. Increased CRH, increased somatostatin, hypercortisolemia, and decreased 5-HT could all be implicated in this process. By contrast, in some cases of depressive disorders with seasonal (winter) pattern there is evidence of a phase delay of the sleep-wake cycle in relation to the nocturnal onset of melatonin secretion. The role of melatonin in the pathophysiology of mood disorders remains unclear.

Brain Structure and Function

Structural Lesions Computed axial tomography and magnetic resonance imaging scans provide sensitive, noninvasive methods to assess the brain, including cortical and subcortical tracts, as well as white matter lesions. The most consistent abnormality observed in the depressive disorders is increased frequency of abnormal hyperintensities in subcortical regions, especially the periventricular area, basal ganglia, and thalamus (Fig. 14.4-5). More common in bipolar I disorder and among the elderly, these hyperintensities appear to reflect the deleterious neurodegenerative effects of recurrent mood episodes. Ventricular enlargement, cortical atrophy, and sulcal widening also have been reported in patients with mood disorders as compared to normal controls. In addition to age and illness duration, structural abnormalities are associated with increased illness severity, bipolar status, and increased cortisol levels. Some depressed patients also may have reduced caudate nucleus volumes, suggesting a defect in the mesocorticolimbic system. Cerebrovascular factors, including strong, often involve subcortical frontal and basal ganglia structures, and appear particularly relevant to late-life depression.

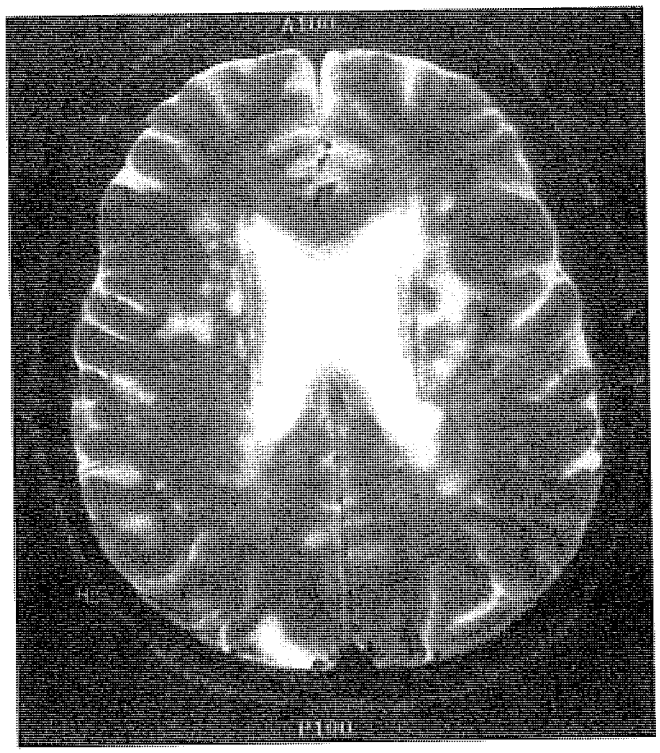

FIGURE 14.4-5 This magnetic resonance imaging (MRI) scan of a patient with late onset major depressive disorder illustrates extensive periventricular hyperintensities associated with diffuse cerebrovascular disease.

Cerebral Metabolic Alterations Positron emission tomography (PET) scanning is currently the most powerful method for visualizing brain metabolism during rest and various states of activation. Normal sadness is associated with an increase in cerebral blood flow to the thalamus and medial prefrontal cortex. This appears to be a nonspecific change associated with diverse emotional responses. More specific activation is seen in the left amygdala, hippocampal formation, and parahippocampal gyrus. Sadness generated by one's own thoughts (as opposed to a video scenario) also is associated with a relative increase in cerebral blood flow to the anterior insular cortex, as is anticipatory anxiety.

Direct activation of limbic structures by intravenous infusions of procaine hydrochloride also has been studied in normal controls. Such activation is characterized by reliable, bilateral increases in cerebral blood flow in the amygdala, parahippocampal gyri, insula, and anterior cingulate cortex. These changes are associated with a wide range of emotions, ranging from euphoria to severe anxiety.

The most widely replicated PET finding in depression is decreased anterior brain metabolism, which is generally more pronounced on the left side. This abnormality appears to be state dependent and has been observed in both depressive and bipolar disorders (Fig. 14.4-6), as well as in depression associated with obsessive-compulsive disorder. There is a reversal of hypofrontality following

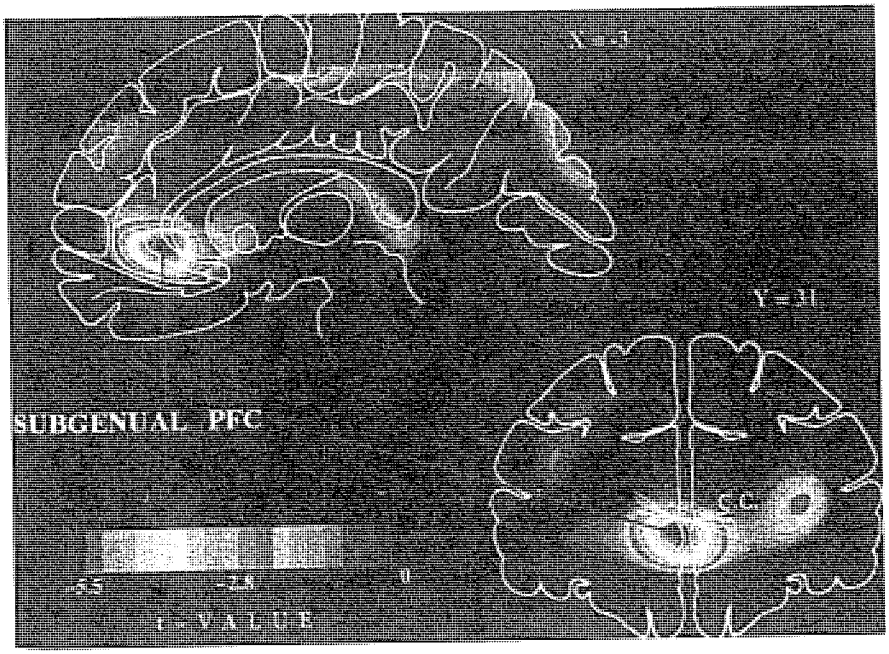

FIGURE 14.4-6 Composite coronal and sagittal sections of positron emission tomography (PET) scans show areas where cerebral glucose metabolism is decreased in depressed patients relative to matched health controls. (Reprinted with permission from Drevets WC: Nature 386:824–827, 1997. © 1997 MacMillan Magazine Limited.)

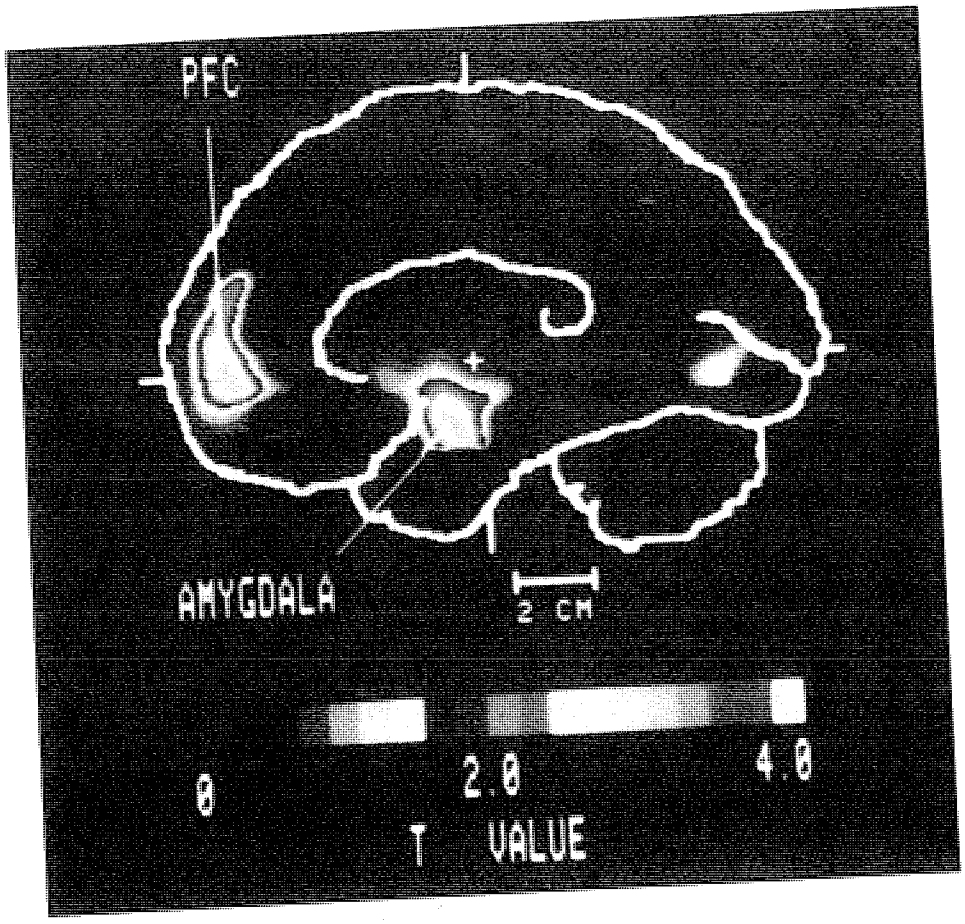

FIGURE 14.4-7 A lateral composite positron emission tomogram (PET) illustrating increased blood flow to the amygdala of patients with pure familial depressive disease as compared to healthy controls. (Reprinted with permission from Drevets WC: Exploring the Functional Anatomy of Depressive Disorder—Part I. In *Masters in Psychiatry,* Cliggott Communications, 1994.)

shifts from depression into hypomania, such that there are greater left-hemisphere reductions in depression compared to greater right-hemisphere reductions in mania.

Other studies have observed more specific reductions of reduced cerebral blood flow and metabolism in the dopaminergically innervated tracts of the mesocortical and mesolimbic systems in depression. There is evidence that antidepressant agents at least partially normalize some of these changes.

In addition to a global reduction of anterior cerebral metabolism, increased glucose metabolism has been observed in several limbic regions. The best evidence of this abnormality comes from studies of patients with relatively severe recurrent depression and a family history of mood disorder (Fig. 14.4-7). This abnormality was found to be reversible with effective pharmacotherapy, but persistent when recently remitted patients were studied again when they were off medication. During episodes of depression, increased glucose metabolism is correlated with intrusive ruminations. If truly state-independent, such amygdalar hypermetabolism could represent the emotional "amplifier" that helps to distort the signal of relatively minor stressors in vulnerable people.

Magnetic resonance spectroscopy has recently been used to study brain phosphorus metabolism in mood disorders. These studies focus on phosphorus metabolites because they reflect metabolic activity of several second messengers, such as cAMP, cyclic guanine monophosphate, and phosphatidylinositol. An asymmetrical abnormality of phosphorus metabolism has been observed in the frontal lobes of patients with bipolar disorder compared to normal controls, as well as the left frontal lobe and basal ganglia of patients with depression.

IMMUNOLOGICAL DISTURBANCE

Depressive disorders are associated with several immunological abnormalities, including decreased lymphocyte proliferation in response to mitogens and other forms of impaired cellular immunity. These lymphocytes produce neuromodulators such as corticotropin-releasing factor and cytokines, which are peptides known as *interleukins*. There appears to be an association with clinical severity, hypercortisolism, and immune dysfunction and the cytokine interleukin-1 may induce gene activity for flucocorticoid synthesis. The precise clinical relevance of these findings requires further investigation.

SEX DIFFERENCES

There is no compelling evidence that a single, sex-related factor accounts for the increased risk of depression in women. Certainly, alterations of sex hormones or hypothalamic gonadotropins in depression have not been documented consistently. Prior to menopause, estrogen and its metabolites may actually "protect" depressed women from developing hypercortisolemia. Although probably not a specific causal factor in depression, menopause may thus represent a point of transition from less severe depressions characterized by reverse vegetative symptoms to melancholia. There are, however, a multitude of risk factors that may contribute to the "gender gap," including greater risk of early sexual abuse and current spousal abuse, higher rates of thyroid disease, oral contraceptive use, and premenstrual or postpartum-onset mood disorders.

Alternatively, gender differences in emotional expressivity may interact with sociocultural factors and the texture of modern life to

create the increased risk of depression for women. Conversely, use of external coping strategies and greater traditional social role expectations to achieve competence outside of the home (and the resultant economic power) may provide men relatively greater protection against depression. Gender differences in rates of depression are not well documented in nonindustrialized cultures and, in the United States, no differences in men's and women's rates of depression were found in the old-order Amish of Pennsylvania.

FUTURE DIRECTIONS

Major depressive disorder is associated with a myriad of neurobiological disturbances, perhaps as varied as the range of effective treatments and clinical presentations. Broadly viewed as traits (either inherited or acquired) or states (abnormalities only apparent during illness), these disturbances begin to show some psychobiological coherence. State-dependent abnormalities, for example, tend to coaggregate in patients with more severe syndromes and, especially past ages 40 to 50, are associated with the more classic endogenous or melancholic manifestations. These changes include increased phasic REM sleep, poor sleep maintenance, hypercortisolism, impaired cellular immunity, global reductions of anterior cerebral blood flow and glucose metabolism, elevated peripheral noradrenergic metabolites, and possibly increased glucose metabolism in the left amygdala. Such changes suggest, almost without exception, the consequences of an exaggerated and sustained stress response. Once manifest in this fashion, the depressive episode tends to be longer, more disabling, more prone to relapse, and more likely to benefit from pharmacotherapy or ECT.

Trait-like abnormalities include reduced slow-wave sleep, reduced REM latency, blunted nocturnal growth hormone response, and various indicators of decreased serotonin neurotransmission. Heritability of these abnormalities is inferred from family studies and other at-risk paradigms. These abnormalities are associated with an early age of onset and perhaps with increased vulnerability to recurrent illness. They may also increase the likelihood of state-dependent biological changes during depressive episodes, probably by reflecting impairments in the ability to dampen or lower stress responses.

Examples of more persistent but "acquired" abnormalities may include global and focal changes, cortical atrophy, hypertrophy of the adrenal cortex, periventricular hyperintensities, and alterations in CRH synthesis. Blunted response of thyroid-stimulating hormone to an infusion of thyrotropin-releasing hormone and dexamethasone nonsuppression may represent "hybrids," in that these abnormalities can be slow to normalize and, when persistent after remission, convey a high risk of relapse.

Although specific genes have not yet been identified, vulnerability to mood disorders is heritable for some people. This type of heritability is most likely polygenetic and, in all likelihood, will be best understood through models that include gene-environment interactions. Nevertheless, increased heritability is associated with an earlier age of onset, greater comorbidity, increased risk of recurrent illness, and an increased likelihood of hypomanic or manic episodes.

Two of the more heritable forms of depression, early-onset chronic depression and bipolar depression, are commonly nonmelancholic in clinical presentation and relatively less likely to manifest state-dependent neurobiological disturbances. Both different genetic vulnerabilities and age-dependent changes in the brain's response to depression might explain this apparent paradox. Hypersomnolence and hyperphagia may thus reflect an episodic yet age-dependent homeostatic response to enhance serotoninergic dysfunction. In contrast, the sharp rise of mania post-pubescently may be related to maturational effects of catecholaminergic systems in the brain.

Aging and an accumulating risk of recurrent episodes are inextricably connected, although the diseases of aging that ravage brain function definitely increase the risk of depression, and these syndromes often prove to be resistant to treatment. The late-onset form of depression associated with periventricular hyperintensities also illustrates a more subtle interplay between vascular disease, brain damage, and mood disorder.

Ultimately, depression remains the most human of the Axis I disorders, partly because everyone can relate to sadness, grief, and the heartbreak of lost love and partly because the cognitive world of animals subjected to prolonged, inescapable stress is inaccessible. Even if their mental equivalents of "Why did this happen to me?" "Why bother—nothing I try will help?" and "I wish I was dead" could be identified, however, the incidence, prevalence, disability, and tragedy of depression in humans cannot be generalized to rodents or primates. Strong, sustaining affective bonds and an enduring sense of self-worth and competence are all-important and assaults on these fundamental aspects of human well-being are so frequent that many individuals succumb to depression. Some individuals are more vulnerable than others, and the association between severe depression and numerous, reproducible changes in brain function are well documented. Understanding the mechanisms of adaptation and brain dysfunction that predispose, initiate, distort, and maintain depressive disorders represents our best hope to prevent and relieve the misery and suffering of tens of millions of people.

SUGGESTED CROSS-REFERENCES

Monoamine neurotransmitters are discussed in Section 1.4, and the contributions of the neural sciences in general are the focus of the other sections of Chapter 1. Biological therapies are covered in Chapter 31.

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▲ 14.5 Mood Disorders: Psychodynamic Aspects

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A contemporary psychodynamic approach to mood disorders takes into account the strong biological underpinnings of these disorders. The domain of meanings is central to psychodynamic thought. Even when psychiatric illnesses can be traced to alternations in neurotransmitters, the symptomatology may acquire specific meanings for the patient. Moreover, psychosocial stressors and interpersonal events appear to trigger certain neurophysiological and neurochemical changes in the brain that significantly alter the balance of neurotransmitters. In other words, the development of an episode of depression or mania is generally regarded as a final common pathway of a complex mixture of psychosocial, genetic, and biological influences.

Clinically significant depression has long been linked to psychosocial stressors, such as the loss of a spouse. In addition, the loss of a parent before age 11 places adults at a higher than usual risk of depression. Some investigators have linked early childhood losses or separations to changes in neuronal receptor sites in the brain. This mechanism, known as kindling, is postulated to work in the following manner. Environmental stressors in childhood (e.g., loss or separation) so sensitize the receptor sites that relatively minor stressors in later life may suffice to trigger an episode of affective disorder. Chronic stress and deprivation of environmental origin may produce alterations in the catecholaminergic system in response to stimulation from the corticotrophin-releasing hormone–adrenocorticotropic hormone (ACTH) axis.

Primate studies have lent some support to the hypothesis that psychosocial influences have permanent effects on neurophysiological factors. 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 concentrations. The sensitivity and number of brain opioid receptors are also significantly affected by repeated separation. Some 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.

Although depression was once divided into endogenous and reactive subgroups, recent research has rendered these distinctions obsolete. Most depression is triggered by stressors, although at times relatively mild to an outside observer, and all depression involves endogenous biochemical factors. In this regard, every case of depression and mania can be regarded as having both a psychosocial and a biological dimension. Similarly, most depressions, except those of extreme severity, respond equally well to psychotherapy and medication.

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 predicting depression. Two other factors, neuroticism and interpersonal relations, also played substantial etiological roles. 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 were all involved in predicting a major depressive episode.

Kenneth Kendler and his colleagues expanded on their twin study by examining information about stressful life events and the onset of major depressive episodes in a population base sample of 1082 female-female twin pairs. They interviewed members of the sample on two different occasions separated by a mean time of 17.3 months. They again found that stressful events significantly predicted onset of major depression in the month of occurrence. The most severe stressors included death of a close relative, serious marital problems, assault, and divorce or breakup. Genetic liability also had a significant impact on the risk of onset of depression. In individuals at lowest

genetic risk (i.e., monozygotic twins with an unaffected cotwin), the probability of having a major depression in a particular month was 0.5 percent if unexposed to a severe life event. However, if the individual did experience such an event, the probability went up to 6.2 percent.

An even more dramatic difference was found by looking at individuals at the highest genetic risk (i.e., monozygotic twins with an affected cotwin). In these cases, the probability of having a major depression in a particular month was only 1.1 percent if no stressor was involved. However, if these individuals were exposed to a severe event, their risk of having a depressive episode skyrocketed to 14.6 percent.

The investigators described the best model for the joint effect of genetic liability and stressful life events on the onset of major depression as follows: genetic factors influence the risk of onset of major depression, at least in part, by altering the sensitivity of individuals to the depression-inducing effect of stressful life events. They emphasized that an individual's genetic endowment is not static. It interacts with the environment and reacts to psychosocial stressors.

One factor not captured by research using large samples is the role of the meaning of a particular stressor. What may seem a relatively mild psychological stressor may have conscious or unconscious meanings to an individual patient that greatly magnify its impact. In examining research on the role of stressful events in the course of unipolar and bipolar disorders, Constance Hammen concluded, "The field has reached considerable consensus that it is not the mere occurrence of a negative life event but rather the person's interpretation of the meaning of the event and its significance in the context of its occurrence." In a longitudinal study of the link between depressive reactions and stressors, Hammen and her colleagues found that stressors whose content matched the patient's area of self-definition were particularly likely to precipitate depressive episodes. In other words, in someone whose sense of self is partly defined by social connectedness, loss of significant interpersonal contacts may precipitate a depressive episode. On the other hand, someone whose self-worth is linked to achievement and efficacy might be more likely to have a depressive episode in response to a perceived failure in the workplace.

Psychodynamic theories of etiology have accumulated over years of clinical experience. These psychodynamic theories must be viewed within a broad dialogue with the neuroscientific data regarding brain changes in affective disorders. The following theories may also be regarded as psychodynamic themes that emerge in the treatment of depressed patients and may assist the clinician in understanding the patient's inner experience.

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, which may or may not be real. A fantasied loss may suffice to trigger a severe depression. Moreover, the patient may actually be unaware of any specific feelings of loss, since 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 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. 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 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 creating 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; and (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 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.

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 highly regarded. 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 at Harvard, and the patient was convinced that his father was ashamed of him for not making the dean's list.

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 perform 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 make him feel 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 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 understand fully 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 her. Admiration, validation, and affirmation are responses that are included in 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 Some contemporary ego psychologists believe 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 Trauma and 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 6 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 separation. 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.

One elegantly designed study documented an increased risk for major depressive disorder in those women who had experienced maternal or paternal separation in childhood or adolescence. A prospective study from the United Kingdom found that women with a history of childhood abuse or neglect are twice as likely to have negative relationships and low self-esteem in adulthood. Those abused or neglected women who have these negative relationships and low self-esteem in adulthood are then ten times more likely to experience depression. One of the clinical implications of this finding is that exploration of the impact of childhood trauma or neglect may be crucial in the psychodynamic therapy of depressed patients.

These empirical findings suggest a stress-diathesis model for mood disorders. In other words, a genetic substrate might serve to diminish monoamine levels in synapses or to increase reactivity of the hypothalamic-pituitary-adrenal axis to stress. Corticotropin-releasing factor (CRF), which induces the pituitary to secrete ACTH, is consistently elevated in the cerebrospinal fluid of depressed patients when compared with normal controls. When the brains of laboratory animals are given additional CRF, they have exhibited behavior similar to depression in humans. In keeping with the stress-diathesis model, some investigators have postulated that if there is no serious stress on the individual, the genetically determined threshold is not necessarily sufficient to induce depression. However, experiences of neglect or abuse in childhood may activate the stress response and induce elevated activity in CRF-containing neurons, which are known to be stress responsive and to be excessively active in depressed people. These cells can become supersensitive in certain individuals and then react dramatically to even mild stressors.

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. 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. 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 with 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.

In an 18-year follow-up study of 89 depressed patients, the investigators found that the personality measure of neuroticism led to poorer outcomes in patients with melancholia. Similarly, an examination of the National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Project data found that patients with personality disorders who were also depressed had poorer outcomes in social functioning and a much greater likelihood of residual depressive symptoms than those who did not have personality disorders. In a third study 76 depressed outpatients were treated with interpersonal psychotherapy. The only significant predictor of time to remission was the degree of personality pathology. Even though patients with the most-severe personality disorders, borderline and antisocial, were excluded from the study, those who had other Axis II conditions responded more slowly to psychotherapy or not at all.

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 (e.g., 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 patients. 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 and the presence of other Axis II diagnoses, another clinical entity gaining increased acceptance is depressive personality disorder. In Appendix B of the fourth edition of *Diagnostic and Statistical Manuel of Mental Disorders* (DSM-IV) the criteria for the disorder emphasize a constellation of personality traits, while the criteria for dysthymia focus on somatic symptoms. These traits include a mood dominated by unhappiness, dejection, and gloominess; a self-concept centered on worthlessness and low self-esteem; a proneness to feel guilt or remorse; a tendency to blame and criticize oneself; a negativistic and judgmental stance toward others; a pessimistic attitude; and a tendency to worry and to brood. Although this diagnostic entity has a long-standing psychoanalytic tradition, there has been controversy regarding whether or not it is truly distinct from dysthymic disorder. Data are emerging suggesting that the distinction between the two is valid and clinically useful. In a study of 54 patients with early onset long-standing mild depressive features, Katherine Phillips and her collaborators identified 30 subjects with and 24 without depressive personality disorder. Sixty-three percent of the subjects with depressive personality disorder did not have dysthymic disorder, while 60 percent did not have current major depressive disorder. The depressive personality disorder patients were more likely than the comparison group to have another personality disorder, but 40 percent of them had no such disorder. Those who were comorbid for another personality disorder tended to have anxious or Cluster C personality disorder, suggesting that defenses and conflicts at a neurotic level were most prominent, in keeping with the psychoanalytic conceptualization of depressive personality disorder. Finally, the duration of psychotherapy was significantly longer for subjects who had depressive personality disorder when compared to those who did not. Antidepressant drugs may be combined with psychotherapy in the treatment of characterological depression.

Clinicians must remember that depression spans the entire spectrum of pathology and health. In addition to being a discrete psychiatric disorder, depression refers to an emotional state that can occur 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.

PSYCHODYNAMIC PSYCHOTHERAPY

Although brief psychodynamic psychotherapy has been shown in meta-analyses to be no better or worse than other forms of psychotherapy, there are few controlled trials of the modality with depressed patients. Even more problematic is the fact that few of the trials that exist have been carried out by advocates of the technique who actively practice it. In most studies brief dynamic therapy was used on a comparison or control group to contrast with the different psychotherapies that the investigators favored. Most studies testing brief dynamic therapy were also done in a group format, even though individual therapy is much more widely practiced by psychodynamic clinicians. A number of the trials involving brief dynamic therapy, in which the investigators favored other therapies, found it significantly less effective than the other interventions.

More recently, well-designed studies show promising results from brief dynamic therapy. In an investigation of depressed caregivers of elderly family members, random assignment was made to one of two treatment cells: brief psychodynamic therapy or cognitive-behavioral therapy. After 20 sessions, 71 percent of the caregivers were no longer clinically depressed. Overall, no differences were found between the two treatment groups. Symptom-oriented measures suggested that those who had been caregivers for more than 3.5 years improved more with cognitive-behavioral therapy, whereas those who had been caregivers for shorter periods showed more improvement from brief psychodynamic therapy.

In the British study known as the second Sheffield Psychotherapy Project, similar findings were obtained in a randomized, controlled trial. Some 120 depressed patients were assigned to either 8 or 16 sessions of cognitive-behavioral therapy or psychodynamic-interpersonal therapy. Both treatments were found equally effective, and their effects equally rapid. Patients with only mild or moderate depression had the same outcome whether they were treated with 8 or 16 weeks of therapy. However, significantly better outcomes were noted in the severely depressed group when 16 weeks of therapy were provided, whether cognitive-behavioral or psychodynamic-interpersonal. At 1-year follow-up no overall differences were found in outcome or maintenance of gains between those receiving the two types of therapy. However, longer periods of therapy appeared to be associated with better long-term outcomes, particularly in the case of psychodynamic-interpersonal therapy.

Systematic controlled studies using randomized assignment are not available for extended psychodynamic psychotherapy and psychoanalysis. Most therapists would agree that these modalities are not indicated as exclusive treatment for patients in the acute phase of major depressive disorder. However, a subgroup of patients who do not respond to medication or brief psychotherapy may benefit from more-extended psychodynamic exploration. Sidney Blatt and his associates reanalyzed the data from the NIMH Treatment of Depression Collaborative Research Project and found that highly perfectionistic and self-critical patients did not respond well to any of the treatment cells, which included 16 weeks of cognitive therapy, 16 weeks of interpersonal therapy, 16 weeks of imipramine (Tofranil) plus clinical management, and 16 weeks of placebo plus clinical management. In two other naturalistic follow-along studies of extended psychotherapy on such patients, self-critical and perfectionistic traits appeared to respond well to intensive psychoanalytic psychotherapy. Hence a subgroup of depressed patients may be particularly well suited to more-extended psychoanalytic therapy. Depressed patients with significant Axis II pathology may also respond poorly to brief therapies or medication and require intensive psychotherapy over a long time. However, no data from controlled trials are available to confirm this clinical impression.

In any depressed patient, certain psychodynamic principles may be useful, no matter which treatment modality is selected. For example, the American Psychiatric Association practice guidelines for depression suggest that psychotherapeutic management should be part of every treatment for depression. Psychodynamic concepts such as therapeutic alliance, transference, resistance, and countertransference apply to all patients, regardless of the type of treatment. The role of the therapeutic alliance may be particularly important in terms

of outcome in both psychotherapy and pharmacotherapy. A team of investigators led by Janice Krupnick looked at 225 cases of depressed patients in the NIMH Treatment of Depression Collaborative Research Program. Clinical raters scored videotapes made of the treatments in all four cells. When outcomes were assessed on these cases, the therapeutic alliance was found to significantly affect clinical outcomes of both psychotherapies, placebo treatment, and the imipramine group. In fact, the patient contribution to the therapeutic alliance accounted for 21 percent of the outcome variance on standardized outcome measures, with more of the variance in outcome attributed to alliance than to the treatment method itself. Among the four cells, none showed significant group differences in terms of the relationship between therapeutic alliance and outcome. Hence attention to the psychotherapeutic relationship is of central importance in all treatment of depression.

Sydney Blatt has suggested that the psychodynamic psychotherapeutic approach must be tailored to the underlying type of depression. His research has delineated two distinct categories of depressed patients: anaclitic and introjective. *Anaclitic depression* is characterized by feelings of helplessness, loneliness, and weakness related to chronic fears of being abandoned and unprotected. These individuals have longings to be nurtured, protected, and loved. They have a vulnerability to having interpersonal relationships disrupted. These types of patients require a therapy that emphasizes the therapeutic relationship rather than interpretation or insight.

By contrast, *introjective depression* is characterized by feelings of unworthiness, failure, guilt, and inferiority. These individuals are also highly self-critical and suffer from a chronic fear of criticism and disapproval from others. They are highly perfectionistic and competitive and are often driven to achieve in work and school. They have a characteristic vulnerability to disruptions of a positive and effective sense of self, and their depression is manifested primarily by dysphoric feelings of guilt, worthlessness, failure, and by a sense that one's autonomy and control have been lost. Interpretive interventions that provide insight seem to be more helpful with this category of depressed patients.

MANIA

Almost all researchers who have studied bipolar disorders have concluded that psychosocial interventions may be crucial in concert with pharmacotherapy for the prevention of relapse. Relapse rates as high as 60 percent over a period of 2 years have been reported, even when maintenance therapy on lithium carbonate (Eskalith) has achieved adequate plasma concentrations. Work status deteriorates in about two-thirds of patients, while social function deteriorates in one-half of patients. In addition, there is a 45 percent separation or divorce rate, compared with 18 percent in controls. In fact, the average 25-year-old female patient can expect to lose nearly 9 years of life, 14 years of effective major activity (work or school), and 12 years of normal health.

A psychodynamic understanding can be extraordinarily helpful in identifying the nature of stressors likely to precipitate episodes. In one 2-year study of 61 outpatients, patients with the highest levels of stress had a 4.53 times greater risk of relapse than patients without stress. In a 10-year follow-up study, two different groups of treatment failures were identified in a cohort of patients with bipolar disorder. One group of patients relapsed because the treating psychiatrist had failed to increase the lithium dosage 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 psychosocial factors.

In one study investigators examined both individual differences in stress reactivity and psychological characteristics of a group of 58 patients with bipolar disorders followed for at least 1 year. The stress level predicted relapse, but personality variables, particularly introversion and obsessionality, were also significant predictors. Hence a psychodynamic perspective on the bipolar disorder patient may help both in identifying psychological and environmental stressors and in dealing with characterological issues that may complicate the treatment. There is an increasing recognition that with refined diagnostic methods, a high degree of comorbidity may exist between bipolar disorders and Axis II disorders. In a study of 66 outpatients with a Research Diagnostic Criteria diagnosis of hypomania and a lifetime diagnosis of bipolar disorder, each patient was interviewed during the hypomanic episode and after recovery. Knowledgeable informants were also interviewed at both times. The researchers found that hypomania was associated with higher levels of maladaptive personality traits than the euthymic state, but even when euthymic, 50 percent of the cohort had at least one personality disorder. They also found that the alleged decrease in maladaptive personality traits following recovery was much greater in the reports by patients than in those by informants.

Some of these characterological features of the personality disorder may contribute to compliance problems with medications designed to stabilize mood. They also may alienate family members who then become more critical and more distant, producing an increased risk of relapse. Often these character traits may require individual dynamic psychotherapy in which they can be addressed in the transference-countertransference dimensions of the treatment.

Even in bipolar disorder patients without a personality disorder, compliance is a major problem. At least half of bipolar disorder patients stop taking medication at least once in the course of their illness. Frederick Goodwin and Kay Jamison found that the most important reasons for noncompliance listed by patients were dislike of having medication control their moods, dislike of the idea of having a chronic illness, aversion to feeling depressed, and dislike of adverse effects. The combination of medication and individual psychotherapy is required for comprehensive treatment and optimal compliance.

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 decreased the sexual behavior and reinstituted the ego defense mechanisms present before the manic episode. In the course of continued psychotherapeutic or psychoanalytic treatment, the patients became consciously aware of their unconscious sexual desires and of the defenses elicited to deal with those desires. This conscious awareness enabled the patients to identify early warning signals of increased sexual impulses, so that future manic episodes could be avoided by increasing their lithium dosage.

These 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. 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 by merging the ego and the superego. Self-criticism is then replaced by euphoric self-satisfaction.

Bertram Lewin 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 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 to master the dangerous bad objects and to restore and to save the loved good objects.

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 so 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. This formulation is also useful in understanding the commonly observed phenomenon of elation after the death of a loved one.

> 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.

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.

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 with psychic causality.

Karen Horney Horney believed that children raised by rejecting and unloving parents are prone to feelings of insecurity and loneliness. In her view, children need to be loved but fear criticism and rejection, which make 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 cannot 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 separation of infants from mothers (or other caregivers) early in life leads to feelings of depression and hopelessness that may in some cases continue throughout the life cycle.

Harry Stack Sullivan Although Sullivan concentrated his efforts more on schizophrenia than on mood disorders, his interpersonal perspective applies to both. He thought that adverse interactions be-

tween 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 present in persons prone to depression. Those distortions, referred to as *depressogenic schemata,* are cognitive templates that perceive both internal and external data in ways that are altered by early experiences. These 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 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 (i.e., they would not attempt 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 improvement of depression is contingent on the patient's learning a sense of control and mastery of the environment.

Psychodynamic Treatment Clinicians who combine pharmacotherapy with a mood stabilizer and individual dynamic therapy focus to a large extent on preventing relapse through greater medication compliance, through detailed understanding of problematic stressors, and through careful examination of relationship difficulties, some of which may relate to Axis II psychopathology. Several major psychodynamic themes are often present in bipolar patients, all of which may be relevant at one time or another in the ongoing treatment of the condition. Denial of illness is one of the major defensive postures encountered with these patients. Many argue that their manic or hypomanic symptoms are not part of an illness but rather a reflection of who they really are. Hence when their collaboration is enlisted in a medication regimen or other component of the treatment plan, they frequently deny having a problem that requires treatment. Patients with bipolar illness are notoriously lacking in insight. In one study of 28 manic patients treated on an inpatient unit, insight was measured at admission and discharge. Even when all other symptoms of mania had improved or remitted, insight remained notably absent. The investigators concluded that poor insight is a prominent characteristic of a bipolar disorder regardless of illness phase.

Often related to denial is another psychodynamic theme—splitting or psychic discontinuity. Many bipolar I disorder patients continue to deny the significance of their prior manic episodes when they are euthymic. They may claim that the behavior was simply a result of being exhausted and not taking care of themselves. They also assert that nothing like that will ever happen again. This involves a form of splitting the self-representation so that the self involved in a manic episode is considered entirely disconnected from the self in the euthymic phase. The discontinuity between the different versions of the self may be regarded with bland denial or indifference.

A 35-year-old dentist was admitted to an inpatient unit with pressured speech, flight of ideas, and extreme hyperactivity. He had been engaging in extensive sexual activity in the days preceding the admission, and he had been spending all of his savings on a variety of outlandish investment schemes. When he finally arrived on the hospital unit, he was singing and dancing around the lounge area to such an extent that he had to be placed in the seclusion room to try to settle him down long enough to conduct a psychiatric interview. The female psychiatric resident who was on call entered the seclusion room with her attending psychiatrist. The patient abruptly stopped his singing and said, "I have a plan." He then pointed to the female resident and said, "I'll screw her, and you watch." The patient was told that his plan was not tenable and that he needed to take medication. With considerable coaxing, he finally agreed to take lithium and an antipsychotic agent.

Seven days later his manic episode had subsided. He was calm, polite, and generally socially appropriate. A teaching conference for residents was held in which the patient was interviewed. The attending psychiatrist asked him about his reasons for hospitalization and the nature of his problems. He went on at some length about how he was experiencing "burnout" on his job because people were always telling dentists their problems. He continued to say that he had gotten rather tired and found his job less than fulfilling. He also said that his marriage was troubled because of his long work hours. The impression he created was that of a hardworking professional who was suffering mild stress as a result of occupational difficulties. At no time did he mention anything to the group of residents attending the conference that reflected his bizarre behavior associated with his recent manic episode.

The attending psychiatrist interviewing the patient finally interrupted him and said that he wondered why he was not bringing up any of the behaviors that had brought him into the hospital 7 nights ago, such as singing and dancing, spending vast sums of money on unwise investments, staying up all night, and engaging in extensive sexual activity. The patient stared at the interviewer blandly and said, "Oh, that? Well, that's not a problem now."

This vignette clearly illustrates how the manic self and the euthymic self are maintained in separate compartments so that no continuity of the self is apparent.

This form of compartmentalization is a major contributor to compliance difficulties. If patients can maintain this kind of discontinuity, they can deny the need for medication or even vulnerability to a subsequent episode. The clinician needs to assemble the self-fragments into a continuous narrative of the patient's life so that maintenance treatment becomes more compelling. Tape recording manic episodes (with the patients' permission) and then playing the recordings back to patients when they are in a euthymic state may be a useful technique.

Another reason for this form of splitting is a wish to avoid the work of mourning and grief that becomes necessary when the manic self and the euthymic self are connected. There may be mourning of the healthy premorbid self, which seems to be forever gone. Also, following a manic episode, patients may become acutely aware of their own destructiveness and feel intense remorse about the harm they have caused others during the manic phase. Splitting it off and denying its significance spares them the pain of this awareness. If the therapist can gently confront them with this defensive maneuver, they can then acknowledge the harm they have done and attempt to make reparation.

Another relevant psychodynamic theme is ego-syntonic attachment to hypomania. Many patients insist that they are more creative, more full of life, and more engaging when they are in a hypomanic or manic episode. They do not want to comply with their mood-stabilizer medication because they feel it interferes with their creativity and their enjoyment of life. Helping them to see that their behaviors clearly had a negative impact on others may help them deal with the attachment and make it more ego dystonic.

Lithium or other mood stabilizers may take on special meanings to bipolar patients. These agents may come to represent something that is taken away from them. If they comply, they have to resign themselves to no longer experiencing the euphoria of their manic periods, and their denial of their illness is challenged. Maintenance medication may have the meaning of having a severe mental illness that requires lifelong treatment. Integrating this notion into their sense of self also requires the work of mourning. Clinicians must always keep in mind that there is a psychological function of mania that runs in parallel with the biological alteration of the brain—namely, manic denial serves to defend against depression and loss. Medication may also have the meaning of identification with specific family members who have had bipolar illness. To take the medication may unconsciously mean that the course of their illness will be the same as their relative's.

The cornerstone of the psychotherapeutic strategy with bipolar disorder patients is to build a therapeutic alliance. Arguing with the patient about whether or not a bipolar disorder is a correct diagnosis is of little value. Psychotherapeutic exploration, empathy, and education are generally more effective. Creation of a mood chart that helps the patient track highs and lows may also be helpful. Transference tends to shift from idealization to devaluation, often in parallel with shifts in mood. The therapist must also be wary of countertransference acting out in response to anger and frustration with the patient's refusal to cooperate with the treatment plan.

Most clinicians now treating bipolar disorders consider the combination of psychotherapy and pharmacotherapy essential.

Jamison, who wrote a vivid personal account of her struggles with bipolar illness, described it as follows:

> Ineffably, psychotherapy heals. It makes some sense of the confusion, reins in the terrifying thoughts and feelings, returns some control and hope and possibility of learning from it all. . . . No pill can help me deal with the problem of not wanting to take pills; likewise, no amount of psychotherapy alone can prevent my manias and depressions. I need both.

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 24.

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▲ 14.6 Mood Disorders: Clinical Features

HAGOP S. AKISKAL, M.D.

HETEROGENEITY OF MOOD DISORDERS

Terminology Mood disorders are characterized by pervasive dysregulation of mood and psychomotor activity and by related biorhythmic and cognitive disturbances. The rubric of "affective disorder," which in some European classifications also subsumes morbid anxiety states, is increasingly being replaced by the nosologically more delimited concept of "mood disorder." Thus *mood disorder* is now the preferred term in both the World Health Organization's (WHO's) 10th revision of *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) and the American Psychiatric Association's (APA's) fourth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV). Official mood disorder categories in current use include bipolar disorders (with manic or hypomanic, depressive, or mixed episodes) and major depressive disorders and their respective attenuated variants known as cyclothymic and dysthymic disorders. Conditions that in earlier editions of these 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 disorder. Although the neurotic-endogenous distinction has been officially deleted, the term "melancholic features" is now used to qualify major depressive disorders in which biological concomitants predominate. While both the American and international classifications recognize the common occurrence of mixed anxiety-depressions, whether they should be classified with mood disorders or with anxiety disorders remains unresolved. It is equally uncertain how to classify the classic neurasthenic conditions, which have recently reemerged and overlap to some extent with the so-called chronic fatigue syndrome.

Destigmatization The reshuffling and reclassification of various affective conditions into the mood disorders chapter of the third edition of DSM (DSM-III) and DSM-IV has, on balance, considerably broadened their boundaries. This change reflects, in part, new developments in pharmacotherapy that have resulted in considerable alleviation of suffering for persons whose illnesses fall short of and sometimes beyond the boundaries of classic mood disorders. As a result, many persons with recurrent mood disorders who would have been disabled can now lead productive lives. Such gratifying results have, in turn, helped to destigmatize this group of disorders. Destigmatization has been further facilitated by published self-revelations of famous persons with depressive and bipolar disorders.

Spectrum of Mood Disorders As often happens when new therapeutic interventions prove successful, the past two decades have witnessed an increased readiness to diagnose mood disorders and their variants. These 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 propensity to mood disorders embraces entities that extend beyond endogenous depression (melancholia in DSM-IV) to subsume a larger variety of depressions, including some encountered in 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 affective dysregulation occurs in as many as one of every three persons. That ratio is similar to the proportion of those who progress to a full depressive syndrome following bereavement, of rhesus monkeys developing depressive-like behavior following a separation paradigm, and of dogs who develop learned helplessness after inescapable shock. The fact that these rates are considerably higher than one observes in clinical populations suggests that many subjects possess protective factors against major depressive episodes; alternatively, the data suggest that other factors determine which person with emotional distress will become a clinical case. A great deal might therefore be revealed about the nature of pathological affective processes through study of self-limiting affective conditions on the border of mood disorders.

The suffering and dysfunction resulting from mood disorders are among the most common reasons for consulting psychiatrists and other physicians. In fully developed cases, all activity stops—including creative powers—and life is grim and in total disarray (as portrayed in Dürer's masterpiece, Fig. 14.6-1).

All great physicians of the past, beginning with Hippocrates, have devoted considerable space in their general medical texts to the clinical characterization of melancholic and manic states, as well as alternations in the same patient. Greco-Roman medicine recognized a broad spectrum of affective disturbances, ranging from the relatively mild temperamental variants (represented in the official nosology by dysthymic and cyclothymic disorders) to their severest forms (including what today is considered mood disorder with mood-congruent and mood-incongruent psychotic features). The ancients also recognized the intimate relation of morbid states of fear to melancholia. Furthermore, 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 remain unresolved. Mood disorders have long been known

FIGURE 14.6-1 *Melancholia* (1514) by Albrecht Dürer.

to be highly comorbid with alcohol use and somatic disease; these trends continue 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 human beings and other primates 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 primates as well as many other 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 also manifested 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 and often vary from one culture to another. Furthermore, the inward emotion and the prevailing affective tone may be discordant. This conflict could be due to deliberate simulation (i.e., the subject does not wish to reveal his or her inner emotion) or it could result from a pathological lesion or process that has altered the emotions and their neural substrates. Thus, evaluating moods and affective expression requires considerable clinical 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 tension disorder" and "maternity blues," they are not psychopathological per se, but those predisposed to mood disorder may develop clinical depression during such times.

Premenstrual Dysphoric Mood Changes In view of the higher prevalence of depressive disorders in women, premenstrual affective changes—dysphoria, tension, irritability, hostility, and labile mood—have received both clinical and research attention. The attempt to establish a specific premenstrual dysphoric disorder has neglected the not uncommon occurrence of premenstrual eutonia, increased energy, and sexual drive. The not uncommon occurrence of these positive emotions, along with the labile mixed affective manifestations, tend to point toward a "bipolar" phenomenon. Although women with severe premenstrual complaints appear to have higher rates of lifetime major mood disorders, a recent twin study found that genetic and environmental factors contributing to premenstrual depression and major depressive disorders are largely distinct. Furthermore, events such as migraine, epileptic attacks, and panic states may, in some instances, be associated with the premenstrual phase. The foregoing considerations suggest the hypothesis that premenstrual psychobiological changes exacerbate different neuropsychiatric disorders to which women are otherwise predisposed. Whether the exaggerated premenstrual variability in emotional equilibrium constitutes a variant of mood disorder must await more definitive studies.

Grief Normal bereavement or grief, considered the prototype of reactive depression, occurs in response to significant separations and losses such as death, divorce, romantic disappointment, leaving familiar environments, forced emigration, or civilian catastrophes. DSM-IV tends to limit the concept of normal grief to loss due to death. However, the work of Elie Karam and colleagues showed that losses associated with the civil war in Lebanon served as potent forces in depression formation. 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 "flight into health." In predisposed persons such reactions might be the prelude to a genuine manic episode. 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. Temperaments tend to cluster into basic types, four of which are of the greatest relevance to mood disorders. The depressive temperament, in which the person easily swings into the sad direction, occurs in 3 to 6 percent of the general population; the hyperthymic temperament, in which the person is naturally inclined toward cheerful moods has been reported in 4 to 8 percent and the cyclothymic temperament swinging between cheerful and sad moods characterizes 4 to 6 percent of young adults. All three types have an early insidious onset and tend to persist throughout adult life. An irritable-explosive type occurs in 2 to 3 percent of young subjects and tends to attenuate by middle age.

An examination of the traits associated with these temperaments can provide the rationale for Ernst Kretschmer's hypothesis about the social functions they served. Thus, the person with a depressive temperament is hard working, dependable, and suitable for jobs that require long periods of devotion to meticulous detail (Table 14.6-1). Such persons shoulder the burdens of existence without experiencing its pleasures. A person with the hyperthymic temperament, endowed with high levels of energy, extroversion, and humor (Table 14.6-1), will assume leadership positions in society or excel in the performing arts or entertainment. In talented persons the cyclothymic temperament, which alternates between sadness and elation, could provide the inspiration and the intensity needed for composing music, painting, or writing poetry. One with the irritable temperament, probably a variant of the cyclothymic type, might be best suited for a military career or even revolutionary action. The danger with such temperaments is that they could swing too far in one or the other direction, or in both directions (i.e., major depressive, manic, or mixed episodes). Use of such substances as alcohol, caffeine, and other stimulants might further destabilize affective regulation in persons with those attributes. Some adolescent girls with the irritable temperament might develop the extreme emotional disequilibrium that in contemporary psychiatry is considered borderline personality disorder.

Table 14.6-1
Attributes, Assets and Liabilities of Depressive and Hyperthymic Temperaments

Depressive	Hyperthymic
Gloomy, incapable of fun, complaining	Cheerful and exuberant
Humorless	Articulate and jocular
Pessimistic, and given to brooding	Overoptimistic and carefree
Guilt-prone, low self-esteem, and preoccupied with inadequacy or failure	Overconfident, self-assured, boastful, and grandiose
Introverted with restricted social life	Extroverted and people seeking
Sluggish, living a life out of action	High energy level, full of plans
Few but constant interests	Versatile with broad interests
Passive	Overinvolved and meddlesome
Reliable, dependable, and devoted	Uninhibited and stimulus seeking

Morbid Mood States Mood disorders represent abnormal or extreme variations of mood and associated manifestations and are 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 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. The pathological process in mood disorders is thus partly defined by the ease with which an intense emotional state is released and especially by its tendency to persist autonomously even when the offending stressor is no longer operative. Rather than being endogenous (i.e., occurring in the absence of precipitants), mood disorders are best conceptualized as endoreactive (i.e., 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 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.

Recurrence 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 an intermittent, subthreshold course over the span of many years, if not a lifetime. Cyclic course and in some cases regular recurrence, or periodicity, are 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, pathologically sustained mood states of depression and elation 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 evolve into unremitting chronicity in 15

to 20 percent of cases. 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, including severity, autonomy, recurrence, and chronicity of the clinical features.

To recapitulate, dysregulation in mood disorders can take different forms. It could be expressed as a single severe episode that persists autonomously for many months and sometimes years or it might recur with episodes of varying severity, years apart or in rapid succession, with or without interepisodic remission. In general, the earlier the age at onset, the more likely are recurrences, especially those of bipolar nature. Thus, depending on the course of the illness, impairment could be state dependent and occur during an episode or it could extend into the interepisodic period. According to National Institute of Mental Health (NIMH) estimates, on 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 and cyclothymic disorders, 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 dilettantes, whereas those with dysthymic disorder often lead morose and colorless lives.

PSYCHOPATHOLOGY

Depressive Syndrome Like other illnesses, depressive disorder clusters into signs and symptoms that constitute what DSM-IV and ICD-10 term major depressive episode (Tables 14.6-2). These criteria attempt to set an operational threshold for depressive disorder based on a specified number of items and their temporal patterns. The diagnosis of clinical depression cannot be accomplished by a checklist: The DSM-IV diagnostic criteria for major depressive disorder provide only a general guide. Only after an in-depth phenomenological approach can a clinician ascertain diagnosis of a depressive disorder. 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.

Table 14.6-2
DSM-IV Criteria for Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-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 either by 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 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Mood Disturbances Mood change, usually considered the sine qua non of morbid depression, appears 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 this broad range of mood disturbances are under investigation at the Salpêtrière Hospital in Paris. Our focus here is primarily on painfully aroused mood (depression) and diminished capacity for pleasure (anhedonia), two mood disturbances given selective weight in DSM-IV and ICD-10.

DEPRESSED MOOD The term "depressed mood" refers to negative affective arousal, variously described as depressed, anguished, mournful, irritable, or anxious. These terms tend to trivialize a morbidly painful emotion, typically experienced as worse than the severest physical pain. Thus depressed mood has a somatic quality that 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. This 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 lift somewhat in the evening. Suicide may represent an attempt to find deliverance from such unrelenting psychic torment; death can be experienced as comforting (Fig. 14.6-2).

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 from headache (Fig. 14.6-3), epigastric pain, precordial distress, and so on, in the absence of any evidence of diagnosable physical illness. Such conditions have been described as "depressio sine depressione," or "masked depression." In such cases, commonly observed in older patients, the physician

FIGURE 14.6-2 *Death Giving Comfort* by Kaethe Kollwitz (1867–1945).

FIGURE 14.6-3 *Headache* by Honoré Daumier (1808–1879).

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 inquiring whether the patient has lost the sense of pleasure is not enough; 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. This is best illustrated by William Shakespeare in Hamlet's disgust: "How weary, stale, flat, and unprofitable seem to me all the uses of the world" (Act I, Scene II). In the extreme, patients 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.

Patients with severe depression may complain of being emotionally cut off from others and experience depersonalization and a world that seems strange to them (derealization). The impact of the loss of emotional resonance can be so pervasive that patients may denounce values and beliefs that had previously given meaning to their lives. For instance, members of the clergy might present with the complaint that they no longer believe in the Church, that they have lost God. The inability of the person with depressive disorder to experience normal emotions (commonly observed among young depressed patients) differs 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 psychomotor changes consist of abnormalities in the motor expression of mental and emotional activity. In severe cases, these changes manifest in specific facial features (Fig. 14.6-4).

PSYCHOMOTOR AGITATION Although agitation (pressured speech, restlessness, hand wringing, and hair pulling) is the more readily observed abnormality, it appears to be less specific to the illness than 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 moderate-to-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.

Long neglected in psychopathological research, psychomotor re-

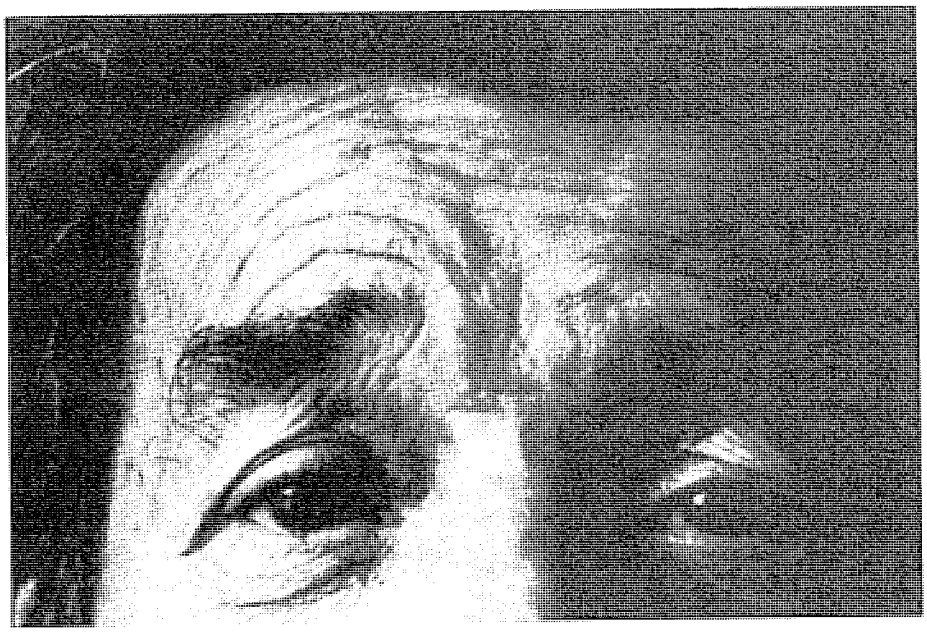

FIGURE 14.6-4 The Swiss neuropsychiatrist Otto Veraguth described a peculiar triangle-shaped fold in the nasal corner of the upper eyelid. The fold, often associated with depression, is referred to as Veraguth's fold. The photograph illustrates this physiognomic feature in a 50-year-old man during a major depressive episode. Veraguth's fold may also be seen in persons who are not clinically depressed, usually while they are harboring a mild depressive affect. Distinct changes in the tone of the corrugator and zygomatic facial muscles accompany depression, as shown on electromyograms. (Courtesy of Heinz E. Lehmann, M.D.)

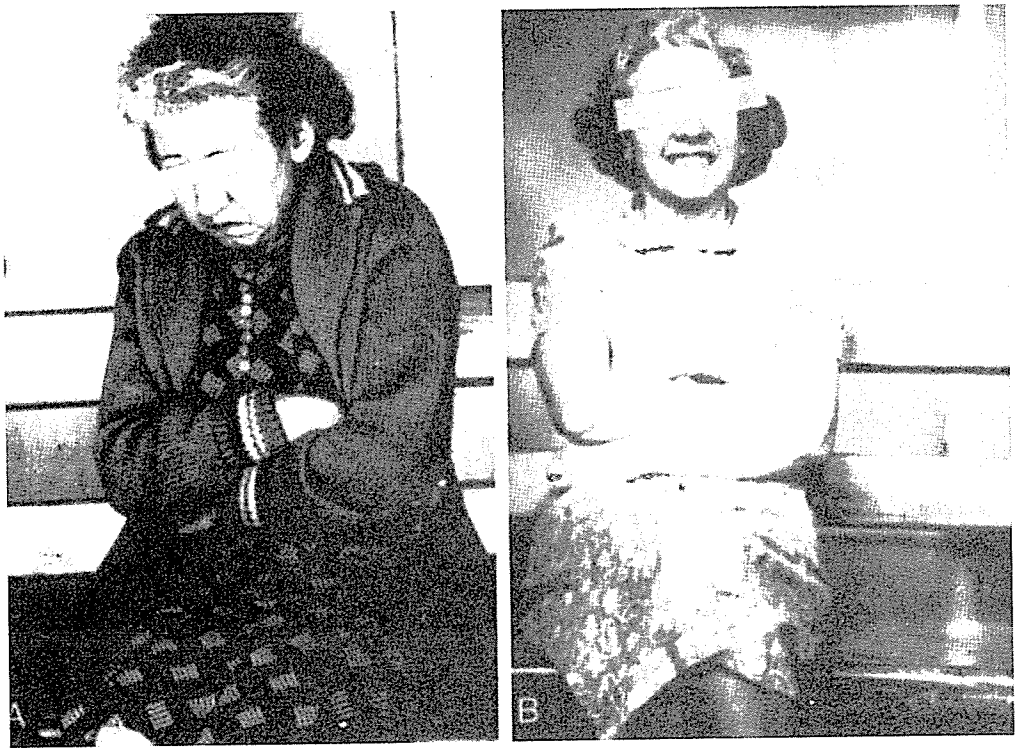

FIGURE 14.6-5 A 38-year-old woman during a state of deep retarded depression **(A)** and 2 months later, after recovery **(B).** Note the turned-down corners of her mouth, her stooped posture, her drab clothing, and her hairdo during the depressed episode. (Courtesy of Heinz E. Lehmann, M.D.)

tardation, can be measured with precision. The Salpêtrière Retardation Scale developed by Daniel Widlöcher and colleagues places special emphasis on the following disturbances: (1) paucity of spontaneous movements; (2) slumped posture with downcast gaze (Fig. 14.6-5); (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, or 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 as pervasive and disabling. This

more 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."

Less linguistically sophisticated patients would simply complain of an inability to perform household chores or difficulty in concentrating on their studies. Such psychomotor deficits in turn underlie depressed patients' diminished efficiency or their inability to work.

PSEUDODEMENTIA The slowing of mental functions can be so pronounced in elderly persons that they experience memory difficulties, disorientation, and confusion.

STUPOR Psychomotor slowing in young persons is sometimes so extreme that patients might slide into a stupor, unable to participate even in such basic biological functions as feeding themselves. Such an episode is often the precursor of bipolar disorder, which later declares itself in a manic episode. Today depressive disorder is diagnosed in its earlier stages, and subtle stupor is much more likely to be encountered clinically.

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 metaphorically describing his total loss of initiative and drive and was engulfed by the disease process. A clinician without the requisite phenomenological training, might consider such a patient bizarre and perhaps even psychotic. Yet the patient responded dramatically to fluoxetine (Prozac) and in 2 weeks was back in school.

Cognitive Disturbances The cognitive view of depression considers negative evaluations of the self, the world, and the future (the negative triad) central to understanding depressed mood and behavior, but it is equally likely that the depressed mood colors perceptions of the self and others or that disturbed psychomotor activity leads to negative self-evaluations. Therefore, instead of being considered causal, the cognitive triad in depression is best approached empirically as a psychopathological manifestation of depression. Those faulty thinking patterns are clinically expressed as (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." Self-evaluations that indicate an extremely low image of self might nonetheless reflect an accurate perception of one's impairment from psychomotor retardation.

MOOD-CONGRUENT PSYCHOTIC FEATURES In depressive disorder with psychotic features (Table 14.6-3), negative thinking acquires grossly delusional proportions and is maintained with such conviction that the thoughts are not amenable to change by evidence to the contrary. According to Kurt Schneider, delusional thinking in depression derives from humankind's four basic insecurities, those

Table 14.6-3
DSM-IV Criteria for Severity/Psychotic/Remission Specifiers for Current (or Most Recent) Major Depressive Episode

Note: 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.

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 here 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 2 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 2 months, no significant signs or symptoms of the disturbance.

Unspecified

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 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 mismanaged their finances and 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 and 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 have fleeting auditory or visual hallu-

cinations with extremely unpleasant content along the lines of their delusions (e.g., hearing accusatory voices or seeing themselves in coffins or graveyards). All of these 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.

MOOD-INCONGRUENT PSYCHOTIC FEATURES Sometimes so-called first-rank or schneiderian-type symptoms can 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 it would comment on every action that she would undertake. The patient recovered fully with thymoleptic medication. There is no reason to believe that in this patient the feelings of somatic passivity and running commentary indicated 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 accompany them. (In other instances, the clinician must seek a history of alcohol or substance use disorder or withdrawal as a putative explanation for mood incongruence in psychotic depression.) In brief, incidental schneiderian first-rank symptoms should not distract from the diagnosis of an affective disorder if otherwise typical signs and symptoms are present.

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 of ever recovering and kill themselves. The suicide attempt is not, however, undertaken in the depth of melancholia. One severely depressed patient 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 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. Hopelessness on mental status evaluation in a patient recovering from depression should alert the clinician to the possibility of such an outcome.

There is no basis for the common belief that inquiring about suicide provokes such behavior. On the contrary, patients are often relieved that the physician appreciates the magnitude of their suffering. Suicidal ideation is commonly expressed indirectly (e.g., in a wish not to wake up or to die from a malignant disease). Some depressed persons are tormented with suicidal obsessions and are constantly resisting unwanted urges or impulses to destroy themselves. Others might yield to such urges passively (e.g., by careless driving or by walking into high-speed traffic). A third group harbors elaborate plans, carefully preparing a will and taking out insurance. Deliberate planning indicates a very high suicidal risk. The foregoing examples are not exhaustive; they are meant to remind clinicians in charge of depressed patients to be always alert to the possibility of suicide.

Vegetative Disturbances

The Greeks considered depression a somatic illness and ascribed it to black bile; hence the term "melancholia." The mood change in depressive disorder is accompanied by measurable alterations of biorhythms that implicate midbrain dysfunction. Once the changes occur, they tend to be independent of the environment throughout much of the episode, and as a consequence, 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 in other circadian rhythms, especially matinal worsening of mood and psychomotor performances. These disturbances are central to the DSM-IV concept of melancholia (Table 14.6-4), a form of depression in which such biological concomitants predominate. A smaller subgroup of depressed persons exhibits a reversal of the vegetative and circadian functions, with increases in appetite and sleep—and sometimes in sexual functioning—and an evening worsening of mood; in this atypical pattern (Table 14.6-5), patients characteristically exhibit mood reactivity and sensitivity to rejection.

ANOREXIA AND WEIGHT LOSS The most reliable somatic indicators of depressive disorder include 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 result from a delusional belief that the food has been poisoned.

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

WEIGHT GAIN Overeating, decreased activity, or both may result in weight gain. In middle-aged patients it may aggravate preexisting diabetes mellitus, 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).

Table 14.6-4
DSM-IV Criteria for Melancholic Features Specifiers

Specify if:

With melancholic features (can be applied to major depressive episodes occurring in major depressive disorder, bipolar I disorder 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 perceived as distinctly different from the kind of feeling experienced after the death of a loved one)
   (2) the depression is regularly worse in the morning
   (3) early morning awakening (at least 2 hours before usual time of awakening)
   (4) marked psychomotor retardation or agitation
   (5) significant anorexia or weight loss
   (6) excessive or inappropriate guilt

Table 14.6-5
DSM-IV Criteria for Atypical Features Specifier

Specify if:

With atypical features (can be applied when these features predominate during the most recent 2 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 2 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, present for most of the time, for at least 2 weeks:
   (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) resulting in significant social or occupational impairment

C. Criteria are not met with melancholic features or with catatonic features during the same episode.

INSOMNIA Sleep disturbance, a cardinal sign of depression, often 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, 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 succeed but ultimately aggravates the sleep patterns and insomnia. This is also true for sedative-hypnotic agents, which are often prescribed by the busy general practitioner who has not spent enough time diagnosing the depressive condition. Although sedatives (including alcohol) effectively reduce the number of awakenings in the short term, they are not effective in the long run because they further diminish stage 3 and stage 4 sleep. They are not antidepressants, and they tend to prolong the depression.

HYPERSOMNIA Young depressed patients, especially those with bipolar tendencies, often exhibit excessive sleep and 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 started the day somewhat slowly, he now could not get out of bed to go to school. That alarmed his mother, prompting sleep consultation. Formerly a B student, he had been failing most of his courses in the 6 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. Extensive neurological and general medical workup had also proven negative. He slept 12 to 15 hours a day but denied cataplexy, sleep paralysis, and hypnagogic hallucinations. During psychiatric interview he denied being depressed but admitted that he had lost interest in everything except his dog. He had no drive, participated in no activities, and had gained 30 pounds in 6 months. He believed he was "brain damaged" and wondered whether it was worth living like that. The question of suicide disturbed him as it was contrary to his religious beliefs. These findings led to the prescription of desipramine (Norpramin) in a dosage that was gradually increased to 200 mg a day over 3 weeks. Not only did desipramine reverse the presenting complaints, but it also pushed him to the brink of a manic episode.

The affective nature of the disorder in such patients is often unrecognized, and their behavior is attributed to "laziness." The vignette also illustrates the emergence of manic behavior during antidepressant treatment. Such shifts in polarity are common in major depressive disorder and necessitate revising the diagnosis to a bipolar disorder (contrary to the admonitions of DSM-IV).

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. These include deficits in stage 4 or delta sleep, as well as more intense rapid eye movement (REM) activity in the first third of the night. More specific to depressive disorders—and whether suffering from insomnia or hypersomnia—nearly two-thirds of patients exhibit a marked shortening of REM latency, the period from the onset of sleep to the first REM period. This abnormality is observed throughout the depressive episode and may also be seen during relatively euthymic periods in persons with recurrent depression. The occurrence of short REM latency in the younger "well" relatives of the affectively ill suggests that neurophysiological abnormalities might precede the overt psychopathological manifestations of the illness; upon closer scrutiny, these well relatives will often be found to meet criteria for subthreshold mood conditions such as dysthymic disorder, intermittent depression or labile temperament.

Few data exist on the consistency of sleep electroencephalographic (EEG) abnormalities in patients from episode to episode. However, clinical experience suggests that a patient observed over time (even during the same episode) may exhibit insomnia and morning worsening of mood and activity during one period of the disorder and hypersomnia extending to late morning hours during 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 disorders. Patients with major depressive disorder tend to exhibit insomnia more stereotypically episode after episode; despite extreme fatigue, they rarely oversleep. Such fatigue coexisting with negative affective arousal is even more exhausting.

SEASONALITY Another classic biorhythmic disturbance in mood disorders is seasonal (especially autumn-winter) accentuation or precipitation of depression. Most of those patients experience increased energy and activation, if not frank hypomania, in the spring. In the fall and winter, they complain of fatigue, tend to crave sugars, and overeat and oversleep. The hypersomnia in some of these patients is associated with delayed (rather than short) REM latencies. These data suggest dysregulation of circadian rhythms in depressive disorders rather than mere phase advance. Although autumnal-winter depression has received the greatest attention, there also exist summer depressions; the former appear related to reduction of daylight (photoperiods), and the latter to increased temperature. The DSM-IV criteria for seasonal pattern specifiers are listed in Table 14.6-6.

SEXUAL DYSFUNCTION Decreased sexual desire is seen in both depressed men and women. In addition, some women experience 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 might mistakenly ascribe the depression to the marital conflict and

Table 14.6-6
DSM-IV 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 2 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 any nonseasonal major depressive episodes that may have occurred over the individual's lifetime.

devote unnecessarily zealous psychotherapeutic attention to conjugal issues. Decreased or lost 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 by the physician's focus on the sexual complaint. Tragically, some men with depressive disorder have been subjected to permanent penile implants before receiving more definitive treatment for their depression. This is less likely to occur in the sildenafil (Viagra) era, but even treatment with such agents would not necessarily resolve the impotence in clinically depressed patients without competent treatment of the mood disorder.

A small subgroup of persons with depressive disorder may exhibit increased sexual drive or activity of a "compulsive" nature. These patients tend to have other atypical features as well; hence the increased sexual drive can be considered the "fifth reverse vegetative sign" (after evening or morning worsening of mood, initial insomnia, hypersomnia, and weight gain). In these depressed persons, increased sexual drive may indicate a mixed episode of bipolar disorder. Further scrutiny in such cases will often reveal a premorbid cyclothymic or hyperthymic temperament.

Manic Syndrome As with clinical depression, the psychopathology of mania (Table 14.6-7) 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 share such symptoms as irritability, anger, insomnia, and agitation. Actually, an excess of such symptoms of escalating intensity suggests a mixed phase or mixed episode (Table 14.6-8) of mania and depression occurring simultaneously. Manic and mixed episodes represent the hallmark of what was once termed manic-depressive psychosis and is currently termed bipolar I disorder.

Table 14.6-7
DSM-IV Criteria for Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 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 3 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: Manic-like 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 14.6-8
DSM-IV 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 1-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: Mixed-like 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.

Although milder mania (hypomania [Table 14.6-9]) can contribute to success in business, leadership roles, and the arts, recurrences of even mild manic symptomatology are typically disruptive. The elated mood tends to produce overoptimism concerning one's abilities, which coupled with the impulsivity characteristic of mania, often leads to disaster. Thus, accurate and early diagnosis is paramount.

Classic mania as formulated in the DSM-IV operationalization of manic episode (Table 14.6-7) is relatively easy to recognize. Misdiagnosis was once rampant in North American practice as clinicians

Table 14.6-9
DSM-IV Criteria for Hypomanic Episode

A. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout 4 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 3 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: Hypomanic-like episodes that are clearly precipitated by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of bipolar II disorder.

confused severe mania with schizophrenia, and its milder variants with normality or with narcissistic and sociopathic personality disorders. Like the misdiagnosis of depressive conditions, such errors of clinical judgment are due to a lack of familiarity with the phenomenology of the classic illness. Again, DSM-IV criteria provide only a guideline. The actual diagnosis requires careful history and phenomenologic understanding. The manic patient lifts the observer's mood, makes the examiner smile and even laugh, and can often be irritating. The patient's speech is fast and may even appear "loose," but it also can often be witty. Finally, the behavior is typically dramatic, expansive, and jesting. For the experienced clinician, the overall gestalt experienced in the presence of such patients is emotionally and qualitatively distinct from that of persons with schizophrenia or frontal lobe diseases; the latter conditions tend to leave the examiner "cold." These considerations become clearer when the clinical observer systematically examines the psychopathology of mania in the areas of mood, behavior, and thinking.

Mood Disturbance Mood disturbance in mania represents a contrast to that observed in depression, but not entirely.

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

LABILITY AND IRRITABILITY The prevailing positive mood in mania is not stable, and momentary crying or bursting into tears is common. Also, the high is so excessive that many patients experience it as intense nervousness. When crossed, patients can become extremely irritable and hostile. Thus, lability and irritable hostility are as much features of the manic mood as is elation.

Psychomotor Acceleration Accelerated psychomotor activity, the hallmark of mania, is characterized by overabundant energy and activity and rapid, 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 associations are difficult to follow; such clang associations are often based on rhyming or chance perceptions and can be lightning fast. The pressure to speak may continue despite development of hoarseness.

IMPULSIVE BEHAVIOR Manic patients are typically impulsive, disinhibited, and meddlesome. They are intrusive in their increased involvement with others, leading to friction with family members, friends, and colleagues. They are distractible and move quickly, not only from one thought to another, but also 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; paying the bills of total strangers in bars; giving away furniture; impulsive marriages; engaging in risky business ventures; gambling; and sudden trips. Such pursuits can lead to personal and financial ruin.

DELIRIOUS MANIA An extremely severe expression of mania (once known as "Bell's mania"), delirious mania involves frenzied physical activity that continues unabated and leads to a life-threatening medical emergency. This complication, the manic counterpart of stupor, is rare today. (There is no need to invoke here the concept of catatonic features as advocated by DSM-IV (Table 14.6-10). The DSM-IV position is terminologically confusing and phenomenologically imprecise).

Table 14.6-10
DSM-IV 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

Vegetative Disturbances Vegetative disturbances are more difficult to evaluate in mania than in depression.

HYPOSOMNIA The cardinal sign is decreased need for sleep—the patient sleeps only a few hours but feels energetic on awakening. Some patients may actually go sleepless for several days. This practice could lead to 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, frequent bars, and squander their savings on prostitutes. 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 specter of AIDS.

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

GRANDIOSITY, LACK OF INSIGHT, AND DELUSION FORMATION The patient exhibits inflated self-esteem and a grandiose sense of confidence and achievements. Behind that facade, however, 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. This is a serious omission because this lack of insight leads manic patients to engage in activities that harm themselves 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, mania nearly always reaches delusional proportions, including delusions of exceptional mental and physical fitness and exceptional talent; delusions of wealth, aristocratic ancestry, or other grandiose identity; delusions of assistance (i.e., well-placed persons or supernatural powers are assisting 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 (e.g., 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. (Lack of insight also unfortunately means that hospitalization must usually be arranged on an involuntary basis).

MOOD-INCONGRUENT PSYCHOSIS Psychosis in the setting of mania and mixed manic episodes is typically mood congruent. The sense of physical well-being and mental alacrity is so extraordinary that it is understandable why manic patients 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 that have been traditionally considered mood incongruent can be understood phenomenologically to arise from the powerful mental experiences of mania.

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 he had responded to lithium (Eskalith, Lithobid) each time, 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 could more accurately 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 disseminate knowledge about the true nature of mania to psychiatrists and all others concerned. That's why I will never accept lithium again—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.

The vignette illustrates the possibility that even some of the most psychotic manifestations of mania represent explanatory delusions, the patient's attempt to make sense of the experience of mania. The DSM-IV criteria for severity/psychotic specifiers for manic and mixed episode (Tables 14.6-11 and 14.6-12) are more concerned with operational rigor than with the phenomenological sophistication needed to understand such core manic experiences. (Many manic patients abuse alcohol and stimulants to enhance their mental state; 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. Diagnostically, history of a partial manic syndrome is preferably obtained from significant 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. DSM-IV stipulates a minimum duration of 4 days for hypomania; however, the Memphis and Zurich studies found a modal duration of 2 days. Finally, although DSM-IV states that treatment-emergent hypomania in a depressed patient does not count toward a diagnosis of bipolarity, prospective observations show that nearly all such episodes are followed eventually by spontaneous hypomania (or mania).

DIAGNOSTIC CLASSIFICATION

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 between bipolar and depressive (unipolar) disorders. Thus, bipolar disorders range from the classic manic and depressive episodes of psychotic intensity (bipolar I disorder) through recurrent major depressive episodes, alternating with hypomanic episodes (bipolar II

Table 14.6-11
DSM-IV Criteria for Severity/Psychotic/Remission Specifiers for Current (or Most Recent) Manic Episode

Note: 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 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 2 months following the end of the manic episode.

In full remission: During the past 2 months, no significant signs or symptoms of the disturbance were present.

Unspecified.

Table 14.6-12
DSM-IV Criteria for Severity/Psychotic/Remission Specifiers for Current (or Most Recent) Mixed Episode

Note: Can be applied to a manic 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 2 months following the end of the mixed episode.

In full remission: During the past 2 months, no significant signs or symptoms of the disturbance were present.

Unspecified.

disorder), and cyclothymic mood swings. Likewise, depressive disorders include those with psychotic severity, melancholia, atypical features, and dysthymic variants.

Major and specific attenuated subtypes are distinguished on the basis of severity and duration. In dysthymic and cyclothymic disorders a partial mood syndrome—consisting of such subthreshold features as subdepressive and hypomanic periods—is maintained, intermittently or continuously, for at least 2 years. Subdepressive periods dominate in dysthymia; in cyclothymia, they alternate with hypomania. The onset is typically in adolescence or childhood, and most persons with these diagnoses seen in young adulthood have had low-grade mood symptoms for 5 to 10 years. Major mood disorders, which generally begin much later in life, require the presence of either a full manic episode or a full depressive episode—sustained for at least 1 or 2 weeks, respectively—and an episodic course, typically permitting recovery or remission from episodes. DSM-IV recognizes that a significant minority of persons with major depressive disorders fails to achieve full symptomatic recovery and should thus be qualified as chronic or in partial remission. They are no longer considered dysthymic (the misleading convention in DSM-III).

Dichotomy or Continuum? Although, in the extreme, bipolar and depressive (unipolar) disorders can be discriminated clinically and therapeutically (Table 4.6-13), clinical observations testify to a vast overlap between those extremes. 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 that tends to persist after the resolution of manic or major depressive episodes. Even more common is major depressive disorder complicating cyclothymic dis-

Table 14.6-13
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	3 to 6 months	3 to 12 months
Psychomotor activity	Retardation > agitation	Agitation > retardation
Sleep	Hypersomnia > insomnia	Insomnia > hypersomnia
Family history		
Bipolar disorder	Yes	±
Unipolar disorder	Yes	Yes
Alcoholism	±	Yes
Pharmacological response		
Cyclic antidepressants	Induce hypomania-mania	±
Lithium carbonate	Acute antidepressant effects	Ineffective

Table 14.6-14
DSM-IV 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

order, which should be reclassified as an important course variant of bipolar II disorder. Likewise, recent evidence indicates that dysthymic disorder may precede major depressive disorder in as many as a third of cases. Moreover, one in four persons with major depressive disorder subsequently develops hypomanic or manic episodes and so should be reclassified as having bipolar disorder. Finally, unexpected crossing from dysthymic disorder to hypomanic or 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. Epidemiological studies in the community have also shown much fluidity between various subthreshold and major mood disorders.

Heterogeneity undoubtedly exists among mood disorders; however, the foregoing observations suggest that much of the unipolar terrain might be "pseudo-unipolar" (i.e., soft bipolar). The clinical significance of these considerations lies in the fact that many DSM-IV subtypes of mood disorders are not pure entities, and considerable overlap and switches in polarity take place. They also provide some rationale, for instance, for why lithium (or lithium 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 hyperthymic traits. Finally, several studies have shown that bipolar patients with cyclothymic premorbid adjustment and interepisodic adjustment are at considerable risk for antidepressant-induced rapid cycling, defined as a rapid succession of major episodes with few or no intervals of freedom.

Such considerations further testify to the wisdom of supplementing major mood diagnoses with temperamental attributes. DSM-IV only makes subtle or oblique hints concerning this, and instead provides the practitioner with an unwieldly, if not useless, array of episode and course specifiers. The DSM-IV criteria for longitudinal course specifiers are given in Table 14.6-14.

As Kraepelin illustrated in his monograph, course is best captured graphically. DSM-IV only provides examples of this for depressive disorders (Fig. 14.6-6) and limits itself to four patterns. Kraepelin, after diagramming 18 illustrative patterns for the entire spectrum of manic-depressive illness, declared that the illness pursued an indefinite number of courses.

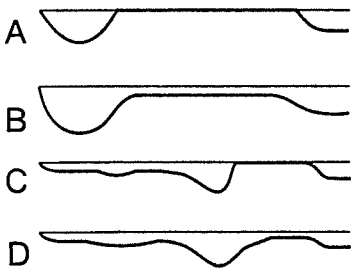

FIGURE 14.6-6 Graphs depicting prototypical courses. **A,** Course of major depressive disorder, recurrent, with no antecedent dysthymic disorder and a period of full remission between the episodes. This pattern predicts the best future prognosis. **B,** Course of major depressive disorder, recurrent, with no antecedent dysthymic disorder but with prominent symptoms persisting between the two most recent episodes (i.e., partial remission is attained). **C,** 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,** Course of major depressive disorder, recurrent, with antecedent dysthymic disorder and no period of full remission between the two most recent episodes. This pattern, commonly referred to as double depression, is seen in about 20 to 25 percent of persons with major depressive disorder. (Reprinted with permission from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders,* ed 4. Copyright, American Psychiatric Association, Washington, DC, 1994.)

Table 14.6-15
DSM-IV 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 hypomanic-like 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

DEPRESSIVE DISORDERS

The broad category of depressive disorders includes major depressive disorder, dysthymic disorder, and depressive disorder not otherwise specified.

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 2 weeks, and (4) cannot be explained by another process known to cause depressive symptoms, such as normal bereavement, certain physical conditions commonly associated with depression, or another mental disorder. It can be single and, more commonly, recurrent. (Tables 14.6-15 and 14.6-16).

Comorbid Physical Disease Those considerations raise the question whether major depressive disorder should be limited to depressions of unknown etiology (i.e., those without documented

Table 14.6-16
DSM-IV 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 2 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 manic-like, mixed-like, or hypomanic-like 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 14.6-17
DSM-IV 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 delirium or dementia.

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 depressive-like 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 symptoms of both mania and depression are present and neither predominates

physical causes). The DSM-IV approach has basically been that when the cause is known, the condition should be diagnosed as mood disorder due to a general medical condition (Table 14.6-17) which must be specified, or substance-induced mood disorder (Table 14.6-18). The problem with this approach is that many common medical factors historically associated with depression (e.g., use of certain antihypertensive agents) do not seem to be causative in the etiological sense, but rather are triggering agents in otherwise predisposed persons. This is analogous to the situation with life events, which no longer are used in making distinctions between reactive and endogenous subtypes of depression. A more troubling implication is that major depressive disorders without demonstrable physical disease are not medical or otherwise biological. More importantly there appears to be no reliable or valid way for a clinician to decide that a depressive condition is due to a specified medical condition. For this reason it is generally more practical to diagnose the depressive disorder on Axis I and specify the contributing physical condition on Axis III. In brief, the designation "due to a general medical condition" is both cumbersome and redundant. The author considers major depressive disorder to represent the final common pathway of multifactorial interacting factors—both physical and psychological—a syndrome that should be diagnosed irrespective of presumed cause.

Diagnostic Threshold Another question concerning the DSM-IV definition of major depressive disorders relates to the threshold at which a constellation of depressive features becomes a condition distinct from the ordinary blues. According to the current definition, a person who responds to a setback with lowered spirits and self-doubt, difficulty in sleeping and concentration, and decreased sexual interest for 14 days qualifies for a diagnosis of a major depressive disorder of mild intensity. Many clinicians would consider such a condition a relatively minor departure from normality, probably no more than an adjustment disorder. Obviously, criteria other than signs, symptoms, and duration are necessary to differentiate a depressive disorder from adjustment reactions to life situations. The presence of the following characteristics might assist in such a differentiation.

- By definition, a major depressive disorder should be incapacitating. Previously, much attention was paid to the interpersonal consequences of depression. Recent evidence indicates that measurable deficits in work performance are often early manifestations. Afflicted persons also do not benefit from taking leisure time, and hence prescribing vacations is futile.
- Depressive disorder is usually perceived as a break from a person's usual or premorbid self, which can be so striking that sufferers may feel as though they are losing their minds. 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.
- 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 neuraglia wholly unknown to healthy life.

Table 14.6-18
DSM-IV 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 substance intoxication or withdrawal, and the symptoms in A developed during, or within a month of, significant substance intoxication or withdrawal.
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 symptoms precede the onset of the substance abuse or dependence; persist for a substantial period of time (e.g., about a month) after the cessation of acute withdrawal or severe intoxication; are substantially in excess of what would be expected given the character, duration, or amount of the substance used; or there is other evidence suggesting the existence of an independent non–substance-induced mood disorder (e.g., a history of recurrent non–substance-related major depressive episodes).
D. The disturbance does not occur exclusively during the course of 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 amphetamine-like substance]; cocaine, hallucinogen; inhalant; opioid; phencyclidine [or phencyclidine-like 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

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

- History of past episodes.
- 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, one study that prospectively followed persons with minor or neurotic depression found that such pedigrees predicted the development of future major episodes. DSM-IV makes no provision for considering such familial factors in diagnostic decisions. In clinical practice these factors often strongly influence whether depression is taken seriously.

Single Episode and Recurrent Subtypes About a third of all major depressive episodes do not recur (Table 14.6-15). Such patients tend to be older and less likely to have a positive family history for mood disorders, and have a more protracted (1 to 2 years) course of the disorder. Patients with major depressive disorder, single episode should be distinguished from those experiencing their first episodes of major depressive disorder, recurrent (Table 14.6-16). 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 established that recurrent major depressive disorders are more familial than their single-episode counterparts. The average length of episodes is 6 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, in contrast to an average of eight to nine major episodes in bipolar disorder.

Melancholic Features In DSM-III the neurotic-endogenous distinction was deleted. Neurotic depression was largely absorbed by dysthymic disorder and the major depressive disorders that complicate it; endogenous depression became "melancholic features," a qualifying phrase for major depressive disorders in which anhedonia, guilt, and psychomotor-vegetative disturbances dominate the clinical picture (Table 14.6-4). DSM-IV retains these 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 (i.e., 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 common in clinical practice, well-conducted studies in the United States and Europe have shown that the prospective follow-up course of those patients is heterogeneous, including melancholic and even psychotic depressions and, in some instances, bipolar transformation. The progression of a precipitated, relatively mild depression (reactive illness) to severe psychotic depression—or one with melancholic autonomy—during prospective observation suggests 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. This is embodied in Donald Klein's concept of endogenomorphic depression, which could be precipitated and mild (endoreactive) while exhibiting disturbances of hedonic mechanisms refractory to current interpersonal contexts. Many authorities believe that such features dictate 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 pre-

ferred nosological term for the revised concept of endogeneity; 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 from the rank of those with melancholic features, develop into delusional depressions. In young persons they tend to be retarded, even stuporous, and are best considered initial episodes of a bipolar disorder. More typically, psychotic depression that develops for the first time after the age of 50 often presents with severe agitation, delusional guilt, hypochondriacal preoccupations, early-morning awakening, and weight loss. The premorbid adjustment of such patients is classically characterized as "obsessoid." Their mournful-anxious mood and agitation are autonomous, being refractory to psychological interventions, and they endure great psychic suffering. Except for the fact that generally one to two episodes occur in late-onset (so-called involutional) depressions, they represent a severe variant of DSM-IV melancholia. Kraepelin's postulation of a cerebrovascular basis for such cases makes the ventricular enlargement and white matter opacities reported in psychotic depressions of some interest. Their etiological specificity for persons with late-onset psychotic depression has been controversial, however, since younger (more bipolar) persons with psychotic depression exhibit similar findings. 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; hence the decision in DSM-IV to use psychotic features merely as a specifier for major depressive episode (Table 14.6-3). Emerging data, nonetheless, might eventually force a change in this convention. For instance, William Coryell and collaborators in the NIMH collaborative study of depression have shown psychotic depression to be the most consistent unipolar subtype across episodes. Alan Schatzberg's work, originally conducted at Harvard, likewise underscores the uniqueness of psychotic depression based on neuroendocrine and putative neurochemical considerations.

Chronic Depression The DSM-IV criteria for chronic specifier appear in Table 14.6-19. The clinical situation, however, is much more complex than these conventions. For instance, the symptom profile in chronic depressions usually displays low-grade intensity rather than 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. 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, 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. The leisure deficits and 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 common. That these 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 pharmacologic 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 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. Therefore, observed pathological characterological changes—clinging or hostile dependence, demandingness, touchiness, pessimism, and low self-esteem—are best considered as "postdepressive personality" changes. A dangerous stereotypical thinking holds that because a patient has not responded adequately to standard treatments (the illness has become chronic), the disorder must have a characterological substrate. The long duration of the disorder often leads the patient to identify with the failing functions of depression, producing the self-image of being a depressed person. This self-image itself represents a malignant cognitive manifestation of the depressive disorder and dictates vigorous treatment targeted at the mood disorder.

Table 14.6-19
DSM-IV Diagnostic 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 2 years

Dysthymic Disorder Dysthymic disorder (Table 14.6-20) is distinguished from chronic 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 patients reach their 20s. A late-onset subtype, much less prevalent and not well characterized clinically, has been identified among middle-aged and geriatric populations, largely through epidemiological studies in the community.

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

Table 14.6-20
DSM-IV 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 2 years. **Note:** In children and adolescents, mood can be irritable and duration must be at least 1 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 2-year period (1 year for children or adolescents) of the disturbance, the person has never been without the symptoms in criteria A and B for more than 2 months at a time.

D. No major depressive episode has been present during the first 2 years of the disturbance (1 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 2 months) before development of the dysthymic disorder. In addition, after the initial 2 years (1 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 before age 21 years
Late onset: if onset is age 21 years or older

Specify (for most recent 2 years of dysthymic disorder):
With atypical features

(1) low-grade chronicity for at least 2 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 document that many patients invest whatever energy they have in work, leaving none for leisure and family or social activities, which results in marital friction. These 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."

The dedication of persons with dysthymic disorder to work has been suggested to be an overcompensation and a defense against their battle with depressive 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 what some clinicians might consider "existential depression," with feelings of being empty and lacking any joy in life outside their work. Such persons have been described as leading monocategorical existences. Others present clinically because their low-grade dysphoria has intensified into a major depression 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; hence the designation "double depression" as a prominent course pattern illustrated in DSM-IV for depressive illness (Fig. 14.6-6). This pattern, commonly seen in clinical practice, consists of the baseline dysthymic disorder fluctuating in and out of depressive episodes. The more prototypical patients with dysthymic disorder often complain of having been depressed since birth or of feeling depressed all the time. They seem, in the apt words of Kurt Schneider, to view themselves as belonging to an "aristocracy of suffering." Such 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 raises uncertainty as to whether dysthymic disorder belongs in Axis I or 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). This means that marked disturbances in appetite and libido are uncharacteristic, and psychomotor agitation or retardation is not observed. This all translates into a depression with attenuated symptomatology. However, subtle endogenous features are not uncommonly observed: inertia, lethargy, and anhedonia that are characteristically worse in the morning. Because patients presenting clinically often fluctuate in and out of a major depression, the core DSM-IV criteria for dysthymic disorder tend to emphasize vegetative dysfunction, whereas the alternative criterion B for dysthymic disorder (Table 14.6-21) in a DSM-IV appendix lists cognitive symptoms.

Although dysthymic disorder represents a more restricted concept than 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 dysthymia" or, in the framework of Peter Tyrer, as part of 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 habit-

Table 14.6-21
DSM-IV 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

ual 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 14.6-1). Dysthymia then can be viewed as a more symptomatic form of that temperament (introduced in a DSM-IV appendix as a depressive personality disorder). Sleep EEG data indicate that many persons with dysthymic disorder at baseline exhibit the sleep patterns of those with acute major depressive disorder, providing support for the constitutional nature of the disorder. Further evidence for that position comes from studies demonstrating high rates of familial affective disorder in dysthymic disorder, depressive temperament, or both.

The clinical picture of dysthymic disorder that emerges from the foregoing description is quite varied, with some patients proceeding to major depression, while others manifest the pathology largely at the personality level. The foregoing considerations suggest that a clinically satisfactory operationalization of dysthymia must include symptomatic, cognitive, and trait characteristics.

A 27-year-old, male, grade-school teacher presented with the chief complaint that life was a painful duty that 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 "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 feelings; sexual activity, in which he had engaged with two different women, had involved pleasureless orgasm. He said he felt empty, going through 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 out suicide, believing that it would hurt his students and the small community in which he lived.

Dysthymic Variants Dysthymia is not uncommon in patients with chronically disabling physical disorders, particularly among elderly adults. Dysthymia-like clinically significant subthreshold depression lasting 6 or more months has also been described in neurological conditions, including stroke. According to a recent WHO conference, this condition aggravates the prognosis of the underlying neurological disease and, therefore, deserves pharmacotherapy. Ongoing studies should provide more explicit clinical recommendations on this topic.

Prospective studies on children have revealed an episodic course of dysthymia with remissions, exacerbations, and eventual complications by major depressive episodes, 15 to 20 percent of which might even progress to hypomanic, manic, or mixed episodes postpuberty. Persons with dysthymic disorder presenting clinically as adults tend to pursue a chronic unipolar course that may or may not be complicated by major depression. They rarely develop spontaneous hypomania or mania. However, when treated with antidepressants, some of them may develop brief hypomanic switches that typically disappear when the antidepressant dose is decreased. Although DSM-IV would not allow the occurrence of such switches in dysthymia, systematic clinical observation has verified their occurrence in as many as a third of dysthymic patients. In this 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.

Depressive Disorder Not Otherwise Specified The DSM-IV criteria for depressive disorder not otherwise specified, are presented in Table 14.6-22. What follows are descriptions of conditions that are commonly used in the epidemiological, clinical, or pharmacological literature but do not easily fit into the official nosology of depressive disorders. Some represent complex interweaving of depression with personality constructs. For instance, community studies have revealed a prevalent pattern of intermittent depressive

Table 14.6-22
DSM-IV 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 1 week postmenses.
2. Minor depressive disorder: episodes of at least 2 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 2 days up to 2 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 14.6-23
DSM-IV 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 2-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)
      (i) 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
   (2) the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
   (3) 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)
   (4) the symptoms are not better accounted for by bereavement (i.e., a normal reaction to the death of a loved one)
B. There has never been a major depressive episode, and criteria are not met for dysthymic disorder
C. 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 hypomanic-like episodes are substance or treatment induced
D. The mood disturbance does not occur exclusively during schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, or psychotic disorder not otherwise specified

manifestations with brief episodes, below the 2-week duration threshold for major depressive disorder. In so-called minor depressive disorder (Table 14.6-23), observed in primary care settings, the depression is subthreshold, milder than major depression and yet not protracted enough to be considered dysthymic. These varied manifestations of depression argue for a continuum model (Fig. 14.6-7) as originally envisaged by Kraepelin. Lewis Judd and collaborators at the University of California at San Diego have suggested that subthreshold depressive symptoms—without necessarily meeting the criterion for mood change—might actually represent the most common expressions of a depressive diathesis. From such a subsyndromal symptomatic depressive base, individuals predisposed to depressive illness are said to fluctuate in and out of the various DSM-IV and subthreshold subtypes of depressive disorders. This viewpoint is presently most cogent for subsyndromal symptomatic depression that follows major depressive disorder, a strong predictor of subsequent frequent relapse or chronic course. There is an important message for the clinician here: treat subsyndromal symptomatic depression residual to major depressive disorder.

Recurrent Brief Depressive Disorder Now in a DSM-IV appendix (Table 14.6-24), recurrent brief depressive disorder derives

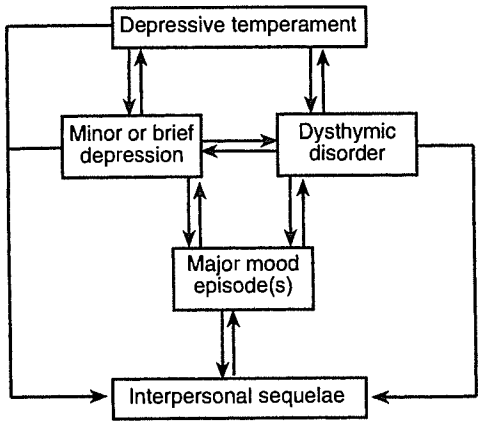

FIGURE 14.6-7 Relation of various depressive conditions supporting a spectrum concept. (Reprinted with permission from Akiskal HS: Dysthymia: Clinical and external validity. Acta Psychiatr Scand *89*(Suppl):19, 1994.)

Table 14.6-24
DSM-IV 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 2 days but less than 2 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 hypomanic-like 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.

from British work on young adults with frequent suicide attempts and epidemiological studies conducted in a young adult cohort in Zurich. It is described as short-lived depressions that usually recur on a monthly basis but are not menstrually related. They could coexist with major depressive disorder and dysthymic disorder. Such patients are believed to be more prevalent in primary care than in psychiatric settings. Those seen in psychiatric settings are likely to be given Axis II diagnoses such as borderline personality disorder.

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.

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

Conceptually, however, one can 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 psychodynamic authors invoke the concept of masochism to explain why certain persons cannot rid themselves of painful life situations, implying that they somehow contribute to their maintenance. Current thinking is that some of those presumed self-defeating traits are more situation specific than previously believed and might resolve with the elimination of the situation. So-called self-defeating features then are best considered psychodynamic mechanisms rather than indicators of a specific personality. At the present stage of knowledge, they do not deserve to be raised to the level of a nosological entity (hence, their disappearance from DSM-IV). Chronic adjustment disorder might describe the chronic demoralization observed among some individuals stuck in chronically unsatisfactory life situations. Many more might fulfill the criteria for dysthymia.

Neurasthenia A century-old term developed by the American neuropsychiatrist George Beard, neurasthenia 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 is now used more in China than in the rest of the world, the recent worldwide popularity of the concept of chronic fatigue syndrome attests to the clinical acumen of classic physicians. Despite much energy invested in finding a viral or immunological cause, current descriptions tend to suggest an anxiety or mood disorder basis for some (but not all) of those with the syndrome. However, what circumstances would lead anxiety or depression to manifest primarily in fatigue is as elusive as it was 100 years ago. Like many 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.

Postpsychotic Depressive Disorder of Schizophrenia

DSM-IV describes postpsychotic depressive disorder of schizophrenia 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.

According to DSM-IV, persons whose presentation meets those research criteria (Table 14.6-25) would be diagnosed as having depressive disorder not otherwise specified. As already pointed out, mood or depressive disorder not otherwise specified represents such a hodgepodge of clinical situations that the designation not otherwise specified is at best meaningless and at worst countertherapeutic. In all postpsychotic depressions, one must first exclude a missed bipolar diagnosis. Negative symptoms due to classic antipsychotics—especially depot phenothiazines and those due to the residium of schizophrenia once positive symptoms are brought under control—should be distinguished from the depressive episodes that complicate the course of schizophrenia in young, intelligent patients.

Table 14.6-25
DSM-IV 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.

BIPOLAR DISORDERS

Four bipolar disorders are included in DSM-IV: bipolar I disorder, bipolar II disorder, cyclothymic disorder, and bipolar disorder not otherwise specified.

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 with schizophreniform features; only when a more classic manic episode occurs is the affective nature of the disorder clarified. In a third group several depressive episodes take place before the first manic episode. A careful history taken from significant others often reveals dysthymic or cyclothymic traits that antedated the frank onset of manic episodes by several years.

According to DSM-IV, bipolar I disorder, single manic episode (Table 14.6-26) describes patients 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 (Tables 14.6-27 through 14.6-31. For clinicians and researchers alike it is more meaningful to chart a patient's course in color over time—for example using red rectangles for manic, blue for depressive, and violet for mixed episodes, with hypomanic, dysthymic, and cyclothymic periods 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, originally championed by Kraepelin, is routinely used in mood clinics. Robert Post at the NIMH has developed this approach into systematic clinical science.

On average, manic episodes predominate in youth, and depressive episodes in later years. Although the overall sex ratio is about one to one, men on 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 in boys, and mixed-manic (dysphoric-explosive) presentations are the mode. Childhood-onset depression must also be considered a major risk for ultimate bipolar transformation. This is based on the following characteristics: (1) early age of onset; (2) even sex ratio; (3) prominence of irritability, labile moods, and explosive anger, suggesting mixed episodes; (4) questionable response to antidepressants, hypomanic switches, or both; (5) high recurrence rate after depression; and (6) familial affective loading. Mania can also first appear after age 65, though a diligent search often reveals a past mild, forgotten, or untreated depressive episode in earlier years.

Table 14.6-26
DSM-IV 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 2 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 14.6-27
DSM-IV 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 14.6-28
DSM-IV 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

Acute Mania Mania typically escalates over a period of 1 to 2 weeks; more-sudden onsets have also been described. The DSM-IV criteria (Table 14.6-7) stipulate (1) a distinct period that represents a break from premorbid functioning, (2) a duration of at least 1 week, (3) an elevated or irritable mood, (4) at least three to four classic

Table 14.6-29
DSM-IV 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 14.6-30
DSM-IV 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

Table 14.6-31
DSM-IV 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

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. Florid grandiose psychosis with paranoid features, a common presentation of mania, further contributes to the aggression. Alcohol use, observed in at least 50 percent of bipolar I patients (often during 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, hallucinatory, even first-rank, psychotic experiences in mania has been described. Recent research has 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 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 type I disorder, which has strong genetic determinants. Available evidence does not permit separating recurrent mania without depressive episodes from that type as a distinct nosological entity.

Secondary Mania Although there is some suggestion that postpartum mania without depression is distinct from familial bipolar I disorder (in which depressive, manic, and especially mixed manic episodes 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 include the postpartum-onset specifier [see Table 13.4-3], rather than a separate mood disorder diagnosis). Mania without prior bipolarity can arise in the setting of such somatic illnesses as 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, syphilis, 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. These patients do not easily fit into the DSM-IV category of mood disorder due to a general medical condition (Table 14.6-17) because most of the conditions appear to be cerebral. Such factors must always be diligently sought in manias of late life.

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 psychodynamically as a denial of loss. Although such explanations may be plausible in individual cases, no systematic data suggest that these 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 abuse of stimulant drugs, treatment with antidepressants, or sleep deprivation. In all of these 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 can also occur in persons who abruptly abstain from alcohol after one or more decades of chronic use and then develop classic bipolar I disorder.

Chronic Mania DSM-IV does not specifically address the diagnostic questions posed by the 5 percent of bipolar I patients who have a chronic manic course. These cases commonly represent deterioration of course dominated by recurrent manic episodes grafted on a hyperthymic baseline. Noncompliance with pharmacological treatment is the rule. Recurrent excitement is personally reinforcing, subjective distress is minimal, and insight is seriously impaired. Thus the patient sees no reason to adhere to treatment. Episodic or chronic alcohol abuse, prevalent in such patients, has been suggested as a contributory cause of the chronicity. Some authorities further consider comorbid cerebral pathology responsible for nonrecovery (and increased mortality) from manic excitements occurring in late life.

Grandiose delusions (e.g., 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 subsumed such patients under the category "manic dementia." Organic factors such as head trauma and chronic alcohol abuse may contribute to the deterioration. Nonschizoid premorbid adjustment, a family history of bipolar I disorder, and the absence of flagrant formal thought disorder can be marshaled in establishing the affective basis of these poor-prognosis manic states.

Bipolar Mixed Phase Momentary tearfulness and even depressed mood are commonly observed at the height of mania or during the transition from mania to retarded depression. These transient labile periods, which occur in most bipolar I disorder patients, must be contrasted with mixed episodes proper.

The latter, variously referred to as "mixed mania" or "dysphoric mania," are characterized by dysphorically excited moods, irritability, anger, panic attacks, pressured speech, agitation, suicidal ideation, severe insomnia, grandiosity, and hypersexuality, as well as persecutory delusions and confusion. Severely psychotic mixed states that involved hallucinations and schneiderian symptoms risk being labeled "schizoaffective." A correct diagnosis is mandatory because conventional antipsychotic drugs tend to exacerbate the depressive component and failure to use mood stabilizers can prolong the patient's misery.

New research data from mood centers worldwide on mixed mania suggest that dysphoric mania—mania and full-blown depression occurring simultaneously—is relatively uncommon. Two to four depressive symptoms from the list of depressed mood, helplessness, hopelessness, fatigue, anhedonia, guilt, and suicidal ideation, or impulses, or both, in the setting of a manic syndrome, appear to suffice for the diagnosis of mixed manic states, which occurs in 50 percent of patients with bipolar disorder sometime during their lives. Mixed states occur predominantly in females in whom mania is superimposed on a depressive temperament or a dysthymic baseline. These considerations suggest that the DSM-IV concept of mixed episode (Table 14.6-8) as a cross-sectional mixture of mania and depression is simplistic and phenomenologically naive. The emerging conceptualization of mixed mania is a manic state intruding upon long-term depressive traits.

Depressive Phase Psychomotor retardation, with or without hypersomnia, marks the uncomplicated depressive phase of bipolar I disorder. Onset and offset are often abrupt, though onset can also occur gradually over several weeks. Patients may recover into a free interval or switch directly into mania. Switching into an excited phase is particularly likely when antidepressants have been used. However, not all patients develop mania after antidepressant treatment of bipolar depression. Some develop a mixed agitated depression; indeed, patients may be stuck for many months in a severe depressive phase with some manic admixtures such as racing thoughts and sexual arousal. DSM-IV does not specifically recognize a mixed depressive phase with few manic symptoms occurring during full-blown depression. Such recognition is necessary because these patients don't need continued aggressive antidepressant therapy but mood stabilizers, ECT, or both.

Delusional and hallucinatory experiences are less common in the depressive phase of bipolar I disorder than in the manic and mixed manic phases. Stupor is the more common psychotic presentation of bipolar depression, particularly in adolescents and young adults. Pseudodemented organic presentations appear to be the counterpart of stupor in elderly adults.

Cyclothymic Disorder An attenuated bipolar disorder that typically begins insidiously before the age of 21, cyclothymic disorder is characterized in DSM-IV by frequent short cycles of subsyndromal depression and hypomania (Table 14.6-32). The author's research has revealed alternating patterns of moods, activity, and

Table 14.6-32
DSM-IV Diagnostic Criteria for Cyclothymic Disorder

A. For at least 2 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 1 year.

B. During the above 2-year period (1 year in children and adolescents), the person has not been without the symptoms in criterion A for more than 2 months at a time.

C. No major depressive episode, manic episode, or mixed episode has been present during the first 2 years of the disturbance. **Note:** After the initial 2 years (1 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 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 14.6-33
Clinical Features of Cyclothymic Disorder

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

Behavioral manifestations:

- 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

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

Table 14.6-34
Spectrum of Bipolar Disorders Compared With Unipolar Depression

	Bipolar I:	At least one manic episode
Soft bipolar	Bipolar II:	Recurrent depressions with hypomania and cyclothymic disorder
Soft bipolar	Bipolar III: (pseudounipolar)	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 14.6-35
DSM-IV 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.
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
Chronic
With catatonic features
With melancholic features
With atypical features
With postpartum onset

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

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cognition (Table 14.6-33), which are more explicit than the DSM-IV criteria. The course of cyclothymia is continuous or intermittent, with infrequent periods of euthymia. Shifts in mood often lack adequate precipitants (e.g., sudden profound dejection with social withdrawal for a few days switching into cheerful, gregarious behavior). Circadian factors may account for some of the extremes of emotional lability, such as the person's going to sleep in good spirits and waking up early with suicidal urges. The mood changes of cyclothymia are best described as "endoreactive" in the sense that endogenous overreactivity seems to determine the sudden shifts in mood and behavior (e.g., falling in love with a person one has just met and as quickly falling out of love).

Mood swings in these ambulatory patients are overshadowed by the chaos that the swings produce in their personal lives. Repeated romantic breakups or marital failures are common because of interpersonal friction and episodic promiscuous behavior. Uneven performance at school and work is also common. Persons with cyclothymic disorder are dilettantes; they show great promise in many areas, but rarely bring any of their efforts to fruition. As a result, their lives are often a string of improvident activities. Geographical instability is a characteristic feature; easily attracted to a new locale job, or love partner, they soon lose interest and leave in dissatisfaction. Polysubstance abuse which occurs in as many as 50 percent of such persons, is often an attempt at self-treatment.

Bipolar II Disorder (and the Soft Bipolar Spectrum) Research conducted during the past three decades showed 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 (pure unipolar disorder), exists an overlapping group of intermediary forms characterized by recurrent major depressive episodes and hypomania. Table 14.6-34 summarizes the author's observations in defining the clinical subtypes within this intermediary realm best described as "soft bipolarity." The most accepted of the subtypes is bipolar II disorder (with spontaneous hypomania), elevated to the status of a nosological entity in DSM-IV (Table 14.6-35). Current data worldwide indicate that bipolar II disorder is actually more prevalent than bipolar I disorder. This certainly appears true in the outpatient setting, where 30 to 50 percent of persons with major depressive disorder have been reported to conform to the bipolar II pattern.

The following 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.

This vignette is nearly identical to the autobiographical description provided by the British poet William Cowper three centuries earlier:

> I have known many a lifeless and unhallowed hour . . . long intervals of darkness interrupted by short returns of peace and joy . . . For many succeeding weeks to rejoice day and night was all my employment. Too happy to sleep much, I thought it was lost time that was spent on slumber.

The hypomania at the end of depressive episodes in most bipolar II patients does not persist long; it is usually measured in days. The modal duration of hypomania found in Memphis and Zurich studies was 2 days. Another common form of bipolar II disorder is major depressive disorder superimposed on cyclothymic disorder, in which hypomania precedes and follows major depression, the entire interepisodic period characterized by cyclothymic mood instability. As a result, these are difficult bipolar II patients to manage in clinical practice.

Hypomania in bipolar II disorder can be defined as minimanic episodes occurring spontaneously. Bipolar II disorder—especially when major depressions are superimposed on cyclothymia—is thus best characterized as cyclical or "cyclothymic depression."

The depressive episodes of patients with bipolar disorder often have admixtures (e.g., flight of ideas, increased drives and impulsivity in sexual and other domains). The phenomenon of lithium augmentation is perhaps best explained by the high prevalence of pseudounipolar depressions with subtle hypomania either during or following a depressive episode, as well as the mixed simultaneous presence of depressive and hypomanic symptoms. The latter are not as severe as dysphoric mixed states, but are refractory to antidepressants nonetheless.

Hypomania The common denominator of the soft spectrum of bipolar disorders is the occurrence of hypomania. Hypomania (Table 14.6-9) refers to a distinct period of at least a 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; distractibility is uncommon in hypomania, and insight is relatively preserved. Hypomania is distinguished from mere happiness in that it tends to recur (happiness does not) and can sometimes be mobilized by antidepressants. In cyclothymic disorder it alternates with minidepressions; in hyperthymic temperament it constitutes the person's habitual baseline. These 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 or chronic hypomanic traits).

Because hypomania is experienced either as a rebound relief from depression or as pleasant, short-lived, ego-syntonic mood state, persons with bipolar II disorder rarely report it spontaneously. Skillful questioning is thus required to make 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 hypomanic manifestations for hypomania in the DSM-IV scheme basically list the signs and symptoms of mania in criterion A and B for mania (Table 14.6-9) but require fewer items and shorter duration. Clinical and epidemiological studies in the United States and Europe have revealed a richer range of manifestations including an increase in cheerfulness and jocularity; gregariousness and people seeking; greater interest in sex; talkativeness, self-confidence, and optimism; and decreased inhibitions and sleep need. The clinician must ascertain that those experiences were not due to stimulant or alcohol withdrawal. Depressive and hypomanic periods are often not easily discerned because chronic caffeinism, stimulant abuse, or both complicate the depression. In such instances, diagnosis should be based on clinical observation for 1 month after detoxification.

When in doubt, direct clinical observation of hypomania—sometimes elicited by antidepressant pharmacotherapy—provides definitive evidence for the bipolar nature of the disorder. Unfortunately DSM-IV denies bipolar status to treatment-emergent hypomanic episodes. Follow-up studies in juvenile and young adults with pharmacological hypomania have demonstrated that nearly all such individuals progress to spontaneous hypomanic (or manic) episodes. Although DSM-IV stipulates a minimum duration of 4 days for hypomania, any recurrent hypomania coupled with major depression should count toward the diagnosis of bipolar II.

Seasonal Patterns Seasonality is observed in many cyclic depressions, often with autumn or winter anergic depression and energetic periods in the spring. This natural propensity explains why phototherapy may provoke mild hypomanic switches. Although not specifically identified by DSM-IV, seasonal depressions conform, in large measure, to the bipolar II or III pattern. Furthermore, preliminary evidence suggests that treatment with classic antidepressants disrupts the baseline seasonality, with the depressive phase appearing in the spring and summer. The changes antidepressants induce in seasonal depressions probably represent a special variant of the rapid-cycling phenomenon.

Temperament and Polarity of Episodes New systematic clinical observations have revealed that bipolar II disorder (characterized predominantly by depressive attacks) arises more often from a hyperthymic or cyclothymic baseline, whereas bipolar I disorder (defined by manic attacks) not uncommonly arises from the substrate of a depressive temperament. When the hyperthymic temperament occurs in bipolar I disorder, it is usually associated with a recurrent mania, which is an uncommon bipolar course. A prospective 11-year NIMH study of major depressive disorder patients who switched to bipolar II disorder showed that "mood-labile" (cyclothymic) and "energetic-active" (hyperthymic) temperament traits were highly specific and reasonably sensitive predictors of such an outcome.

Bipolarity is conventionally defined by the alternation of manic (or hypomanic) and depressive episodes. The foregoing data on temperaments suggest that a more fundamental characteristic of bipolarity is the reversal of temperament into its "opposite" episode (in the case of the bipolar II spectrum, from cyclothymia and hyperthymia to major depression). Such findings suggest that the intrusion of cyclothymic and hyperthymic traits into a depressive episode may underlie the instability of the bipolar II subtype and could partly explain why bipolar II depression often has mixed features. These considerations may have important implications for preventing recurrence. For instance, a prospective study of the onset of bipolar disorder in the offspring or sibs of adults with the disorder found that children with depressive onsets as their first episode (and which were usually treated with antidepressants) had significantly higher rates of recurrence than those with manic or mixed onsets (treated with lithium) during a 3-year prospective observation. It appears that tem-

peramental 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 interepisodic cyclothymia and hyperthymia. The relation appears particularly strong in the teenage and early adult years, when the use of such substances often represents self-medication for the mood instability. It is not just self-treatment for selected symptoms associated with the down or up phases (e.g., alcohol to alleviate the insomnia and nervousness characteristic of both phases), it also augments certain desired ends (e.g., stimulants to enhance high-energy performance and sexual behavior associated with hypomania). How many display alcohol and substance abuse secondary to an underlying bipolar diathesis remains to be determined. But in view of findings suggesting a link between polysubstance abuse and suicide in adolescents with bipolar familial backgrounds, the use of mood stabilizers in these adolescents should be strongly considered. Although alcohol and stimulant use continues into adult years in a considerable number of bipolar disorder patients, such use is often unrelated to familial alcoholism, and frequently tends to dwindle during long-term follow-up, which supports the self-medication hypothesis. To complicate matters, in a substantial minority of cases, bipolar mood swings appear for the first time after abrupt cessation of long-term alcohol use; it is not uncommon for such mood swings to escalate into full-blown bipolar syndromes.

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 (Table 14.6-36). Thus rapid cyclers are rarely free of affective symptoms and suffer serious vocational and interpersonal incapacitation. Lithium is often only modestly helpful to those patients, as are traditional antipsychotic agents; most antidepressants readily induce excited episodes and thus aggravate the rapid-cycling pattern. A balance among mood stabilizers, antipsychotic drugs, and antidepressants may be difficult to achieve. Many such patients require frequent hospitalization because they develop explosive excitement and precipitous descent into severe psychomotor inhibition. The disorder is a roller coaster nightmare for the patient, significant others, and the treating physician. Treating these patients is an art.

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) borderline hypothyroidism; (3) menopause; (4) temporal lobe dysrhythmias; (5) alcohol, minor tranquilizer, stimulant, or caffeine abuse; and (6) long-term, aggressive use of antidepressant medications. Most clinically identified patients are bipolar II women in middle age or upper social classes. Rapid cycling is uncommon from a bipolar I base.

Table 14.6-36
DSM-IV Diagnostic 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 2 months or a switch to an episode of opposite polarity (e.g., major depressive episode to manic episode).

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, self-confidence and eloquence 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 application. Notable artistic achievements are found among those with soft bipolar disorders, especially cyclothymic disorders. 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 central to the creative process. As talent is the necessary ingredient of creativity, how might soft bipolarity contribute? The simplest hypothesis is that depression might provide insights into the human condition, and the activation associated with hypomania helps in producing the artistic work. A more profound interpretation suggests 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 in the parent's or the patient's life often create the unique biographical landmarks that might be immortalized in an artistic medium.

Bipolar Disorder Not Otherwise Specified The criteria for bipolar disorder not otherwise specified are listed in Table 14.6-37.

Recurrent hypomanic episodes without intermittent depressions

Table 14.6-37
DSM-IV 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 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

(example 2 in the DSM-IV criteria for bipolar disorder not otherwise specified are almost never observed clinically.

Recurrent Brief Hypomania Recurrent brief depressive disorder as a transitional form between dysthymia and major depression or brief hypomanic episodes often have been missed during evaluations performed by nonclinicians. Some patients who meet the Zurich description might therefore belong in the soft bipolar spectrum. Indeed, subsequent evaluation and analyses have revealed high rates of comorbidity between recurrent brief depression and brief hypomania. Thus, some recurrent brief depressive cases appear to be variants of bipolar disorder. The subtle bipolar nature of recurrent brief depressive disorder is clinically supported by the fact that the very few such patients the author has encountered in his own practice did poorly with antidepressant monotherapy but benefited from mood stabilizers used alone or combined with antidepressants.

The recurrent hypomanic counterpart of recurrent brief depressive disorder is described under soft bipolar conditions. By DSM-IV criteria, it represents an instance of bipolar disorder not otherwise specified.

Hysteroid Dysphoria The category hysteroid dysphoria 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 (i.e., 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 synthesis of endogenous antidepressants in the brain. The use of the epithet "hysteroid" was used to convey that the apparent character pathology was secondary to a biological disturbance in the substrates governing affect, drives, and reward. The intense, giddy, unstable life of the patient with hysteroid dysphoria suggests links to cyclothymic disorder or bipolar II disorder. This 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). Like patients with bipolar depression, they respond preferentially to monoamine oxidase inhibitors (MAOIs). In brief, hysteroid dysphoria appears to be a variant of bipolar II with cyclothymic-irritable traits. Other variants of bipolar II disorder with hyperthymic-narcissistic traits are described under soft bipolar disorder and represent instances of bipolar disorder not otherwise specified.

Bipolar III Disorder In bipolar III disorder (which is not an official nosological term but can be subsumed under bipolar disorder not otherwise specified) evidence of bipolarity is softer, such as a single brief episode of an antidepressant-mobilized switch. In a related subgroup of cryptic bipolar disorders, strong evidence for familial bipolarity raises the possibility that some phenotypically "unipolar" depressed patients are nonetheless constitutionally bipolar; in such cases, history for hypomania occurring in discrete episodes is not obtained; 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, bipolar III patients may constitute 10 to 20 percent of those with major depressive disorder. Thus, many patients with so-called unipolar depression are actually "pseudounipolar." The presence of marked narcissistic traits is a helpful clinical clue that a clinically depressed patient might belong to the group of those with hyperthymic depressions.

MOOD DISORDERS NOT OTHERWISE SPECIFIED

After all diagnostic information has been obtained, some depressed and bipolar or otherwise affective patients do not meet the specific criteria for the mood conditions described thus far. Mood disorders not otherwise specified is a statistical concept for filing purposes and not a clinical description. The author prefers to consider such cases as undiagnosed mood disorders rather than using the DSM-IV categories of depression disorder not otherwise specified, bipolar disorder not otherwise specified or mood disorder not otherwise specified.

What follows are descriptions of conditions that commonly appear in the psychiatric literature but do not easily fit into the official nosology of mood disorders. They represent hybrids between mood and anxiety disorders.

Mixed Anxiety-Depressive Disorder The inclusion of anxious depressive states in a DSM-IV appendix acknowledges the simultaneous occurrence of anxious (e.g., the threat loss represents) and depressive (e.g., the despair of loss) cognition in a person confronted with a major aversive life situation. The admixture implies that the psychopathology progresses from anxiety to depression, that the patient's mental state is still in flux, and that the ongoing dynamics partly explains the subacute or chronic nature of the disorder. Anxious depression serves to point to the common presence of anxiety in depressive states, especially its greater visibility when the depression is less prominent. Patients with the latter presentation are reportedly most prevalent in general medical settings. This should not come as a surprise, because depressive symptoms that motivate medical consultation commonly complicate generalized anxiety states with a subthreshold level of symptomatology. Some authorities argue that neurotic depressions arise as maladaptive responses to anxiety and on that basis suggest retaining the "neurotic depression" rubric. Recent preliminary genetic data indirectly support the contention that certain (unipolar) depressive and (generalized) anxiety states are related. However, more research is needed before such an entity can be unequivocally accepted as an official nosological category. The difficulty is that as currently defined, anxious depressions are heterogeneous. In patients refractory to anxiolytic or antidepressant treatment or both, practitioners must entertain the diagnosis of a complex bipolar II disorder with mixed features. Indeed, recent genetic investigations suggest that bipolar II disorder with panic attacks might represent a special form of bipolar disorder.

Atypical Depression Although a delimited version of atypical depression was incorporated into DSM-IV as "atypical features (Table 14.6-5) to qualify the cross-sectional picture of depressive disorders, this construct is much broader in the clinical research literature. Originally developed in England and currently under investigation at Columbia University in New York, atypical depression 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). Sleep is disturbed in the first half of the night in many persons with atypical depressive disorder, so irritability, hypersomnolence, and daytime

fatigue would be expected. The temperaments of these patients are characterized by inhibited-sensitive traits. The MAOIs and serotonergic antidepressants seem to show some specificity 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. Increasing evidence indicates considerable affinity between atypical depression and bipolar II and III disorders. Furthermore, many patients with dysthymic disorder exhibit atypical features at various times. Actually, atypical depression might be an artifact of the DSM-IV definition of hypomania of 4 or more days. Recent Italian research suggests that many patients with atypical depressive meet criteria for brief hypomania or cyclothymic disorder.

The categories of not otherwise specified in the DSM-IV mood disorders schema largely reflect inadequacies of the operational approach to capture patients whose symptomatology falls between or on the boundaries of more classic diagnoses.

DIFFERENTIAL DIAGNOSIS

A missed mood disorder diagnosis means that the disorder does not receive specific treatment, which has serious consequences. Many such persons drop out of school or college, lose their jobs, get divorced, or may commit suicide. Those with unexplained somatic symptoms are frequent users of the general health system. Others are unwell despite interminable psychotherapy. Some, treated with dopamine receptor antagonists 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 and mental health professionals. Psychiatrists, in particular, should develop the competence to detect the entire spectrum of mood disorders. Despite massive educational efforts, underdiagnosis and undertreatment of mood disorders remain serious problems worldwide.

Although much enthusiasm was generated a decade ago about the potential use of certain biologic markers (e.g., REM latency, dexamethasone (Decadron) suppression test, and the thyrotropin-releasing-hormone test) to corroborate the differentiation of mood disorder from adjacent disorders, no definitive progress justifies their routine use in clinical practice. Faced with unusual or confusing presentations, a systematic clinical approach is still the best method in differential diagnosis (1) to detail all 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 periodically or cyclically, (4) to substantiate adequate 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 the family.

Using the foregoing validating approach, one can examine the affective links of many DSM-IV disorders currently listed under mood disorders not otherwise specified, as well as controversial nosological entities currently categorized as nonmood disorders. The latter include conduct disorders; borderline personality disorder; impulse-control disorders; polysubstance abuse; psychotic disorder not otherwise specified; pain disorder; hypochondriasis; hypoactive sexual desire disorder; circadian rhythm sleep disorder, delayed sleep phase type; bulimia nervosa; and adjustment disorder (with work inhibition). These conditions place special emphasis on selected affective features, such as disinhibited behavior, temperamentality, mood lability, vegetative disturbances, and psychomotor anergia. 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 alcohol and substance use disorders with mood disorders cannot be explained as merely the chance occurrence of two prevalent disorders. Self-medication for mood disorders is insufficiently appreciated by both psychiatrists and other professionals who deal with addiction. Given the clinical dangers of missing an otherwise treatable disorder, mood disorder should be seriously considered as the primary diagnosis if marked affective manifestations persist or escalate after detoxification (e.g. 1 month). This consideration also pertains to cyclothymic disorder and dysthymic disorder, which appear particularly likely to invite self-medication. The clinical validating strategies listed above can further buttress a mood disorder diagnosis.

The DSM-IV category of substance-induced mood disorder (Table 14.6-18) is difficult to validate clinically because in the absence of an affective diathesis, detoxification should, in principle, rapidly clear affective disturbances in persons whose primary problem is that of substance abuse. In the author's view, a dual diagnosis of both a mood disorder and a substance use disorder is a more realistic clinical approach to this group of patients. Bipolarity, particularly bipolar II disorder, should be sought in the interface of mood and substance use disorders.

A 27-year-old married businessman employed in an international family venture owned by his father presented with a court-ordered request for psychiatric treatment. He had been found "bringing" cocaine across the U.S.-Mexican border and was briefly jailed. He had used stimulants since his late teens to enhance his already high level of energy. His family was rich, and he had no difficulty affording cocaine. During the previous year, he had needed more cocaine because of greater moodiness and fleeting suicidal ideation, which he linked to increasing tensions between him and his father: "My father was never satisfied with me and demanded greater and greater performance from me." His arrest by police was a major embarrassment for him and his family and motivated his compliance with psychiatric hospitalization to detoxify him. He had not had cocaine for 10 days, exhibited marked lability of mood, and gradually sank into a severe hypersomnic-retarded depression of stuporous proportions. He was treated with tranylcypromine (Parnate) 20 mg twice a day, and within 10 days he switched into hypomania, his mind "exploding with creativity and confidence," marked jocularity and witticisms that entertained other patients, and marked seductiveness toward the nurses. His wife recalled that the patient previously had had several such periods naturally (i.e., "off cocaine"), which had strained their marriage due to "brief sexual liaisons." Reducing the tranylcypromine dosage by 50 percent did not eliminate the hypomanic behavior and lithium 900 mg a day was added. He has since been maintained on a combination of tranylcypromine and lithium for 4 years; he has not relapsed into cocaine use, and following few psychoeducational sessions involving father and spouse, relationships with family and spouse have been less tempestuous. (Since consultation was sought by the patient's 60-year-old mother, an attractive, sophisticated woman, who confessed that for years she had been engaging in "love relationships" with young artists, with apparently her husband's "silent consent"; since at least her mid-20s, she by history would meet the criteria for bipolar II, only treated "on the couch," and both her sister

and brother had received treatment for "alcohol excesses.") Patient states that pharmacotherapy—which did require adjustment now and then—has helped in balancing the "rough edges" of his "high-nervous temperament" and his "periodic lapse into paralyzing fatigue states that occurred at stressful times."

If clinicians had assumed that primarily due to cocaine withdrawal, they would have never treated the patient's bipolar II disorder. DSM-IV conventions in this regard unfortunately bias diagnosis in favor of substance use disorders and, more tragically, against the realistic chance of cure from substances.

There is emerging interest in treating dually diagnosed patients with mood stabilizers, especially anticonvulsants. The intention is to attenuate any withdrawal phenomena from substances of abuse, while treating any underlying or emerging soft bipolar disorders.

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 and should focus instead on competent treatment of the mood disorder. Even in those with chronic or subthreshold mood disorders, personality maladjustment is best considered postaffective, arising from the distortions and conflicts that affective 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 females. The DSM-IV diagnostic criteria for the disorder indicate a liberal mélange of low-grade affective symptoms and behavior. Table 14.6-38 shows that the overlap between borderline personality and mood disorders is extensive, so that giving a "borderline" diagnosis to a person with mood disorder is redundant. Use of personality disorder diagnoses may lead to neglect of the mood disorder or perhaps half-hearted treatment of the mood disorder; failure to respond would then be blamed on the patient's "self-defeating character" or "resistance to getting well," thus exculpating the clinician.

Although more-systematic research is needed on the complex interface of personality and mood disorders, clinically they are often inseparable. As with alcohol and substance use disorders, it is generally preferable to diagnose mood disorders at the expense of personality disorders, which should not be difficult to justify in most cases that satisfy the validating strategies outlined above. When features of personality and mood disorders coexist, it is good practice to defer Axis II diagnoses and embark upon competent treatment of the concurrent mood disorder. Although not all personality disturbances recede with the competent treatment of mood disorders, so many experienced clinicians have seen such disturbances melt away with the successful resolution of the mood disorder that erring in favor of mood disorders is justified.

A 19-year-old single woman presented with the chief complaint that "all men are bastards." Since her early teens, with the onset of her menses, she had complained of extreme variability in her moods on a nearly daily basis; irritability with hostile outbursts was her main affect, though more protracted hypersomnic depressions with multiple overdoses and wrist slashings had led to at least three hospitalizations. She also suffered from migrainous headaches that, according to the mother, had motivated at least one of those overdoses. Despite her tempestuous and suicidal moods that led to these hospitalizations, she complained of "inner emptiness and a bottomless void." She had used heroin, alcohol, and stimulants to overcome this troubling symptom. She also gave history of ice-cream craving and frequent purging. She was talented in English and wrote much-acclaimed papers on the American confessional poet, Anne Sexton. She said she was mentally disturbed because of a series of stepfathers who had all forced "oral rape" between the ages of 11 and 15. She subsequently gave herself sexually to any man she met in bars, no longer knowing whether she was a "prostitute" or a "nice little girl." On two occasions she had inflicted cigarette burns on her vagina "to feel something." She had also engaged in a "brief lesbian relationship" that ultimately left her "emptier" and guilt-ridden; nonetheless, she now believed that she should burn in hell, because she could not get rid of "obsessing" about the excitement of mutual cunnilingus with her much older female partner. The patient's mother, who owned an art gallery, had been married five times and gave history of unmistakable hypomanic episodes; a maternal uncle had died from alcohol-induced cirrhosis. The patient's father, a well-known lawyer known for his "temper and wit," had committed suicide. The patient was given phenelzine (Nardil), eventually raised to 75 mg a day, at which point the mother described her as "the sweet daughter she was before age 13." At her next premenstrual phase, patient developed insomnia, ran away from home at night, started "dancing like a go-go girl," met an "incredibly handsome man" of 45 years (actually, a pornography shop owner) and got married. Lithium augmentation controlled this excited episode. After many dosage adjustments, she is maintained on a combination of lithium (900 mg a day) and divalproex (Depakote) (750 mg a day). The patient now attends college and has completed four semesters in art history. In addition to control of her irritable and suicidal moods, bulimic and migraine attacks have abated considerably. Her marriage has been annulled on the basis that she was not mentally competent at the time of the wedding. She is no longer promiscuous and now expresses fear of intimacy with men she is attracted to. She is receiving individual psychotherapy for this problem.

The author often hears the complaint that even when a mood disorder is diagnosed in a "borderline" patient, response to antidepressants is disappointing. The problem is that affective disorders in these patients usually conform to bipolar II disorder—often complicated by ultrarapid cycling—and many clinicians, including some with biological orientation, may lack sufficient experience in the art of pharmacologically managing patients who markedly deviate from classic bipolar I disorder.

The interface of mood disorders and behavioral disturbances (conduct and attention-deficit/hyperactivity disturbances) in children is even more problematic than in adult psychiatry. Nonetheless, progress has occurred in clinically recognizing certain behavioral

Table 14.6-38
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 Akiskal H, Chen S, Davis G, Puzantian V, Kashgarian M, Bolinger M: Borderline: An adjective in search of a noun. Clin Psychiatry *46:* 41, 1985.

Table 14.6-39
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

Adapted from Akiskal HS, Downs J, Watson S, Daugherty D, Pruitt DB: Affective disorders in referred children and younger siblings of manic-depressives. Arch Gen Psychiatry 43:996, 1985.

manifestations as possible signs of depression in juvenile subjects, including periodic marked decline in school performance; restlessness and pulling or rubbing hair, skin, or clothing; outbursts of complaining, shouting, or crying; and aggressive or antisocial acts (such as kicking the mother, shoplifting) out of character to the child; as well as other acute personality changes ranging from defiant attitudes to negativism and avoidant behavior. Examined carefully, children and pubescent youth with these characteristics often meet the specific criteria for the diagnosis of major depressive disorder or dysthymic disorder. However, most children do not complain of subjective dysphoria; instead, the clinician can observe the depressed affect in the child's facial expressions or overall demeanor. After much resistance, many child clinicians now accept the existence of childhood mood disorders.

Bipolar disorder in children, even in adolescents, is still grossly underdiagnosed at the expense of so-called externalizing disorders. Table 14.6-39 lists those and related conditions often confused with bipolar disorders in juvenile patients. Many children express bipolar disorder in explosive outbursts of irritable mood and behavior (i.e., as a mixed or dysphoric manic state); another pattern is intermittent hypomania and cyclothymia. Children with bipolar disorder are distinguished from those with so-called externalizing disorders by the fact that they are often, though not always, considered charming and likeable, yet overconfident or delusionally grandiose, and may exhibit age-inappropriate sexual behavior, such as lecherous advances toward adult women (e.g., their elementary school teachers): Moreover, they often get worse on stimulant medication. Correct diagnosis depends on the index of suspicion of a clinician who is convinced that bipolarity exists in juvenile subjects. Depression with first onset before age 18 has an extremely high rate of switching into both bipolar I and bipolar II disorders.

Normal Bereavement Bereaved persons exhibit many depressive symptoms during the first 1 to 2 years after their loss, so how can the 5 percent of bereaved persons who have progressed to a depressive disorder be identified?

- Grieving persons and their relatives perceive bereavement as a normal reaction, while those with depressive disorder often view themselves as sick and may actually believe they are losing their minds.
- Unlike the melancholic person, the grieving person reacts to the environment and tends to show a range of positive affects.
- Marked psychomotor retardation is not observed in normal grief.
- Although bereaved persons often feel guilty about not having done certain things that might have saved the life of the deceased loved one (guilt of omission), they typically do not experience guilt of commission.
- Delusions of worthlessness or sin and psychotic experiences in general point toward mood disorder.
- Active suicidal ideation is rare in grief but common in major depressive disorder.
- Mummification (i.e., keeping the belongings of the deceased person exactly as they were before his or her death) indicates serious psychopathology.
- Severe anniversary reactions should alert the clinician 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 can ensue within a few months of that of a spouse, especially among elderly men. Such considerations (highlighted in the work of Sidney Zisook and his San Diego colleagues at the University of California) suggest that it would be clinically unwise to withhold antidepressants from many persons experiencing an intensely mournful form of grief.

A 75-year-old widow was brought by her daughter because of severe insomnia and total loss of interest in daily routines following her husband's death 1 year before. She had been agitated for the first 2 to 3 months and thereafter "sank into total inactivity—not wanting to get out of bed, not wanting to do anything, not wanting to go out." According to her daughter, she was married at 21, had four children, and had been a housewife until her husband's death from a heart attack. Past psychiatric history was negative; premorbid adjustment had been characterized by compulsive traits. During the interview she was dressed in black, appeared moderately slowed, and sobbed intermittently, saying "I search everywhere for him . . . I don't find him." When asked about life, she said "everything I see is black." Although she expressed no interest in food, she did not seem to have lost an appreciable amount of weight. Her dexamethasone suppression test result was 18 μg/dL. The patient declined psychiatric care, stating that she "preferred to join her husband rather than get well." She was too religious to commit suicide but by refusing treatment she felt she would "pine away . . . find relief in death and reunion."

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. Since anxiety disorders rarely first appear after the age of 40, 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 depressive nature of the illness is further supported by a superior response to ECT.

Periodic monosymptomatic phobic and obsessional states exist that can be regarded as affective equivalents on the basis of a family history of mood disorders and their response to thymoleptic agents. Recent data from a large clinical series suggests that 15 percent of patients with obsessive-compulsive disorders develop unmistakable hypomanic symptoms; these patients are best considered to have bipolar II disorder and treated with lithium salts. Social phobias exist that usher in adolescent depression, even a bipolar disorder.

The psychopathological differentiation of anxiety and depressive states has not been entirely resolved. Cognitive factors may differentiate them best (Table 14.6-40). 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, particularly generalized 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 epiphenomenal 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.

Physical Disease Somatic complaints are common in depressive disorders. Some, such as vegetative disturbances, represent the hypothalamic pathology that is believed to underlie 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. The clinician must be vigilant about the likelihood that somatic complaints in depression can also reflect an underlying physical illness. Table 14.6-41 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 ensure that they are not dealing with pseudodepression: (1) functional loss due to physical illness; (2) vegetative signs, such as anorexia and weight loss, as manifestations of such an illness; (3) stress and demoralization secondary to the hospitalization; (4) pain and discomfort associated with the physical illness; and (5) medication adverse effects. On the other hand, nonpsychiatric physicians who manage such patients must consider the diagnosis of depression in the presence of persistent anhedonia; observed depressed mood with frequent crying; observed psychomotor retardation or agitation; indecisiveness; convictions of failure, worthlessness, or guilt; and suicidal ideation. The physician should also suspect clinical depression in all patients who refuse to participate in medical care.

Diagnosing depression in medically ill elderly patients can be particularly difficult. This task should be undertaken diligently because it was recently reported that (especially in those with cardiovascular disease) mortality is accelerated by depression. Depressed elderly adults often deny being "depressed" but complain of anxiety, fatigue, and worsening memory. Hypochondriacal symptoms and pain are common. Patients may exhibit extreme negativism and querulousness when invited to participate in medical procedures; others develop poor fluid and food intake out of proportion to their physical conditions.

Another important diagnostic problem at the interface of mood disorder and physical disease is the rare development of malignancy in patients with an established mood disorder. Patients who had responded well to a given antidepressant during previous episodes now have an unsatisfactory response to the same medication. Even a small dose may cause such alarming symptoms as agitation, dizziness, depersonalization, and illusions, which might indicate an occult malignancy, perhaps in the abdomen or the brain. The psychiatrist

Table 14.6-40
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

Reprinted with permission from Akiskal HS: Toward a clinical understanding of the relationship of anxiety and depressive disorders. In *Comorbidity of Mood and Anxiety Disorders,* JP Maser, CR Cloninger, editors. American Psychiatric Press, Washington, DC, 1990.

Table 14.6-41
Pharmacological Factors and Physical Diseases Associated with Onset of Depression

Pharmacological	Steroidal contraceptives
	Reserpine; α-methyldopa
	Anticholinesterase insecticides
	Amphetamine or cocaine withdrawal
	Alcohol or sedative-hypnotic withdrawal
	Cimetidine; indomethacin
	Phenothiazine antipsychotic drugs
	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

should always be vigilant about the development of life-threatening physical diseases in patients with preestablished depressive disorder.

A 55-year-old woman had suffered from four previous episodes of severe depression that had responded to ECT or amitriptyline (Elavil) or both in her native city of Cairo, Egypt. She immigrated to the United States at age 43 and encountered several major stresses; including unfamiliarity with English, daughter dating a man of Japanese extraction, and a complicated series of operations for uterine prolapse. Then her husband confessed he had had an affair with a much younger woman. For months the patient had complained of intermittent fatigue and expressed anger toward her husband. Her ensuing fifth depressive episode appeared fully "understandable," but her physician's prescription of 25 mg of amitriptyline resulted in dizzy spells that culminated in syncope. Paroxetine (Paxil) 10 mg did not fare any better. An extensive medical workup revealed a retroperitoneal lymphoma. She died 6 months later.

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. Depressive stupor is relatively easy to distinguish from so-called hysterical mutism; 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 of affective 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 of possible somatic factors.

Depressive Pseudodementia The geriatric equivalent of semistupor in younger persons with depressive disorder, depressive pseudodementia is distinguished from primary degenerative dementia by its acute onset without prior cognitive disturbance; a personal or family history of past affective episodes; marked psychomotor retardation with reduced social interaction; self reproach; diurnal cognitive dysfunction (worse in the morning); subjective memory dysfunction in excess of objective findings; circumscribed memory deficits that can be reversed with proper coaching; and a tendency to improve with sleep deprivation.

Chronic Fatigue Syndrome Chronic fatigue syndrome is a complex differential diagnostic problem in view of the subtle 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, 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 2 months. My response was equally short-lived to phenelzine, imipramine (Tofranil), selegiline (Eldepryl), and bupropion (Wellbutrin). I have not responded to serotonin-specific reuptake inhibitors (SSRIs) 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 6 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.

The foregoing clinical picture is compatible with a pseudounipolar or bipolar III disorder as described by the author. Some virologists and immunologists as well as some psychiatrists believe that abnormal substances circulate in the bloodstream supplying the brains of such patients. Industrial toxins have also been suggested.

While awaiting more definitive research on the etiology of chronic fatigue syndrome, the psychiatrist can cautiously consider certain patients for thymoleptic trials. That decision can be bolstered by the following considerations: the patient wakes up with fatigue and dread of facing the day; fatigue is part of a more generalized psychomotor inertia or lack of initiative; fatigue is associated with anhedonia, including sexual anhedonia; and 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 hypomanic-like periods (as in the above vignette) further supports the link between some cases of chronic fatigue and mood disorder. Use of antidepressants without sedative effects, given in gradually increasing doses as tolerated, is a rational strategy; lithium and valproate, though not formally tested in such patients, are rational augmentation choices. Several recent neuroendocrine challenge studies suggest that some chronic fatigue

patients might have a strong anxiety substrate and could be managed accordingly. This is not to say that chronic fatigue is largely a matter of missed affective diagnoses; yet it would be a pity to miss potentially treatable diagnoses. A family or past personal history of classic affective illness or episodes should strongly weigh in this direction. Obviously definitive data are lacking on the essential nature of chronic fatigue, and practitioners should be guided by their own clinical experience, while awaiting new research developments.

Schizophrenia Cross-sectionally, young patients with bipolar disorder might seem psychotic and disorganized and thus schizophrenic. Their thought processes are so rapid that they may seem loose, but, unlike those with schizophrenia, they display expansive and elated affect, which is often contagious. By contrast, the severely retarded bipolar depressive person, whose affect may superficially seem flat, almost never exhibits major fragmentation of thought. The clinician, therefore, should place greater emphasis on the pattern of symptoms than on individual symptoms in the differential diagnosis of mood and schizophrenic psychoses. No pathognomonic differentiating signs and symptoms exist. 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 14.6-42 summarizes the author's clinical experience in the area and lists the most common pitfalls in diagnosis. In the past many bipolar patients, especially those with prominent manic features at onset, were labeled as having "acute schizophrenia" or "schizoaffective schizophrenia." Such misdiagnoses (which typically led to long-term treatment with antipsychotic agents) has been costly in terms of tardive dyskinesia, vocational and social decline, and even suicide. For instance, some patients with postpsychotic depressive disorder of schizophrenia in the DSM-IV scheme (Table 14.6-25) have postmanic depressions that were treated with neuroleptic monotherapy without the benefit of more definitive thymoleptic agents.

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 have sharply risen during the past two decades, cause considerable social impairment, mood symptoms are so prominent that differentiation from schizophrenia is generally not difficult; also such patients usually display more classic bipolar phases before the rapid cycling).

Postpsychotic depressions in persons with established schizophrenia are sometimes due to inadequate control of schizophrenic symptomology. 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 give such patients a diagnosis of both schizophrenia and a depressive disorder and treat the patient accordingly.

Schizoaffective Disorder As the above considerations suggest, depression in the setting of a schizophrenic disorder does not necessarily constitute a distinct nosological entity. 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. This diagnosis should not be considered for a mood psychosis in which mood-incongruent psychotic features (e.g., 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; or (3) mixed episodes of bipolar disorder (which are notorious for signs and symptoms of psychotic disorganization). Official diagnostic systems such as DSM-IV use the category of schizoaffective disorder broadly. Thus patients with clear-cut manic episodes receive a schizoaffective diagnosis if delusions or hallucinations occur in the interepisodic period, in the absence of prominent affective symptoms. Many psychotic symptoms in mood disorders are often explanatory (albeit delusional), whereby the patient tries to make sense of the core experiences of the affective illness. In patients with recurrent episodes, delusional thinking can be carried over into the interepisodic period. Such patients are thus delusional in the absence of prominent mood symptoms and technically (i.e., 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 limiting its features to discrete episodes is artificial. Although neuroleptic agents might be prescribed on an as needed basis to reduce the strong affective charge of those interepisodic delusions, they do not effectively eliminate the affect-laden experiences. Continued thymoleptic treatment (resorting to ECT, if necessary) and an empathic psychotherapeutic approach are 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 author, 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 fashion, 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,

Table 14.6-42
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 irritable and cantankerous mood to paranoid delusions
- Mistaking 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

Adapted from Akiskal HS, Puzantian VR: Psychotic forms of depression and mania. Psychiatr Clin North Am 2:419, 1979.

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 must be "crazy" to believe in her involvement in an international plot, but she could not help but believe in it. Over several months, seen typically in 60-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 psychotherapeutic 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 based entirely on operational criteria; one's opinion of patient's illnesses is not infrequently changed by their response to treatment.

In the author's view, DSM-IV represents something good (operationalization of diagnostic criteria) carried to extreme (arbitrary precision often divorced from clinical reality).

ICD-10

The ICD-10 criteria for mood disorders, which are used throughout the world, are listed in Table 14.6-43. Although these criteria derive in part from DSM-III-R, they are more flexible and clinician-friendly: they do not pretend to impose arbitrary precision on the clinical universe of psychiatry.

Table 14.6-43
ICD-10 Diagnostic Criteria for Mood [Affective] Disorders

Manic episode

Hypomania

A. The mood is elevated or irritable to a degree that is definitely abnormal for the individual concerned and sustained for at least 4 consecutive days.
B. At least three of the following signs must be present, leading to some interference with personal functioning in daily living:
   (1) increased activity or physical restlessness;
   (2) increased talkativeness;
   (3) distractibility or difficulty in concentration;
   (4) decreased need for sleep;
   (5) increased sexual energy;
   (6) mild overspending, or other types of reckless or irresponsible behavior;
   (7) increased sociability or overfamiliarity.
C. The episode does not meet the criteria for mania, bipolar affective disorder, depressive episode, cyclothymia, or anorexia nervosa.
D. *Most commonly used exclusion clause.* The episode is not attributable to psychoactive substance use or to any organic mental disorder.

Mania without psychotic symptoms

A. Mood must be predominantly elevated, expansive, or irritable, and definitely abnormal for the individual concerned. The mood change must be prominent and sustained for at least 1 week (unless it is severe enough to require hospital admission).
B. At least three of the following signs must be present (four if the mood is merely irritable), leading to severe interference with personal functioning in daily living:
   (1) increased activity or physical restlessness;
   (2) increased talkativeness ("pressure of speech");
   (3) flight of ideas or the subjective experience of thoughts racing;
   (4) loss of normal social inhibitions, resulting in behavior that is inappropriate to the circumstances;
   (5) decreased need for sleep;
   (6) inflated self-esteem or grandiosity;
   (7) distractibility or constant changes in activity or plans;
   (8) behavior that is foolhardy or reckless and whose risks the individual does not recognize, e.g., spending sprees, foolish enterprises, reckless driving;
   (9) marked sexual energy or sexual indiscretions.
C. There are no hallucinations or delusions, although perceptual disorders may occur (e.g., subjective hyperacusis, appreciation of colors as especially vivid).
D. *Most commonly used exclusion clause.* The episode is not attributable to psychoactive substance use or to any organic mental disorder.

Mania with psychotic symptoms

A. The episode meets the criteria for mania without psychotic symptoms with the exception of criterion C.
B. The episode does not simultaneously meet the criteria for schizophrenia or schizoaffective disorder, manic type.

(continued)

Table 14.6-43 *(continued)*

C. Delusions or hallucinations are present, other than those listed as typically schizophrenic in criterion G1(1)b, c and d for schizophrenia (i.e., delusions other than those that are completely impossible or culturally inappropriate, and hallucinations that are not in the third person or giving a running commentary). The commonest examples are those with grandiose, self-referential, erotic, or persecutory content.

D. *Most commonly used exclusion clause.* The episode is not attributable to psychoactive substance use or to any organic mental disorder.

Specify whether the hallucinations or delusions are congruent or incongruent with the mood:
With mood-congruent psychotic symptoms
(such as grandiose delusions or voices telling the individual that he or she has superhuman powers)
With mood-incongruent psychotic symptoms
(such as voices speaking to the individual about affectively neutral topics, or delusions of reference or persecution)

Other manic episodes

Manic episode, unspecified

Bipolar affective disorder

Note. Episodes are demarcated by a switch to an episode of opposite mixed polarity or by a remission.

Bipolar affective disorder, current episode hypomanic

A. The current episode meets the criteria for hypomania.

B. There has been at least one other affective episode in the past, meeting the criteria for hypomanic or manic episode, depressive episode, or mixed affective episode.

Bipolar affective disorder, current episode manic without psychotic symptoms

A. The current episode meets the criteria for mania without psychotic symptoms.

B. There has been at least one other affective episode in the past, meeting the criteria for hypomanic or manic episode, depressive episode, or mixed affective episode.

Bipolar affective disorder, current episode manic without psychotic symptoms

A. The current episode meets the criteria for mania without psychotic symptoms.

B. There has been at least one other affective episode in the past, meeting the criteria for hypomanic or manic episode, depressive episode, or mixed affective episode.

Specify whether the psychotic symptoms are congruent or incongruent with the mood:
With mood-congruent psychotic symptoms
With mood-incongruent psychotic symptoms

Bipolar affective disorder, current episode moderate or mild depression

A. The current episode meets the criteria for a depressive episode of either mild or moderate severity.

B. There has been at least one other affective episode in the past, meeting the criteria for hypomanic or manic episode, depressive episode, or mixed affective episode.

Specify the presence of the "somatic syndrome" in the current episode of depression:
Without somatic syndrome
With somatic syndrome

Bipolar affective disorder, current episode severe depression without psychotic symptoms

A. The current episode meets the criteria for a severe depressive episode without psychotic symptoms.

B. There has been at least one well-authenticated hypomanic or manic episode or mixed affective episode in the past.

Bipolar affective disorder, current episode severe depression with psychotic symptoms

A. The current episode meets the criteria for a severe depressive episode without psychotic symptoms.

B. There has been at least one well-authenticated hypomanic or manic episode or mixed affective episode in the past.

Specify whether the psychotic symptoms are congruent or incongruent with the mood:
With mood-congruent psychotic symptoms
With mood-incongruent psychotic symptoms

Bipolar affective disorder, current episode mixed

A. The current episode is characterized by either a mixture or a rapid alternation (i.e., within a few hours) of hypomanic, manic, and depressive symptoms.

B. Both manic and depressive symptoms must be prominent most of the time during a period of at least 2 weeks.

C. There has been at least one well-authenticated hypomanic or manic episode, depressive episode, or mixed affective episode in the past.

Bipolar affective disorder, currently in remission

A. The current state does not meet the criteria for depressive or manic episode of any severity or for any other mood [affective] disorder (possibly because of treatment to reduce the risk of future episodes).

B. There has been at least one well-authenticated hypomanic or manic episode in the past and in addition at least one other affective episode (hypomanic or manic, depressive, or mixed).

Other bipolar affective disorders

Bipolar affective disorder, unspecified

Depressive episode

G1. The depressive episode should last for at least 2 weeks.

G2. There have been no hypomanic or manic symptoms sufficient to meet the criteria for hypomanic or manic episode at any time in the individual's life.

G3. *Most commonly used exclusion clause.* The episode is not attributable to psychoactive substance use or to any organic mental disorder.

(continued)

Table 14.6-43 *(continued)*

Somatic syndrome

Some depressive symptoms are widely regarded as having special clinical significance and are here called "somatic." (Terms such as biological, vital, melancholic, or endogenomorphic are used for this syndrome in other classifications.)

A fifth character may be used to specify the presence or absence of the somatic syndrome. To qualify for the somatic syndrome, *four* of the following symptoms should be present:

(1) marked loss of interest or pleasure in activities that are normally pleasurable;
(2) lack of emotional reactions to events or activities that normally produce an emotional response;
(3) waking in the morning 2 hours or more before the usual time;
(4) depression worse in the morning;
(5) objective evidence of marked psychomotor retardation or agitation (remarked on or reported by other people);
(6) marked loss of appetite;
(7) weight loss (5% or more of body weight in the past month);
(8) marked loss of libido.

In *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical descriptions and diagnostic guidelines*, the presence or absence of the somatic syndrome is not specified for severe depressive episode, since it is presumed to be present in most cases. For research purposes, however, it may be advisable to allow for the coding of the absence of the somatic syndrome in severe depressive episode.

Mild depressive episode

A. The general criteria for depressive episode must be met.

B. At least two of the following three symptoms must be present:
(1) depressed mood to a degree that is definitely abnormal for the individual, present for most of the day and almost every day, largely uninfluenced by circumstances, and sustained for at least 2 weeks;
(2) loss of interest or pleasure in activities that are normally pleasurable;
(3) decreased energy or increased fatiguability.

C. An additional symptom or symptoms from the following list should be present, to give a total of at least *four*:
(1) loss of confidence or self-esteem;
(2) unreasonable feelings of self-reproach or excessive and inappropriate guilt;
(3) recurrent thoughts of death or suicide, or any suicidal behavior;
(4) complaints or evidence of diminished ability to think or concentrate, such as indecisiveness or vacillation;
(5) change in psychomotor activity, with agitation or retardation (either subjective or objective);
(6) sleep disturbance of any type;
(7) change in appetite (decrease or increase) with corresponding weight change.

A fifth character may be used to specify the presence or absence of the "somatic syndrome":
Without somatic syndrome
With somatic syndrome

Moderate depressive episode

A. The general criteria for depressive episode must be met.

B. At least two of the three symptoms listed for criterion B above must be present.

C. Additional symptoms from depressive episode, criterion C, must be present, to give a total of at least six.

A fifth character may be used to specify the presence or absence of the "somatic syndrome":
Without somatic syndrome
With somatic syndrome

Severe depressive episode without psychotic symptoms

Note: If important symptoms such as agitation or retardation are marked, the patient may be unwilling or unable to describe many symptoms in detail. An overall grading of severe episode may still be justified in such a case.

A. The general criteria for depressive episode must be met.

B. All three of the symptoms in criterion B, depressive episode, must be present.

C. Additional symptoms from depressive episode, criterion C, must be present, to give a total of at least *eight*.

D. There must be no hallucinations, delusions, or depressive stupor.

Severe depressive episode with psychotic symptoms

A. The general criteria for depressive episode must be met.

B. The criteria for severe depressive episode without psychotic symptoms must be met with the exception of criterion D.

C. The criteria for schizophrenia or schizoaffective disorder, depressive type, are not met.

D. Either of the following must be present:
(1) delusions or hallucinations, other than those listed as typically schizophrenic in criterion C1(1)b, c, and d for general criteria for paranoid, hebephrenic, catatonic, and undifferentiated schizophrenia (i.e., delusions other than those that are completely impossible or culturally inappropriate and hallucinations that are not in the third person or giving a running commentary); the commonest examples are those with depressive, guilty, hypochondriacal, nihilistic, self-referential, or persecutory content;
(2) depressive stupor.

A fifth character may be used to specify whether the psychotic symptoms are congruent or incongruent with mood:
With mood-congruent psychotic symptoms
(i.e., delusions of guilt, worthlessness, bodily disease, or impending disaster, derisive or condemnatory auditory hallucinations)
With mood-incongruent psychotic symptoms
(i.e., persecutory or self-referential delusions and hallucinations without an affective content)

Other depressive episodes

Episodes should be included here which do not fit the descriptions given for depressive episodes, but for which the overall diagnostic impression indicates that they are depressive in nature. Examples included fluctuating mixtures of depressive symptoms (particularly those of the somatic syndrome) with nondiagnostic symptoms such as tension, worry, and distress, and mixtures of somatic depressive symptoms with persistent pain or fatigue not due to organic causes (as sometimes seen in general hospital services).

(continued)

Table 14.6-43 *(continued)*

Depressive episode, unspecified

Recurrent depressive disorder

G1. There has been at least one previous episode, mild, moderate, or severe, lasting a minimum of 2 weeks and separated from the current episode by at least 2 months free from any significant mood symptoms.

G2. At no time in the past has there been an episode meeting the criteria for hypomanic or manic episode.

G3. *Most commonly used exclusion clause.* The episode is not attributable to psychoactive substance use or to any organic mental disorder.

It is recommended that the predominant type of previous episodes is specified (mild, moderate, severe, uncertain).

Recurrent depressive disorder, current episode mild

A. The general criteria for recurrent depressive disorder are met.

B. The current episode meets the criteria for mild depressive episode.

A fifth character may be used to specify the presence or absence of the "somatic syndrome," in the current episode:
Without somatic syndrome
With somatic syndrome

Recurrent depressive disorder, current episode moderate

A. The general criteria for recurrent depressive disorder are met.

B. The current episode meets the criteria for moderate depressive episode.

A fifth character may be used to specify the presence or absence of the "somatic syndrome," in the current episode:
Without somatic syndrome
With somatic syndrome

Recurrent depressive disorder, current episode without psychotic symptoms

A. The general criteria for recurrent depressive disorder are met.

B. The current episode meets the criteria for severe depressive episode without psychotic symptoms.

Recurrent depressive disorder, current episode severe with psychotic symptoms

A. The general criteria for recurrent depressive disorder are met.

B. The current episode meets the criteria for severe depressive episode with psychotic symptoms.

A fifth character may be used to specify whether the psychotic symptoms are congruent or incongruent with the mood:
With mood-congruent psychotic symptoms
With mood-incongruent psychotic symptoms

Recurrent depressive disorder, currently in remission

A. The general criteria for recurrent depressive disorder have been met in the past.

B. The current state does not meet the criteria for a depressive episode of any severity or for any other disorder in mood [affective] disorders.

Comment

This category can still be used if the patient receives treatment to reduce the risk of further episodes.

Other recurrent depressive disorders

Recurrent depressive disorder, unspecified

Persistent mood [affective] disorders

Cyclothymia

A. There must have been a period of at least 2 years of instability of mood involving several periods of both depression and hypomania, with or without intervening periods of normal mood.

B. None of the manifestations of depression or hypomania during such a 2-year period should be sufficiently severe or long-lasting to meet criteria for manic episode or depressive episode (moderate or severe); however, manic or depressive episode(s) may have occurred before, or may develop after, such a period of persistent mood instability.

C. During at least some of the periods of depression at least three of the following should be present:
(1) reduced energy or activity;
(2) insomnia;
(3) loss of self-confidence or feelings of inadequacy;
(4) difficulty in concentrating;
(5) social withdrawal;
(6) loss of interest in or enjoyment of sex and other pleasurable activities;
(7) reduced talkativeness;
(8) pessimism about the future or brooding over the past.

D. During at least some of the periods of mood elevation at least three of the following should be present:
(1) increased energy or activity;
(2) decreased need for sleep;
(3) inflated self-esteem;
(4) sharpened or unusually creative thinking;
(5) increased gregariousness;
(6) increased talkativeness or wittiness;
(7) increased interest and involvement in sexual and other pleasurable activities;
(8) overoptimism or exaggeration of past achievements.

Note. If desired, time of onset may be specified as early (in late teenage or the 20s) or late (usually between age 30 and 50 years, following an affective episode).

(continued)

Table 14.6-43 *(continued)*

Dysthymia

A. There must be a period of at least 2 years of constant or constantly recurring depressed mood. Intervening periods of normal mood rarely last for longer than a few weeks, and there are no episodes of hypomania.

B. None, or very few, of the individual episodes of depression within such a 2-year period should be sufficiently severe or long-lasting to meet the criteria for recurrent mild depressive disorder.

C. During at least some of the periods of depression at least three of the following should be present:
(1) reduced energy or activity;
(2) insomnia;
(3) loss of self-confidence or feelings of inadequacy;
(4) difficulty in concentrating;
(5) frequent tearfulness;
(6) loss of interest in or enjoyment of sex and other pleasurable activities;
(7) feeling of hopelessness or despair;
(8) a perceived inability to cope with the routine responsibilities of everyday life;
(9) pessimism about the future or brooding over the past;
(10) social withdrawal;
(11) reduced talkativeness.

Note. If desired, time of onset may be specified as early (in late teenage or the 20s) or late (usually between age 30 and 50 years, following an affective episode).

Other persistent mood [affective] disorders

This is a residual category for persistent affective disorders that are not sufficiently severe or long-lasting to fulfill the criteria for cyclothymia or dysthymia but that are nevertheless clinically significant. Some types of depression previously called "neurotic" are included here, provided that they do not meet the criteria for either cyclothymia or dysthymia or for depressive episode of mild or moderate severity.

Persistent mood [affective] disorder, unspecified

Other mood [affective] disorders

There are so many possible disorders that could be listed that no attempt has been made to specify criteria, except for mixed affective episode and recurrent brief depressive disorder. Investigators requiring criteria more exact than those available in *Clinical descriptions and diagnostic guidelines* should construct them according to the requirements of their studies.

Other single mood [affective] disorders

Mixed affective episode

A. The episode is characterized by either a mixture or a rapid alternation (i.e., within a few hours) of hypomanic, manic, and depressive symptoms.

B. Both manic and depressive symptoms must be prominent most of the time during a period of at least 2 weeks.

C. There is no history of previous hypomanic, depressive, or mixed episodes.

Other recurrent mood [affective] disorders

Recurrent brief depressive disorder

A. The disorder meets the symptomatic criteria for mild, moderate, or severe depressive episode.

B. The depressive episodes have occurred about once a month over the past year.

C. The individual episodes last less than 2 weeks (typically 2–3 days).

D. The episodes do not occur solely in relation to the menstrual cycle.

Other specified mood [affective] disorders

This is a residual category for affective disorders that do not meet the criteria for any other categories above.

SUGGESTED CROSS-REFERENCES

Diagnosis and psychiatry are discussed in Chapter 7, the clinical manifestations of psychiatric disorders are covered in Chapter 8, and the classification of mental disorders is presented in Chapter 9. Schizophrenia is the subject of Chapter 12. The somatic treatment of mood disorders is discussed in Sections 14.7 and 14.8. Psychotherapy is covered in Section 14.9. Mood disorders and suicide in children are the topic of Chapter 45. Anxiety disorders are presented in Chapter 15, and mood disorders in geriatric psychiatry are discussed in Section 51.3d. Somatoform disorder including neurasthenia and chronic fatigue syndrome is covered in Chapter 16.

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▲ 14.7 Mood Disorders: Treatment of Depression

A. JOHN RUSH, M.D.

Many available options now exist for treatment of mood disorders. Depressive disorders have enjoyed major therapeutic advances during the past decade, and the plethora of new options confronts clinicians with the problem of tailoring them to individual patients. Which strategies (types of treatment), applied in what order (strategic planning), and delivered by which methods (tactics) (e.g., dosage, duration) produce the best results for most patients in the shortest period of time? Specifying the objectives of each phase of treatment and careful, timely reappraisal of whether they are met, optimize patient outcomes.

Specific objectives of each treatment phase (i.e., acute, continuation, maintenance) provide a strategic map for managing these patients. For mood disorders, initial treatment objectives include (1) symptom remission (acute phase) and restoration of psychosocial functioning (acute and continuation phases), (2) prevention of a relapse (continuation phase), and (3) prevention of recurrences, or new episodes in patients with recurrent depressions (maintenance phase).

STRATEGIES

When initiating acute-phase treatment, practitioners decide where the patient should be treated (e.g., outpatient, day hospital, or inpatient). Treatment location is dictated by factors such as (1) the imminent risk of suicide, (2) the capacity of the patient to recognize and follow instructions or recommendations (adherence, psychosis), (3) the level of psychosocial resources, (4) the level of psychosocial stressors, and (5) the level of functional impairment.

Next, one chooses among the four common acute-phase treatments (medication, psychotherapy, the combination of medication and psychotherapy, or electroconvulsive therapy [ECT]). For some, light therapy alone or in combination with medications may also be an option.

In general, patients who respond to acute-phase medication (alone or combined with psychotherapy) receive continuation-phase medication at the same dosage. Continuation-phase ECT may be indicated for acute-phase ECT responders if continuation-phase medication does not prevent relapse or if prior medications have been ineffective, although the efficacy of this approach rests on open case series rather than randomized controlled trials of continuation-phase ECT.

While no randomized controlled trials of continuation-phase psychotherapy alone are available, a few open studies suggest that patients responding to acute-phase psychotherapy alone may further benefit from continuation-phase psychotherapy at less frequent intervals for the subsequent 6 to 8 months. The comparative efficacy of the combination of medication and formal psychotherapy during the continuation phase versus continuing medication only has not been investigated.

TACTICS

Tactics are devised to ensure an adequate treatment trial (e.g., adequate dosage and duration of treatment). Adequate implementation is required to determine whether any strategic choice was correct. Adherence is the most important tactical issue. Low adherence may be due to adverse effects, the conscious or unconscious meaning of taking medication, or the desire to leave treatment once improved (perhaps because of the shame and stigma that still surround psychiatric disorders).

A second key tactical issue is adequate evaluation of whether the objective (i.e., symptom remission) was met. Symptom severity may be gauged by careful interviewing or by use of a rating scale. For mood disorders, a serious difficulty is accepting a partial response in place of a full remission, a risk for any acute-phase treatment. A full remission carries a better prognosis and minimal residual symptoms.

STRATEGIC CHOICES

Medication The available antidepressants differ in their pharmacology, drug-drug interactions, and short- and long-term adverse effects. They do not differ in overall efficacy, speed of response, or long-term effectiveness. Substantial evidence shows that failure to tolerate or respond to one medication does not imply failure with other medications. In fact, a shift from one medication class to another carries 1 in 2 chance of response to both the initial medication and to the next medication if the first fails to provide a satisfactory response.

Psychotherapy Formal psychotherapy aims at particular objectives. General clinical management, part of any treatment, includes explaining the diagnosis, treatment plan, treatment objectives,

anticipated treatment period, counseling, management of both adherence and adverse effects, and a regular assessment of whether or not the treatment objectives are being met. It may involve consulting both the patient and significant others.

The objectives of formal psychotherapy used alone to treat mood disorders are identical to those for medication: (1) symptom remission; (2) psychosocial restoration; and (3) prevention of relapse or recurrence. When used in combination with medication, psychotherapies can achieve such additional objectives as reducing the secondary psychosocial consequences of the disorder (e.g., marital discord, occupational difficulties) or increasing medication adherence.

Clinical management aims to increase adherence, but formal psychotherapy can also be beneficial. Individuals who may need more-formal adherence counseling include those with significant prior or current adherence difficulties and those with relatively fixed negative attitudes toward a clearly indicated treatment. Formal psychotherapy to address the psychosocial consequences of the disorder may include individual, family, couples, or occupational approaches. Evidence suggests that used in combination with medication to control symptoms, such treatments improve the targeted difficulty (e.g., marital counseling improves marriages).

Psychotherapy as monotherapy for symptom remission has shown greater efficacy than wait-listing controls in studies of less severely or chronically ill, nonpsychotic, depressed outpatients. In addition, while some evidence suggests that psychotherapy alone as a maintenance treatment has some benefit in prolonging the well interval, in general, when maintenance treatment is anticipated, medications (alone or combined with psychotherapy) are preferred, given the larger number of medication maintenance studies supporting efficacy.

Choosing Among Psychotherapies No established clinical predictors exist to guide selection of a psychotherapy. Cognitive therapy may be slightly less effective in those with more-dysfunctional attitudes, while interpersonal psychotherapy may be somewhat less effective in those with more-interpersonal problems. However, these predictors lack clinical utility. Time-limited therapies are usually preferred over time-unlimited therapies for symptom reduction because they have established efficacy (time-unlimited therapies do not) and because medication is an effective alternative if psychotherapy alone fails.

Some believe that reconstructive (time-unlimited) psychotherapies are more useful in the treatment of Axis II disorders, while reeducative therapies may be more useful with Axis I conditions. No evidence favors use of psychotherapy alone over medication when a concurrent Axis II disorder exists. On the other hand, psychotherapeutic tactics may benefit the medication management of depressed patients with Axis II conditions by ensuring adherence. Logically, psychotherapy, if used alone, should be tried for a finite time period and outcome should be evaluated, just as with medication.

Declaration of psychotherapy failures is largely based on lack of efficacy, although a few patients discontinue treatment unilaterally. When to declare psychotherapy a failure is a complex problem. Some patients respond early, while others may take 8 to 10 weeks. The premature discontinuation rate may be higher in actual practice than it is in efficacy trials. Just as with medication, if a symptomatic patient inappropriately discontinues treatment, one should actively attempt to reengage them since the depression has not remitted and, consequently, the prognosis is poor.

What treatment should follow if psychotherapy alone is ineffective? Medication, given its established efficacy, is the next best logical step. The psychotherapy may be continued or discontinued when medication is begun. Whether a different form of psychotherapy would be effective if the initial psychotherapeutic approach has not been tested.

COMBINED TREATMENT

Medication and formal psychotherapy are often combined in practice, yet data from randomized controlled trials suggest that the combination does not predictably add to the symptom-reducing effects of either treatment alone, at least in less complex, chronically ill patients. Conversely, the combination may result in both symptom reduction and psychosocial restoration, which is an additional rationale for using the combined approach. There are basically three ways to develop a combined treatment: (1) initiate the combination as acute-phase treatment, (2) add formal psychotherapy to medication that has elicited a partial response (particularly when there are residual cognitive, psychological, or interpersonal symptoms or difficulties), or (3) add medication after a partial response to psychotherapy alone.

Using the combination of medication and formal psychotherapy at the outset of acute-phase treatment is called for if either (1) formal psychotherapy is used to increase adherence, while medications are used for symptom control or (2) if the targets of each treatment were somewhat distinct and both needed early remediation (e.g., medication for the depressive symptoms and psychotherapy for marital problems). In addition, clinical experience suggests that combination treatment may be preferable to either treatment alone with (1) a coexisting Axis II disorder, (2) a chronic and recurrent pattern with poor interepisode recovery, or (3) a patient who is discouraged and demoralized as well as clinically depressed.

Diagnosis and medication management must allow time for patients with little prior treatment to collaborate in the optimal use of medication. Thus, it is often simpler to initiate medication and clinical management and then determine whether formal psychotherapy is indicated either for complete symptomatic remission or to address psychosocial problems unrelieved by medication. For example, psychotherapy might be added after a partial medication response (e.g., persistence of cognitive and interpersonal difficulties).

When to add psychotherapy to medication is unclear. Evidence suggests that psychosocial and occupational improvements follow response. Thus, routine use of both treatments initially may not be necessary for psychosocial restoration. The need for adjunctive psychotherapy to redress psychosocial difficulties becomes clearer the longer symptom remission obtains and psychosocial problems persist. A history of long-standing psychosocial difficulties, even during remission of chronic depression, may suggest either beginning with combined treatment or adding psychotherapy shortly after symptoms are controlled with medication.

When combined treatment does not produce a full response, a switch of medication classes with continued psychotherapy is logically the next step, since evidence indicates that switching medication classes is effective.

ELECTROCONVULSIVE THERAPY

ECT is effective, even in patients who have failed to respond to one or more medications or combined treatment. It is effective in both psychotic and nonpsychotic forms of depression. Usually, 8 to 12 treatments are needed. Bilateral ECT is somewhat more effective than unilateral ECT, but it appears to have more cognitive adverse effects.

OTHER TREATMENTS

Light therapy has been most clearly evaluated in mood disorder with seasonal pattern, either as monotherapy or in combination with medication. Patients who respond do so within 2 to 4 weeks.

STRATEGIC ISSUES

Role of Diagnosis in Treatment Selection Maintenance medication effectively prevents recurrences of dysthymic disorder, complicated by recurrent major depressive episodes or not. Psychotic depression usually requires both an antidepressant and an antipsychotic agent. Alternatively, ECT is useful in psychotic depression, either as a first-line treatment or after medication has proven ineffective. For those with atypical features, strong evidence indicates that tricyclic drugs are less effective than the monoamine oxidase inhibitors (MAOIs). There is some suggestion of efficacy for the selective serotonin reuptake inhibitors (SSRIs) in atypical depression.

The concurrent presence of another disorder may also affect initial treatment selection. Presence of nonmood Axis I disorder favors use of medications with demonstrated efficacy in both the mood and nonmood disorder. For example, effective treatment of obsessive-compulsive disorder with depressive symptoms usually results in remission of the depression. Similar findings have been reported for anorexia nervosa and bulimia. When panic disorder co-occurs with major depressive disorder, medications with demonstrated efficacy in each condition are preferred (e.g., tricyclic drugs, SSRIs). In general, the nonmood disorder dictates the choice of treatment.

Concurrent substance abuse raises the possibility of a substance-induced mood disorder, which must be evaluated by history or after several weeks of abstinence, since abstinence results in remission of depressive symptoms in substance-induced mood disorders. If significant depressive symptoms continue, even with abstinence, an independent mood disorder is diagnosed and treated.

Axis II disorders frequently accompany mood disorders, but diagnosis of Axis II disorders remains tentative in the presence of a clinical depression. An Axis II disorder should not be mistaken for recurrent major depressive disorder with poor interepisode recovery, since the treatment objectives and strategies differ.

An Axis II disorder does not contraindicate treating the mood disorder, but its presence may prolong the time to acute-phase treatment response, interfere with adherence, or even preclude full symptomatic remission. In general, the presence of Axis II disorders suggests a less optimistic prognosis, because circumstantial evidence suggests that Axis II disorders are risk factors for subsequent relapse or recurrence.

Axis II disorders raise other tactical issues, such as adherence, establishing a therapeutic alliance, or long-term management. In addition, the response to either medication or time-limited psychotherapy is slower, less complete, or both in the presence of an Axis II disorder.

General medical conditions commonly accompany mood disorders and are established risk factors in their development. Recent evidence indicates that a major depressive episode is associated with increased morbidity or mortality of some associated general medical conditions.

Principles that apply to the treatment of depression without a general medical condition generally apply when these conditions are present. However, treatment strategies and tactics are more complex. The initial choice of treatment is influenced by prior response to antidepressant treatments, the relative medical safety of medications, and clinical judgment about whether psychotherapeutic methods might particularly benefit some of these patients. The tactical choice of medications is affected by drug interactions, the pharmacological profile of the compound, the general medical condition, and drug dosing requirements.

Complex, ongoing, stressful life events or social contextual issues (often profoundly disturbing to patients) should not influence whether or not medication is used. Often, patients in major depressive episodes whose symptoms are reduced by medication become less disabled from the mood disorder and are better able to manage these complex life circumstances. On the other hand, chronic, disturbing, life circumstances (e.g., chronic marital discord, spousal abuse) argue for stronger consideration of combined treatment, either initially or sequenced, to obtain both symptom remission and psychosocial restoration. Table 14.7-1 summarizes the relation between clinical diagnoses and treatment selection.

Selecting Initial Treatment In general, about 45 to 60 percent of all outpatients with nonpsychotic major depressive disorder who begin treatment with medication, psychotherapy, or the combination respond. Consequently, roughly one-half of patients should anticipate a second treatment trial if the initial treatment selected is either intolerable or ineffective. Selection of the initial treatment depends on the chronicity of the condition, the history of recurrences (which predicts the likelihood of future recurrences), family history of illness, symptom severity, associated comorbid general medical or other psychiatric conditions, prior treatment responses to other acute-phase treatments, and patient preference. In general, the less severe, less chronic, and less complex the depression (i.e., less current comorbidity), the greater the role for patient preference, since evidence for selecting between time-limited, depression-targeted psychotherapy and medication is lacking. Furthermore, it is believed

Table 14.7-1
Relation of Diagnosis to Treatment Selection

Diagnosis	Treatment Recommendations
Major depressive disorder (mild-to-moderate severity)	Medication or time-limited, depression-targeted psychotherapies* No maintenance-phase treatment
Major depressive disorder, recurrent	Consider maintenance-phase treatment
Major depressive disorder with psychotic features	Antipsychotic plus antidepressant medication Electroconvulsive therapy
Major depressive disorder with melancholic or severe features	Medications essential
Depression with atypical features	Nontricylic drugs preferred Monoamine oxidase inhibitors have established efficacy
Depression with seasonal pattern	Light therapy or medications
Dysthymic disorder	Medications; time-limited, depression-targeted psychotherapies; or their combination Consider maintenance-phase therapy
Complex† or chronic depressions	Medication plus psychotherapy‡

* Interpersonal psychotherapy, cognitive therapy, or behavior therapy.
† Complex refers to depression co-occurring with other psychiatric conditions (e.g., anxiety disorders, Axis II conditions).
‡ Psychotherapy may aim at adherence enhancement, symptom reduction, relapse prevention, or psychosocial restoration.

that the combination of medication and formal psychotherapy is less likely to be needed for milder, uncomplicated depressions.

Moderate-to-severe mood disorders with prominent chronicity or prior recurrences generally require maintenance treatment. Since medications are the maintenance treatments with established efficacy, medication treatment (alone or combined with psychotherapy) is recommended.

The evidence for the efficacy of medication alone in more-severe depressions is clear; psychotherapy alone is less well studied. Psychotherapy alone appears to be less predictably effective than medication in outpatients with endogenous or melancholic symptom features. Whether psychotherapy alone is effective in depressions with atypical symptom features is under study. However, the MAOIs and SSRIs have established efficacy in this group.

Selecting Second Treatment Options If the first treatment fails (e.g., due to intolerance or lack of efficacy), a strategic decision on the second treatment after the differential diagnosis (including occult general medical condition or substance abuse) has to be reconsidered.

For those receiving medication initially, dose adjustments, extending the trial period, switching to an alternative treatment (either medication or psychotherapy), or adding a second treatment to the initial one are common options. Factors recommending dose escalations are (1) no adverse effects, (2) a prior history consistent with rapid drug metabolism, or (3) low therapeutic blood concentrations. However, blood concentrations of newer-generation medications are related to outcome although they are for desipramine (Norpramin, Pertofrane), imipramine (Tofranil), and nortriptyline (Pamelor). Extending the initial trial is indicated if (1) it has been less than 6 weeks, (2) there is a partial response by 6 weeks, or (3) prior medication trials were unsuccessful and shorter than 6 weeks.

Likewise, partial response to psychotherapy by week 6 argues for extending the trial period. Nonresponse by 8 weeks often predicts an ultimate poor response. Extending a trial of light therapy beyond 3 weeks in nonresponders has not been evaluated. Clinical experience suggests that extending ECT beyond 10 trials with complete nonresponse is unlikely in most cases to elicit a subsequent response, although careful studies are lacking.

The choice to switch from the initial single treatment to a new single treatment (as opposed to adding a second treatment) depends on the philosophy guiding the clinician, the patient's prior treatment history, and other clinical issues. The best-documented augmentation strategies involve inexpensive medicines (e.g., lithium or thyroid hormones) and response, if it occurs, is often within 2 weeks. Conversely, a switching strategy sometimes involves a washout period (e.g., switching from fluoxetine [Prozac] to an MAOI) for safety reasons as well as the need to wait longer than 2 weeks for a full effect. Alternatively, how long to continue augmentation is not clear, and lithium augmentation entails some expense and inconvenience (i.e., blood concentration monitoring).

If the initial trial is the patient's first treatment and other clinical or economic reasons favor monotherapy, switching rather than augmenting is preferred. On the other hand, augmentation strategies, particularly the use of two different medications, seem effective in patients who have failed one or more well-conducted single medication trials. Thus, switching might be preferable for those with only one or two prior treatment attempts, while augmentation is preferable for those who have failed several single-treatment trials. Recent reviews indicate that if the initial medication is ineffective or cannot be tolerated, it is reasonable to switch medication classes. In psychiatric settings, augmentation may be preferable, since more psychiatric patients have failed several adequate prior single treatments.

The value of augmenting medication with psychotherapy is not well evaluated. Many clinicians believe that if the residual symptoms after a partial response to medication are largely cognitive or psychological, either augmentation with psychotherapy or prolonging the initial medication trial are preferred to switching medications or augmenting with another medication, based on the assumption that these symptoms represent residual psychosocial sequelae. On the other hand, if anhedonia persists after an initial medication trial, switching or augmentation with another medication rather than psychotherapy is often preferred since such symptoms suggest ongoing limbic/paralimbic system dysfunction. However, these suggestions are largely based on clinical experience rather than scientific evidence.

TACTICAL ISSUES

The strategic choices of treatment focus on selection of the initial therapy, or for those who fail the initial therapy, the selection of a second treatment option. Implementation of these strategies requires (1) careful attention to adherence, (2) careful evaluation of outcome, (3) proper dosing and duration of the trial, and (4) timely declaration of treatment failure.

Adherence Treatment adherence is increased if patients understand anticipated objectives and common strategies, if fewer daily doses are required (e.g., once-a-day versus three-times-a-day dosing), and no personality disorder is present. Evidence also suggests more-frequent early visits (e.g., weekly versus monthly) improve adherence. Whether other current psychiatric conditions affect adherence is unclear; it is not related to gender, educational level, or socioeconomic status. The best predictor of future adherence is prior adherence.

Thus, general clinical management of medication treatment should include discussions with patients (and, potentially, significant others) about the objectives of treatment, anticipated treatment period, and adherence obstacles. It is best to anticipate and identify obstacles to adherence prior to prescribing medication or initiating psychotherapy and to make adherence checks a routine part of each visit.

Initially, visits should be frequent enough to ensure adherence and permit timely intervention for adverse effects. Several brief telephone contacts during the initial weeks of treatment help adherence by reassuring patients, ensuring that adverse effects are avoided, countering demoralization and pessimism that impairs adherence, and providing information to overcome short-term concentration and recall problems that are part of depressive episodes.

Choosing Among Medications If medication (alone or in combination with psychotherapy) is part of the first step, the practitioner must select from a variety of available compounds. Medications differ in their short- and long-term adverse effects and spectrum of action but not in overall efficacy or speed of response. If maintenance medication is anticipated, long-term adverse effects are more important than short-term effects in selection (e.g., tertiary tricyclic drugs are associated with greater weight gain than SSRIs over the long run).

Table 14.7-2 lists commonly used antidepressant agents presently available in the United States and groups them on the basis of their

Table 14.7-2
Antidepressant Medications*

Generic (Brand) Name	Usual Daily Dosage (mg)	Common Side Effects	Clinical Caveats
Norepinephrine reuptake inhibitors			
Desipramine (Norpramin, Pertofran)	75–300	Drowsiness, insomnia, agitation, OSH, CA, weight ↑, anticholinergic†	Overdose may be fatal; dose titration needed
Protriptyline (Vivactil)	20–60	Drowsiness, insomnia, agitation, OSH, CA, anticholinergic†	Overdose may be fatal; dose titration needed
Nortriptyline (Aventyl, Pamelor)	40–200	Drowsiness, OSH, CA, weight ↑, anticholinergic†	Overdose may be fatal; dose titration needed
Maprotiline (Ludiomil)	100–225	Drowsiness, CA, weight ↑, anticholinergic†	Overdose may be fatal; dose titration needed
5-HT reuptake inhibitors		All SSRIs may cause insomnia, agitation, sedation, GI distress, sexual dysfunction	All SSRIs have various effects on cytochrome P450 enzyme systems; are better tolerated than tricyclic drugs; and have high safety in overdose
Citalopram (Celexa)	20–40		
Fluoxetine (Prozac)	10–40		
Fluvoxamine (Luvox)‡	100–300		
Paroxetine (Paxil)	20–50		
Sertraline (Zoloft)	50–150		
5-HT-norepinephrine reuptake inhibitors			
Amitriptyline (Elavil, Endep)	75–300	Drowsiness, OSH, CA, weight ↑, anticholinergic†	Overdose may be fatal; dose titration needed
Doxepin (Adapin, Sinequan)	75–300	Drowsiness, OSH, CA, weight ↑, anticholinergic†	Overdose may be fatal
Imipramine (Janimine, Tofranil)	75–300	Drowsiness, insomnia/agitation, OSH, CA, GI distress, weight ↑, anticholinergic†	Overdose may be fatal; dose titration needed
Trimipramine (Surmontil)	75–300	Drowsiness, OSH, CA, weight ↑, anticholinergic†	
Venlafaxine (Effexor)	150–375	Sleep changes, GI distress	Higher dosages may cause hypertension; dose titration needed
Presynaptic and postsynaptic active agents			
Nefazodone (Serzone)	300–600	Sedation	Dose titration needed; no sexual dysfunction
Mirtazepine (Remeron)	15–30	Sedation, weight ≤	No sexual dysfunction
Dopamine reuptake inhibitor			
Bupropion (Wellbutrin)	200–400	Insomnia, agitation, CA, GI distress	b.i.d. dosing with sustained release; no sexual dysfunction
Mixed-action agents			
Amoxepine (Asendin)	100–600	Drowsiness, insomnia/agitation, CA, weight ↑, OSH, anticholinergic†	Movement disorders may occur; dose titration needed
Clomipramine (Anafranil)	75–300	Drowsiness, weight ↑	Dose titration needed
Trazodone (Desyrel)	150–600	Drowsiness, OSH, CA, GI distress, weight ↑	Priapism possible

* Dosage ranges are for adults in good general medical health, taking no other medications, aged 18 to 60. Doses vary depending on the agent, concomitant medications, the presence of general medical or surgical conditions, age, genetic constitution, and other factors. Brand names are those used in the United States.
† Dry mouth, blurred vision, urinary hesitancy, constipation.
‡ Not FDA approved for treatment of depression.
Abbreviations: 5-HT, serotonin; GI, gastrointestinal; OSH, orthostatic hypotension; CA, cardiac arrhythmia.

presumed mechanisms of action (e.g., presynaptic or postsynaptic activity). However, as basic neuroscientific knowledge expands, further actions will likely be discovered. For example, the number of serotonin receptor types has increased faster than our understanding of their physiological roles. Further, the actions of some (e.g., venlafaxine [Effexor]) are affected by the dosages used or levels attained in the central nervous system (CNS). Venlafaxine exerts proportionally more serotonin than norepinephrine reuptake blockade at lower dosages than at higher dosages.

Table 14.8-2 lacks two commonly used drug combination treatments (lithium plus antidepressants and liothyronine [Cytomel] augmentation of tricyclic drugs). A Table 14.8-2 provides selected clinical caveats. This list is not exhaustive. Drug-drug interactions, at either the neuronal level (pharmacodynamics) or at the level of absorption, metabolism, and excretion (pharmacokinetics) affect selection of agents, their dosing, and ultimately the risk-benefit equation for individual patients. Patients should be advised what adverse effects to anticipate and encouraged to report them as early as possible. Management of adverse effects may include lowering the dosage, switching medications, or treating the adverse effects with an additional medication.

The MAOIs (tranylcypromine [Parnate] and phenelzine [Nardil]) still have a role in the treatment of depression, the depressed phase of bipolar disorders, and in depressions unresponsive to other treat-

ments. However, because of the necessity of regulating diet (Table 14.7-3) and evaluating concomitant medications (Table 14.7-4), the MAOIs are not used as first-line drugs.

Among the tricyclic medications, the secondary amines (desipramine or nortriptyline) have fewer adverse effects than the tertiary amines. Since nortriptyline has a well-established therapeutic window, drug concentration monitoring can ensure that patients who need minimal medication exposure obtain a therapeutic concentration. Conversely, the upper limit of the nortriptyline window may be a disadvantage when deciding to switch or augment treatments, as the blood concentrations may be used to declare a nonresponse.

Choosing more-sedating antidepressants (e.g., amitriptyline [Elavil, Endep]) for more-anxious depressed patients, or more-activating agents (e.g., desipramine) for those more psychomotor retarded is not based on evidence of differential efficacy. However, some clinicians believe that such choices based on adverse-effect profiles increase adherence in the initial weeks of treatment. That is, patients with marked insomnia and anxiety obtain some immediate relief from these associated symptoms before the full antidepressant effect of the drug appears and thus are more likely to comply with acute-phase treatment. These clinical observations are not supported by empirical data, however. In fact, attrition associated with paroxetine (Paxil) or fluoxetine (less-sedating drugs) is lower in acute-phase treatment than that with imipramine or amitriptyline (more-sedating drugs). In addition, the longer-term cost of a possibly beneficial short-term adverse effect advantage must be considered. For example, initially sedating antidepressants often continue to be sedating in the longer run, which may lead patients to prematurely discontinue continuation or maintenance phase treatment, thus increasing the risk of relapse or recurrence.

Some practitioners combine adjunctive medications (e.g., hypnotics or anxiolytics) with antidepressants to provide more immediate symptom relief either routinely from the outset or when the need for such adjunctive medications arises in an individual patient. Adjunctive medications used briefly to cover adverse effects to which most patients ultimately adapt can be useful. Conversely, discontinuing adjunctive medications can result in some return of symptoms or adverse effects to which the patient has not adapted.

Several disadvantages are associated with the routine use of adjunctive medications: (1) the potential risk, inconvenience and expense of unnecessary medications (i.e., many patients may not require them); (2) difficulty identifying the cause of medication intolerance or adverse effects (e.g., an allergic rash) when treatment with an antidepressant and an adjunctive medication is begun at the same time; (3) difficulty in judging response to the antidepressant medication alone if adjunctive medication addresses critical symptoms used to gauge the success of acute-phase treatment, (discontinuing the adjunctive medication to see if the apparent response holds on the antidepressant alone may unnecessarily increase the number of visits or delay a timely revision in the treatment plan); and (4) adjunctive medications may cover adverse effects that if observed would lead to either a dose reduction or to switching treatments. For

Table 14.7-3
MAOI Dietary Restrictions

High Tyramine Content—Not Permitted	
Aged, matured cheeses (unpasteurized)	Cheddar, Camembert, Stilton, blue, 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	Bouillon, 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)	

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Table 14.7-4
MAOI Drug Incompatibilities

Generally Contraindicated Hazardous Potentiations*	
Stimulants	Weight-reducing or antiappetite drugs; amphetamine, 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
Tricyclics	Imipramine, desipramine, clomipramine
MAOIs	Tranylcypromine, after other MAOIs
Sympathomimetics	Dopamine, Metaraminol
Amine precursors	L-dopa, L-tryptophan
Narcotics	Meperidine (Demerol)
Some Potentiation Possible	
Opioids	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, tricyclics 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.

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example, a sedative-hypnotic agent used in conjunction with an SSRI may inappropriately delay a strategic decision to either decrease the dosage or switch to an alternative agent.

In addition to adverse effects, medication choice is affected by prior history of response, cross-sectional symptom features, patient preference, dosing convenience (which affects adherence), drug interactions (if patients are, or will be, taking other medications), current general medical conditions (making one adverse-effect profile preferred over another), and a family history of response. A patient's prior treatment history is important because prior response typically predicts current response. In addition, a documented failure on a properly conducted trial of a particular antidepressant class (e.g., SSRIs, tricyclics, or MAOIs) suggests choosing an agent from an alternative class. Switching classes for those who fail on one class appears to be associated with roughly a 50 percent response rate with the second class of drugs.

History of a first-degree relative responding to a tricyclic drug or an MAOI is associated with a better response to the same class of agents in the patient. Whether family history of response predicts response to the newer antidepressant compounds is not known.

Dosage and Duration Tactical issues surrounding medication use include dosing steps, drug metabolism, pharmacokinetics, drug interactions, and adverse effects. The tricyclic drugs typically are initially given at low dosages and increased to the maximally tolerated dosage or (in the case of nortriptyline) until a therapeutic concentration is obtained. Gradual dose escalations are important to ensure adherence and avoid severe initial adverse effects. Thus, the tricyclic drugs require visits roughly once a week for outpatients as dosages are adjusted. Tricyclic blood concentration monitoring may reduce dosage adjustment time. Dosing is less complicated for the SSRIs than for the tricyclic drugs; fewer dose increments are needed, and the proper dosage is attained earlier because of their better adverse-effect profiles. Some newer agents (e.g., SSRIs, bupropion [Wellbutrin]) need fewer dosage adjustments, but with others (e.g., venlafaxine and nefazodone [Serzone]), raising the dosage increases the likelihood of response, so several adjustments are often helpful.

Safety in overdose is an issue, especially early in treatment. Thus, a 1-week prescription is recommended (without refills) so patients return for frequent medication visits when adverse effects and dosage levels are managed. Tricyclic drugs account for a greater percent of completed suicides than the newer agents, which are far safer in overdose.

Evaluation of Outcome The objective of acute-phase treatment (medication, psychotherapy, their combination, or ECT) is symptom remission, not just symptom reduction. Partial response is associated with a stormier prognosis. Thus, careful interviewing for criterion symptoms at each visit is essential. Self-reported or clinician-rated instruments can facilitate this assessment. Often the patient is slower to recognize the early therapeutic effect of the treatment than the clinician. Thus, a clinician-rated scale may be preferred to a self-reported instrument.

Timely Declaration of Treatment Failures Growing evidence indicates that acute phase medication trials should last 6 (and preferably 8) weeks to determine the full extent of symptom reduction attainable, although most (but not all) patients who ultimately respond fully show at least a partial response by weeks 3 or 4 if the dose is adequate during the initial weeks of treatment. Clinical impression and recent reports suggest that no response by 3 to 4 weeks (e.g., <25 percent reduction in symptoms) indicates that a treatment change is needed (i.e., a few patients respond over the next several weeks), assuming an adequate dosage in the initial 3 to 4 weeks.

Each treatment step should be applied optimally (e.g., dosage and duration) to determine its effectiveness. There is a clinically important tension involved in evaluating the initial treatment—providing sufficient treatment for a long enough time to determine whether it is effective, while at the same time not prolonging (or overdosing) ultimately ineffective treatment.

Medication dosage obviously affects clinical outcome and adverse effect burden. Some patients metabolize certain drugs more rapidly or more slowly than others. Slow metabolizers, especially for the more anticholinergic tricyclic drugs, encounter adverse effects earlier in treatment or at lower dosages. High blood concentrations may cause arrythmias, seizures, or delirium. Fast metabolizers may exhibit virtually no adverse effects or benefits, even with rather large dosages. However, adverse effects, especially for desipramine and nortriptyline, do not predict blood concentrations. Indeed, orthostatic hypotension can occur even with low blood concentrations. Such cases argue for the value of a therapeutic blood concentration to determine dosing strategies, especially when tricyclic drugs are used in medically fragile patients.

Patients may not respond to a medication because (1) they cannot tolerate the adverse effects, even with a good clinical response; (2) an idiosyncratic adverse event occurs; or (3) the clinical response is not adequate. Idiosyncratic or serious adverse effects (e.g. seizures, allergic reactions), while rare, are most likely to be encountered in the first several weeks of treatment and often occur with dosage escalation or as medication concentrations rise to a steady-state level. Some of these adverse effects are dose dependent (e.g., sedation) and can be reduced by decreasing the dosage or slowing the rate of escalation. Moderate adverse effects, when encountered, argue for holding the dosage constant and allowing time for physiological adaptation, which often reduces adverse effects. Some adverse effects are less dose dependent (e.g., orthostatic hypotension), and tolerance to them is less likely. In these cases, gradual dosage escalation is less useful, and a change in treatment is often indicated.

Lack of efficacy is the most common reason for medication failure, but this cannot be fully gauged until patients have had several weeks of treatment at adequate dosages (4 to 6 weeks). Thus, careful evaluation of symptoms during acute-phase treatment (whether formally conducted with a rating scale or informally by assessing each criterion symptom of the mood disorder) is a useful gauge of the adequacy of medication response.

CONTINUATION TREATMENT

Continuation treatment typically lasts 4 to 9 months. In theory, the duration depends on an estimate of when the episode would have remitted spontaneously. Thus, patients with longer prior episodes (e.g., 9 to 15 months) who have had only 2 months of a current depression, for example, would be candidates for 5 to 11 months of continuation treatment, assuming that acute treatment lasted 2 months. Follow-up studies of those with psychotic depressions 1 year after acute-phase treatment indicate a poorer prognosis than for nonpsychotic depression. Thus, continuation-phase treatment for psychotic depressions should be longer.

Continuation-phase medication treatment should end with a gradual taper of medication and careful symptom assessment during, and for several months following, discontinuation. When medication is used alone or in combination with formal psychotherapy for acute-

phase treatment, continuation medication treatment is recommended, because early medication discontinuation is associated with a higher relapse rate than later discontinuation. Whenever clinically feasible, continuation medication should be at the dosage used during acute-phase treatment. This recommendation is based on evidence from maintenance trials using lower-dosage tricyclic drugs, which suggested a higher recurrence rate than was obtained with full-dosage treatment.

Psychotherapy may be added to continuation-phase medication if psychosocial residua do not remit with medication alone. Whether to continue psychotherapy following response to acute-phase combined treatment is unclear and is entirely a matter of clinical judgment at this time. Continuation-phase psychotherapy alone (after acute-phase response to psychotherapy alone), has only indirect evidence of efficacy.

MAINTENANCE TREATMENT

Strategic Issues Maintenance treatment aims at preventing new episodes (recurrences). It is appropriate for recurrent (but not for single episode) major depressive disorder. Maintenance medication treatment has been found effective in virtually all studies to date. Strong evidence indicates that those with three or more episodes should receive maintenance-phase treatment, and indeed even at 5 years, maintenance medication has prophylactic efficacy.

Whether those with only two major depressive episodes should receive maintenance treatment is less clear. Information that helps with this decision includes poor recovery between the two episodes, presence of two episodes within the last 3 years, or a positive family history for depression or bipolar disorder; any of these factors increase the likelihood of recurrence. However, clinicians and patients must decide collaboratively whether to initiate maintenance treatment or provide more-diligent monitoring with no treatment until a need is established by the development of a new episode. If a new episode develops when the patient is free of treatment, early intervention shortens the length of the new episode.

Tactical Issues An important issue in both continuation and maintenance treatment is symptom breakthrough, which may be modest and time-limited, requiring only minor shifts in the treatment plan (e.g., dosage adjustment, reassurance). On the other hand, if symptom breakthrough is profound or prolonged or does not respond to dosage adjustment and reassurance, it must be treated. No randomized controlled trials have addressed this issue. Perhaps the simplest approach is to augment the current medication with an additional one (e.g., lithium, thyroid hormone, or another antidepressant). If this strategy is effective, then the augmenting medication may be discontinued after a time, to determine whether it is necessary over the longer term. If the augmenting medication fails, then a switch in treatment to another medication may be needed.

Symptom breakthrough could also be remediated by psychotherapy, but this option has not been formally studied. Perhaps psychotherapy is indicated if the symptoms were caused by disturbed interpersonal relationships or life events (e.g., divorce or unemployment).

Another tactical problem encountered in both continuation and maintenance treatment is the management of the depression when intercurrent general medical illnesses requiring medication, surgery, or pregnancy occur. For patients who need a "window in time" for surgery or pregnancy, medication discontinuation should be gradual. Pregnancy lasts for a prolonged period and given the evidence for the efficacy of interpersonal therapy alone as a maintenance treatment, psychotherapy without medication may provide an extended drug-free period. The development of other general medical illnesses and the need for nonpsychotropic medications during continuation or maintenance treatment is not uncommon. These circumstances need to be managed with consideration of the pharmacokinetics and drug interactions between the psychotropic and nonpsychotropic agents.

When to discontinue maintenance medication treatment is unclear. As noted above, a recently completed study in patients with highly recurrent depressions (more than three episodes) indicates the efficacy of maintenance treatment continues for at least 5 years. Some patients may require very prolonged (e.g., a decade) or even lifetime maintenance medication treatment. Discontinuation requires careful monitoring, because the first 6 months following discontinuation appear to be a particular risk period for recurrences.

PATIENT PREFERENCE

Patients should become more informed about depressive disorders and their treatment. Even so, some patients are adamantly opposed to medication, while others are equally opposed to psychotherapy. Patient preference can play a greater role when evidence does not strongly support a specific choice. While patients may exercise their first preference initially, a contingency plan should be developed early in the management of the patient in case a second treatment trial is needed. Therefore, it might be wise to plan at the outset for at least two short-term treatment trials, to avoid inappropriate discouragement and consequent premature attrition if the initial treatment fails to provide full remission. Treatment tactics to optimize outcome include attention to adherence, careful titration of medication to attain maximal benefit with minimal adverse effects, and careful symptom evaluation to ensure that remission, not just improvement, has occurred. Establishing explicit goals and following a stepwise plan to attain them can help both practitioners and patients obtain the best outcomes.

SUGGESTED CROSS-REFERENCES

Classification of mental disorders is discussed in Chapter 9, treatment of mood disorders in Chapter 14, psychotherapies in Chapter 30, biological therapies in Chapter 31, mood disorders and suicide in children in Chapter 45, and diagnosis and treatment of psychiatric disorders in late life in Chapter 51.

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14.8 Mood Disorders: Treatment of Bipolar Disorders

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Treatment of the mood disorders has reached a new level of sophistication based on a variety of advances. The descriptive and diagnostic aspects of bipolar disorders are now explicitly spelled out, recognizing that it is almost always recurrent with potential for severe morbidity and even mortality. There is increasing recognition that bipolar affective disorders have a prominent genetic component interacting with environmental events, and neurobiological alterations have been documented with biochemical assays and functional brain imaging. Thus, different treatment approaches are recognized as a function of type, severity, and course and as in other branches of medicine require the utmost clinical management skills.

Convergent with this increased knowledge about the classification, course, and mechanisms underlying acute episodes and their recurrences is an expanding array of effective psycho- and pharmacotherapeutic modalities and related somatic treatments. Whereas single drugs in one or two classes were available for the treatment of bipolar disorders several decades ago, multiple therapeutic modalities now exist, often including many agents within each class. Thus, the physician must be aware of the nuances in approach to the patient with acute and recurrent mood disorder, so that treatment can be optimized from the outset and the impact of the illness on patients and families minimized.

A growing consensus surrounds a series of new treatment principles. Early recognition and intervention in an acute episode may not only save the patient months of pain and suffering, but also may be life saving. More-careful assessment of the efficacy of an agent at early and regular intervals and early revision of the treatment modality if no improvement is shown are recognized guidelines. This is the case for somatic treatments and also for targeted psychotherapeutic approaches using cognitive, behavioral, and interpersonal therapies.

A substantial body of evidence indicates the efficacy of long-term prophylactic treatments in the management of the recurrent affective disorders. Moreover, earlier institution of long-term prophylaxis is critical to the patient with recurrent mood disorders; it will affect the morbidity of the illness and likely also its subsequent course and treatment responsiveness. Consensus is growing that a patient with a positive family history and a first episode of bipolar disorder is a candidate for continuation therapy after resolution of that episode and for long-term prophylaxis. These factors have dramatically changed the physician's approach to the patient with an acute episode of a mood disorder. The illness should be approached with the same respect accorded the early diagnosis and treatment of a malignancy. Delayed or inadequate treatment may be associated with considerable acute and long-term morbidity from both the illness and its secondary consequences. Thus, it appears appropriate to reconceptualize the recurrent mood disorders not as illusory mental phenomena that can be modified by the patient's will, but as a serious and potentially life-threatening medical illness that has clearly defined mood, cognitive, motor, somatic, and neurobiological concomitants.

Bipolar I disorder occurs in approximately 1 percent of the population, which translates into 2.5 million people in the United States alone. It is estimated that the average woman with onset of bipolar illness at age 25 will lose 14 years of effective lifetime functioning through her illness. Bipolar II disorder and bipolar disorder not otherwise specified may each account for another 1 percent or more. Fifteen to 20 percent of patients with bipolar illness commit suicide. It is against this backdrop of a recurrent, potentially disabling, medical illness that diagnostic and long-term treatment approaches should be conceptualized.

HISTORY

Over the course of this century a revolution has occurred in the treatment of bipolar disorders. In the first half of the century no adequate treatment was available; in the second half, lithium (Eskalith) emerged as a wonder drug for short-term and prophylactic management of the disorder. However, oscillations in the assessment of lithium's safety, efficacy, and utility have persisted. The drug was initially abandoned as unsafe until its concentration could be adequately monitored in blood, which virtually eliminated its most serious and potentially lethal cardiovascular and central nervous system (CNS) toxicities. However, concerns about long-term renal complications have not entirely dissipated after the kidney scare of the 1980s.

There is also greater recognition of lithium's efficacy limitations. As with penicillin, these limitations do not imply that lithium no longer works, but that the spectrum of therapeutic efficacy is narrower. More than 50 percent of patients do not show adequate response to lithium even with adjunctive antidepressant and neuroleptic treatment and using conservative criteria for clinical response (e.g., one episode of illness in a 2-year follow-up).

In the middle of the century electroconvulsive therapy (ECT) emerged as the most effective approach to treating acute episodes. Antipsychotics rapidly became a mainstay of treatment for both mania and psychosis. In the 1960s the first-generation monamine oxidase inhibitors (MAOIs) and tricyclic drugs were introduced and widely used in conjunction with lithium. Now, selective serotonin reuptake inhibitors (SSRIs), bupropion (Wellbutrin), venlafaxine (Effexor), mirtazapine (Remeron), and monoamine oxidase (MAO) type A selective modalities are available. Similarly, the phenothiazine, butyrophenone, and thiothixine antipsychotic classes have given way to the serotonin-dopamine antagonists (atypical antipsychotics), such as clozapine (Clozaril) and risperidone (Risperdal); olanzapine (Zyprexa); quetiapine (Seroquel); and sertindole (Serlect). These new agents include drugs with novel structures and mechanisms of action and more benign adverse effect profiles than the original agents.

This new range of psychopharmacological agents raises a series of important issues for the clinician, particularly when these agents must be chosen on the basis of an inadequate literature on relative

efficacy or clinical and biological markers of responsiveness. There is a consensus that with the exception of ECT, no antidepressant modality is more effective or more rapid in onset than another. Thus, the choice of agents is typically based on their adverse effect profile and clinical lore regarding syndromal selectivity of response.

Fortunately, as the limitations of lithium as a mood stabilizer have been increasingly recognized, a variety of other treatment modalities have become available, particularly the anticonvulsants carbamazepine (Tegretol); valproate (Depakene); divalproex (Depakote); as well as the calcium channel inhibitors. Other promising anticonvulsants are being explored as possible third-generation mood stabilizers, including lamotrigine (Lamictal), and possibly gabapentin (Neurontin), and topiramate (Topamax). However, as with targeting therapeutic modalities to specific patients in the depressive disorders, the data are not yet adequate to choose among the accepted mood stabilizers or establish how to use them in combination, which has been increasingly necessary in recurrent bipolar disorders.

Thus, the clinician often has to resort to educated guesses and systematic and sequential clinical trials in individual patients to delineate optimal responsivity (Table 14.8-1). Even with the availability of many new treatments, episodes of illness can often emerge through otherwise partially successful pharmacoprophylaxis and necessitate adjunctive measures. The role of complex combination therapies is well recognized in many branches of medicine and is indispensable in the approach to tuberculosis, acquired immune deficiency syndrome (AIDS), congestive heart failure, or cancer chemotherapy. Systematic research of combination therapies has lagged markedly behind clinical practice, and clinicians are often left to their own devices, without the aid of controlled studies in the literature to guide the optimal algorithm for approaching the patient who is refractory to standard treatment interventions.

IMPEDIMENTS TO SHORT- AND LONG-TERM TREATMENT

Although the bipolar disorders are eminently treatable, illness-related variables complicate diagnosis, accessibility to treatment, and the ability of the patient to follow through with treatment. It is estimated that as many as 40 percent of bipolar I disorder patients in community surveys are not in treatment.

Depressed patients often do not recognize that their symptoms are related to a medical illness, and the symptoms themselves (e.g., motor retardation, a sense of inertia, and hopelessness) may preclude the patient's seeking treatment. Thus, the patient's family, acquaintances, and physician may have to actively encourage the patient to initiate treatment.

Treatment must be conducted against the backdrop of the patient's distorted depressive cognitions (e.g., hopelessness, and view of the untreatability of the illness), which must be explained as symptoms of the illness that are not consistent with optimism of treatment response on the basis of the literature and the physician's knowledge base. The therapist's empirical basis for hope of recovery needs to be conveyed to the patient without the promise of immediate results, so that the expected lags in response are not further misinterpreted as a confirmation of the patient's worst fears. Moreover, each phase of the treatment needs continual review in relation to the potential for suicide.

There are major impediments to effective treatment of manic patients. In the early stages of hypomania, the sense of well-being and increased productivity may lead the patient to ignore more severe aspects of the illness, including irritability, argumentativeness, insomnia, poor judgment, and engaging in sexual and other high-risk behaviors without appropriate appreciation of the consequences. These deleterious activities may severely affect the patient's social structure, marriage, and employment. Early recognition that these symptoms and the denial of illness (anosognosia) are components of the illness itself may be crucial to instituting appropriate treatment and preventing escalation to destructive and full-blown manic episodes.

Again, family participation is crucial in both the diagnostic evaluation and the ongoing treatment. The family can assist in overcoming

Table 14.8-1
Steps in the Treatment Algorithm of the Bipolar Patient

A *Diagnostic clarification*
1. Retrospective course (bipolar I disorder, bipolar II disorder, bipolar disorder not otherwise specified, recurrent brief mania, or cycling)
2. Medication history (antidepressant induced, tolerance, or seasonal pattern)
3. Family history of bipolar disorder and medication response
4. Principle: treat first; determine blood concentrations and chemistries later

B *Maximize current regimen*
1. Increase dosage if adverse effects allow
2. Change timing of dose (especially at night—for sleep adverse effects, compliance)
3. Treat dose-limiting adverse effects:
   a. Use another antimanic agent if possible (i.e. one with two-for-one return)
      1. Propranolol (for lithium tremor)
      2. Calcium channel inhibitor (for lithium diarrhea)
      3. Lithium (for carbamazepine →↓ WBC)
      4. Thyroid (for lithium → ↓ thyroid)
   b. Decrease dosage (if response allows)
   c. Discontinuation (for intolerable adverse effects)

C *Augment*; especially with partial efficacy; occasionally with little or no efficacy (i.e., do not discontinue ineffective lithium without careful reconsideration of risk to benefit ratio, including its antisuicidal effects)
1. p.r.n. high-potency benzodiazepine (clonazepam or lorazepam)
2. With second mood stabilizer (especially acute efficacy)
3. Use third mood stabilizer if needed
4. p.r.n. antipsychotic (low dose)
   Typical: haloperidol, pimozide, chlorpromazine
   Atypical: olanzapine, clozapine, risperidone
5. Use drug with new mechanism of action (i.e., with profile of effects in different cycle frequencies or illness patterns)
   a. Calcium channel inhibitor (for ultradian cycling)
   b. Clonidine (for panic and opiate withdrawal)
   c. Valproate (for migraine)
   d. Carbamazepine (as atypical antidepressant-mood stabilizer) active at peripheral-type benzodiazepine receptor
   e. Consider trimipramine as atypical antidepressant with D_2 blocking and antipsychotic effects

D *Discontinuation of potential mania-inducing or cycle-inducing agents such as*
1. Antidepressants and alprazolam
2. Cocaine and related stimulants
3. Steroids (if possible)

E *Substitution* (if adverse effects occur and drug is ineffective)
1. Drug with different adverse-effects profile
2. Use drugs with different mechanisms of action

F *Refocus on early warning system (EWS) and prophylaxis*
1. Mood chart and contract of medication changes and contact doctor for given degrees of symptom emergence
2. Education and compliance
3. Principle: maintain effective prophylaxis
   a. Be conservative when good medication responses are achieved
   b. Be more radical and make changes in face of previous inefficacy

illness denial and thought disorder associated with hypomania and mania, which can be as problematic to receiving adequate treatment as the hopelessness and suicidality of the depression.

Therefore, therapeutic activism, engagement of the family, and early and aggressive treatment of both manic and depressive syndromes are of paramount importance. Individual patients and their families should receive initial and ongoing informational support regarding the medical aspects of the illness, its potential course, and response to treatment, with the long-term goals of increasing compliance, "medicalizing", and destigmatizing the illness. Destigmatization may become a crucial issue later in therapy when recommendations for long-term prophylaxis may elicit society's negative attitudes toward taking maintenance medications for psychiatric indications (in contrast to most other types of medicine). Conceptualizing the recurrent mood disorders as medical illnesses deserving the same attention, care, and long-term respect as disorders of other organ systems and may help the patient and family accept appropriate long-term treatment options.

A variety of societal, attitudinal, and illness-related variables may interfere with appropriate help-seeking and maintenance behavior in the various treatment phases, including initiation of acute care, continuation treatment, and long-term prophylaxis. During each of these phases patients and their families should be helped to evaluate the medical data and the potential impact of the illness on the patient. Do not introduce all of these variables at the beginning; approach them sequentially in each phase as appropriate. For example, it may be better to discuss the importance of continuation and long-term prophylactic therapy after patients have begun to show an antimanic or antidepressant response, rather than raise this issue with acutely ill patients and possibly frighten them from pursuing further treatment.

Early discussion of long-term prophylaxis—with graphic, statistical, and both written and verbal presentation of the data to the patient and family—may be critical for achieving an optimal outcome. Even in an illness such as juvenile diabetes, where it is unequivocally demonstrated that the patient cannot survive without adequate insulin treatment, many adolescents nevertheless directly or indirectly test the need for insulin and suffer periods of marked hyperglycemia, often requiring hospitalization. In a parallel fashion, patients with bipolar disorder are likely to be tempted to discontinue treatment, especially when the data regarding the morbid or lethal consequences are less well delineated. Nevertheless, the treating clinician must provide the patients and their families with the now overwhelming data showing the high likelihood of a recurrence in a relatively short period of time in patients with one or more prior episodes and the ability of a variety of agents to prevent recurrences of both manic and depressive episodes.

In bipolar disorders the high likelihood of relapse (50 percent in the first 5 months following lithium discontinuation and 80 to 90 percent within the first year and a half) is now also widely recognized and should be explained to the patient. In addition, it has always been assumed that patients who experience a relapse will be readily treatable once their former therapeutic modality has been reinstituted. Most investigators have observed lithium-discontinuation-induced refractoriness in which a small percentage of patients who discontinue successful prophylactic treatment and experience a relapse fail to respond when the treatment is reinstituted. In other instances, patients may not respond as rapidly as they did initially or require increased adjunctive neuroleptic medication.

Many studies report that lithium is less effective in patients who have had more than three or four prior episodes than in those whose prophylaxis is initiated earlier in the illness course. Thus, not only should the potential morbidity and mortality of an episode itself be factored into the decision-making process for long-term prophylaxis, but also the possibility that new episodes could affect the subsequent course of the illness and its pharmacological responsivity.

PSYCHIATRIC HISTORY

A thorough medical history and examination are important, given the many syndromes that mimic both manic and depressive syndromes. The older patient with late-onset illness, in particular, should be approached with the possibility of an associated medical cause, and attention should be paid to obvious or subtle hallmarks of associated pathology. The physician should be alert to symptoms indicating CNS neuropathology, underlying endocrinopathy, or other associated medical illness. Although physicians should aggressively explore these themes with patient and family, they should remember—and even directly tell the patient—that all of the somatic and vegetative symptoms reported are consistent with, and most likely indicate, typical primary affective illness.

The earliest parts of the history can be used to uncover diagnostic clues and to educate the patient about the types of symptoms that are typical of the disorder, are associated with its natural course of spontaneous exacerbation and remission of episodes, and are likely to respond to somatic and pharmacological intervention. The medical history and examination should also seek evidence of cardiac, renal, or thyroid abnormalities that may help guide subsequent treatment choices.

The physician should cover each psychological and somatic symptom category associated with depression while simultaneously educating the patient, providing target symptoms for future assessment of the efficacy of psychological and pharmacological intervention, and constructing the framework for longitudinal monitoring of the patient. The symptoms that are typical for a given patient are likely to be involved in a future episode, and thus they provide an early warning system for illness detection and institution of additional treatment.

A detailed family history of medical and psychiatric illness is also crucial to the initial diagnostic assessment of the patient. Graphic construction of a formal family tree is recommended, with each first-degree relative specifically inquired about for their potential diagnosis, course of illness, and response to therapy (Fig. 14.8-1), since these may help guide the choice of therapies for the patient. A positive family history of bipolar illness may further support the recommendation of long-term prophylaxis after the emergence of the first manic episode.

A bipolar disorder family history, especially one with bilineal loading for mood disorder, should markedly raise suspicion of a juvenile- or adolescent-onset bipolar disorder, even if its presentation is less than typical. The clinician should recognize that even in an adult-onset bipolar disorder, the passing of a decade between affective symptom onset meeting diagnostic thresholds and the initiation of treatment is not uncommon. Moreover, in the prepubertal child, a bipolar disorder may present differently from the classic adult picture (Fig. 14.8-2). Instead of showing discrete episodes that easily meet the durational criteria of the fourth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), there may be a pattern of tantrums, mood lability, irritability, and marked and rapid fluctuations in mood and behavior. Hypersexuality and grandiosity (if not frank delusions), high-risk behaviors, sleep disturbance, extremes of anger or aggression, or expressions of suicidal ideas may be particular clues that one is dealing with more than attention-deficit/hyperactivity disorder in the hyperactive and inattentive child. Moreover, prepubertal onset of a psychotic depression may herald the beginning

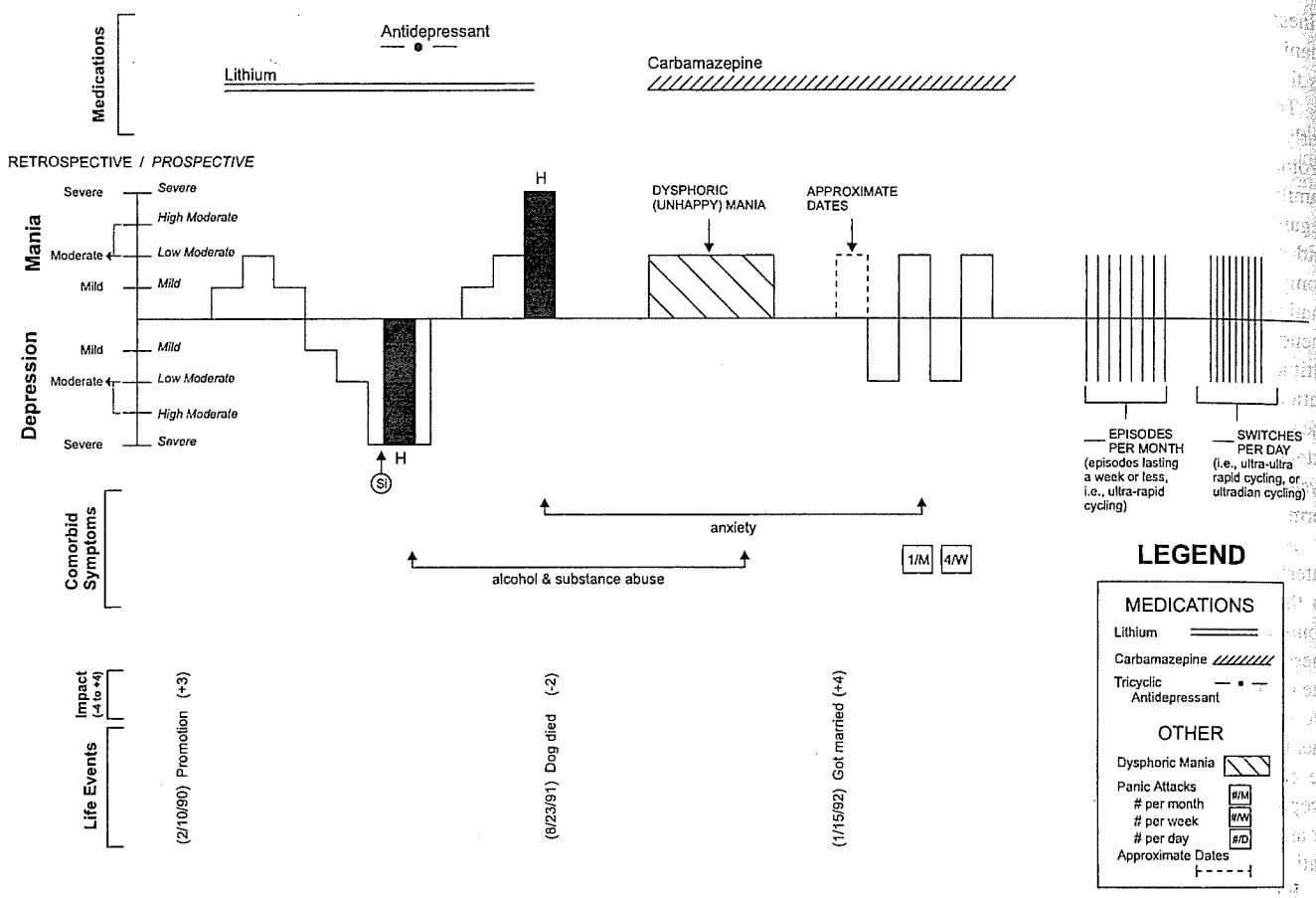

FIGURE 14.8-1 Schema for graphing the course of mood disorders: Retrospective and prospective.

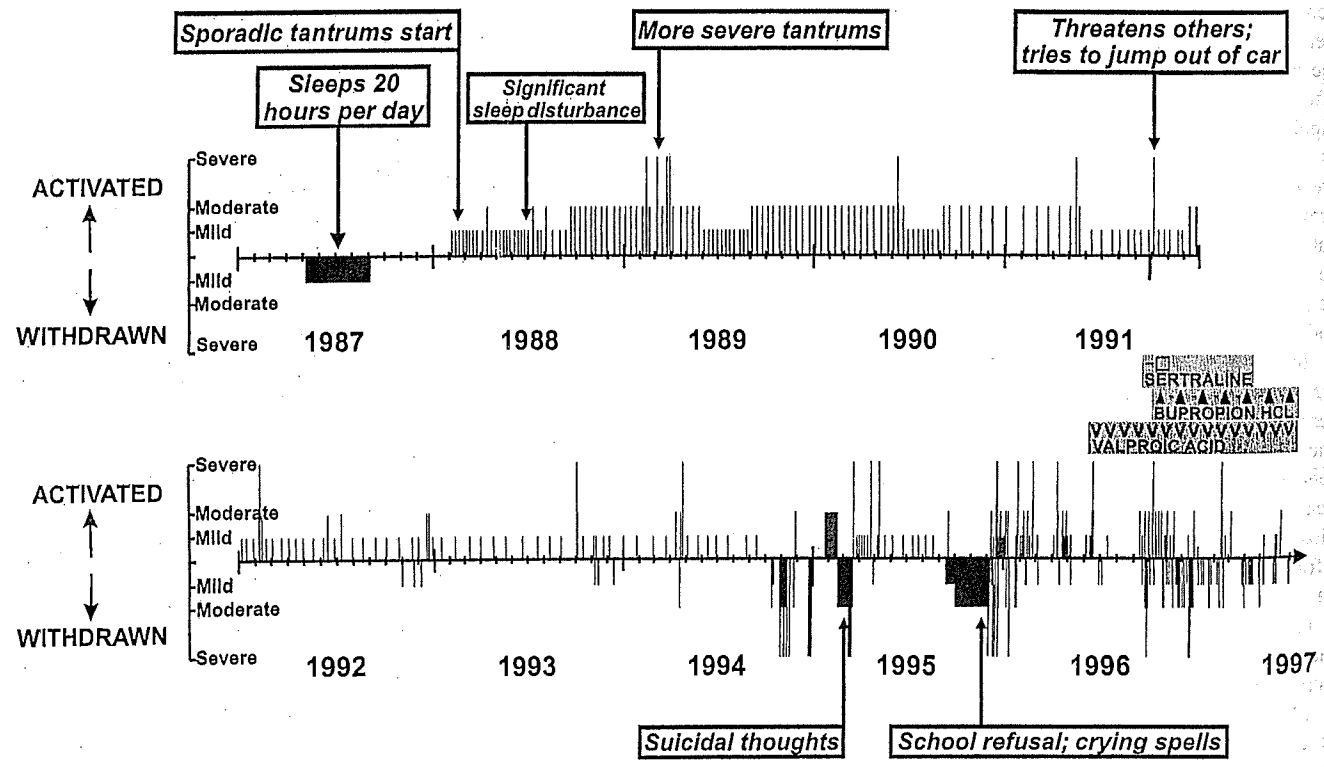

FIGURE 14.8-2 Kiddie Life Chart (K-LCM) of a 10-year-old child with affective dysfunction from the first year of life.

of bipolar illness, since a 30 percent switch rate into mania upon treatment with antidepressants has been reported. Similarly, bipolar disorders may present atypically in adolescence, either with extremes of mood lability or with more psychotic and schizophreniform features. In prepubertal children and adolescents, antidepressants may exacerbate the illness, and mood stabilizers, often in combination, are frequently required.

Graphing the Course of Illness The author suggests developing a graphic representation of the patient's prior depressive and manic episodes (Fig. 14.8-3). This graph will form a basis for evaluating the efficacy of previous treatments and assessing current and future prescription. A formal graphic representation of the patient's longitudinal course of illness is useful for several reasons: (1) it provides a clear picture of the earlier illness course, which appears to be the best predictor of the future episode pattern; (2) it clarifies prior and future medication responsiveness; (3) it helps medicalize the patient's history and management, as well as facilitate the recognition of low-level manic symptoms, and (4) it encourages the patient's collaboration and thus may enhance the doctor-patient relationship, making the patient an active partner rather than a passive participant.

If a number of past episode recurrences are uncovered in the history, such a graph may also help in the subsequent long-term approach to the illness and in the patient's compliance with prescribed regimens. Moreover, the author has found that this process often uncovers important psychosocial events and possible precipitants of the illness, as well as unique characteristics of the illness, such as cycle characteristics, illness rhythmicity or lack thereof, seasonal variation, relation to anniversaries, and other longitudinal treatment response patterns (such as tolerance or cycle acceleration) not easily uncovered without systematic, graphic representation of the illness. Carefully examining the periods of increased vulnerability to illness provides a template for future treatment intensification or augmentation of therapeutic modalities as appropriate.

With a little practice, the course of an illness can easily be graphically depicted. The author suggests that this be done as part of the initial intake session and be the primary mode of recording a patient's history, even preferable to an extensive written account intended for later conversion to a graph. In this way, both the patient and the physician are immediately and systematically focused on the longitudinal course of the illness and its variation over time, rather than having this focus develop later or possibly be completely sidetracked by attention to acute symptoms. The graphic approach and its associated temporal landmarks can also facilitate recall of important events, dates, and episodes that would otherwise be obscured or forgotten. Typically in this process, supposed first-episode patients will often uncover multiple prior minor or major episodes.

Levels of Severity Physicians can devise their own ways of plotting the course of illness or adopt a system like the one the author and his colleagues have used successfully over the past decade, that is, graphing three levels (mild, moderate, and severe) of mania or depression on the basis of the degree of associated symptom-driven functional incapacity, which can be most readily assessed retrospectively, on the National Institute of Mental Health NIMH–life chart method (NIMH-LCM) (Fig. 14.8-3).

At the mild level, the patient or family notes a distinct change in the patient's mood, with no notable impairment in the patient's social, educational, or employment roles. This state is readily recognized by depressed patients and may represent the dysthymic baseline from which more severe episodes erupt (i.e., double depression). However, hypomanic patients may deny this mild state, so additional information and input from family members and relatives is important. This observation also reemphasizes the utility of a nonpsychoanalytic approach to the patient's diagnosis and treatment, including the participation and support of family members from the outset. This may be of value both in gaining historical information, and in managing potential suicidality of depression and denial of the adverse consequences of hypomania and mania.

Hypomanic signs and symptoms representing distinct periods of increased energy, productivity, and creativity and decreased need for sleep should be sought directly, and not raised in a negative fashion. These milder periods may be easier to explore after the more severe phases of a patient's illness have been detected and the characteristics of their early presentation agreed upon.

Moderate levels of depression and mania that represent phases with distinct functional impairment are graphed at the next level. Patients can continue their social or employment responsibilities, but only with obvious difficulties, such as absences from work or not being able to perform some routine social tasks. In prospective forms of the NIMH-LCM, moderate dysfunction has been divided into low and high categories, representing some and much dysfunction in usual roles, respectively (Fig. 14.8-4). The manic patient may reveal these levels of dysfunction more easily if asked whether coworkers, friends, or family members are commenting or complaining about the patient's behavior or directing them to seek help.

In severe impairment patients are functionally incapacitated and unable to perform their usual roles. Hospitalizations can be coded by shading in the severe manic or depressive episode on the graph. A past episode whose precise timing is unknown or unavailable can be graphed and coded with broken or dotted lines.

For prepubertal onsets a Kiddie-LCM is available that allows graphic depiction of symptom-driven dysfunction whether or not these often highly disturbed and dysfunctional children meet the artificial durational criteria intended for classical adult presentations. Such documentation may be crucial to a child's receiving adequate pharmacological intervention, which is often withheld because of diagnostic controversy and the attendant fears of using medications in children. Professional and societal attitudes and stigma would appear to be highly relevant here, as there is less concern about medications in children with epilepsy, rheumatoid arthritis, infections, malignancies, asthma, and many other medical illnesses with typical or atypical early onsets. Not only is childhood- and adolescent-onset bipolar illness prognostically more disabling than the adult variety in some long-term outcome studies, but the illness also puts the child at increased risk for alcohol and other substance abuse and for other potentially deleterious high-risk behaviors. Moreover, adolescent suicide is one of the fastest growing categories of early mortality.

Psychopharmacological Interventions The history of prior psychopharmacological interventions should be plotted directly above the episodes on this retrospective template of mood fluctuation as illustrated in Figure 14.8-1 of the life-chart schema and in the case example in Figure 14.8-5. When graphed in this fashion, the efficacy of earlier treatments is often more precisely categorized and reclassified. On careful reexamination, a treatment previously deemed ineffective may have partially decreased the frequency or severity of prior episodes. If so, one may now want to consider supplementing this partially effective treatment rather than abandoning it. Previous psychotherapeutic interventions should also be noted,

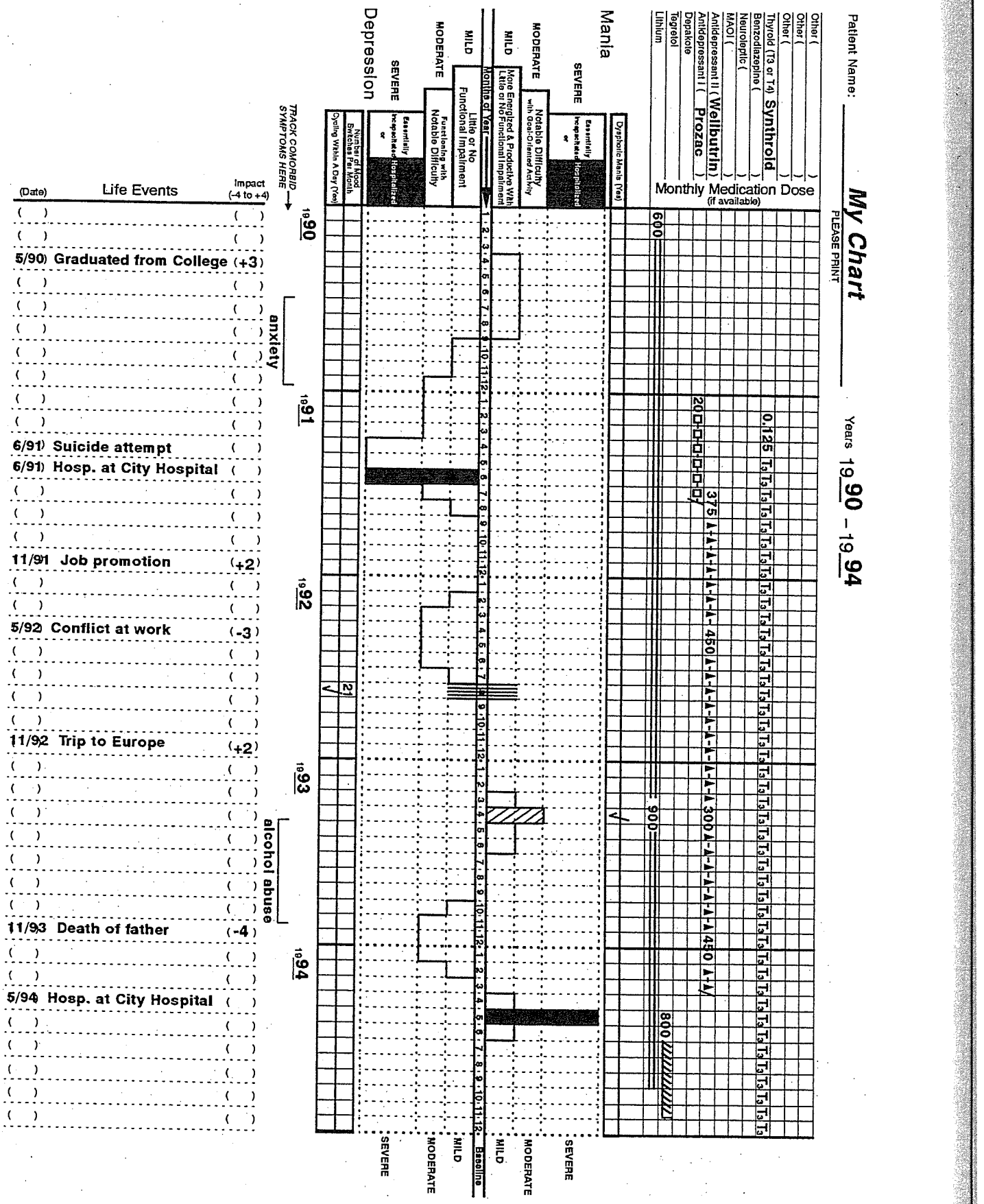

FIGURE 14.8-3 National Institute of Mental Health (NIMH)-life chart method (LCM) self ratings—retrospective.

Name: My Chart (PLEASE PRINT) Patient ID# 0000 City Bethesda Month 10 Year 1994

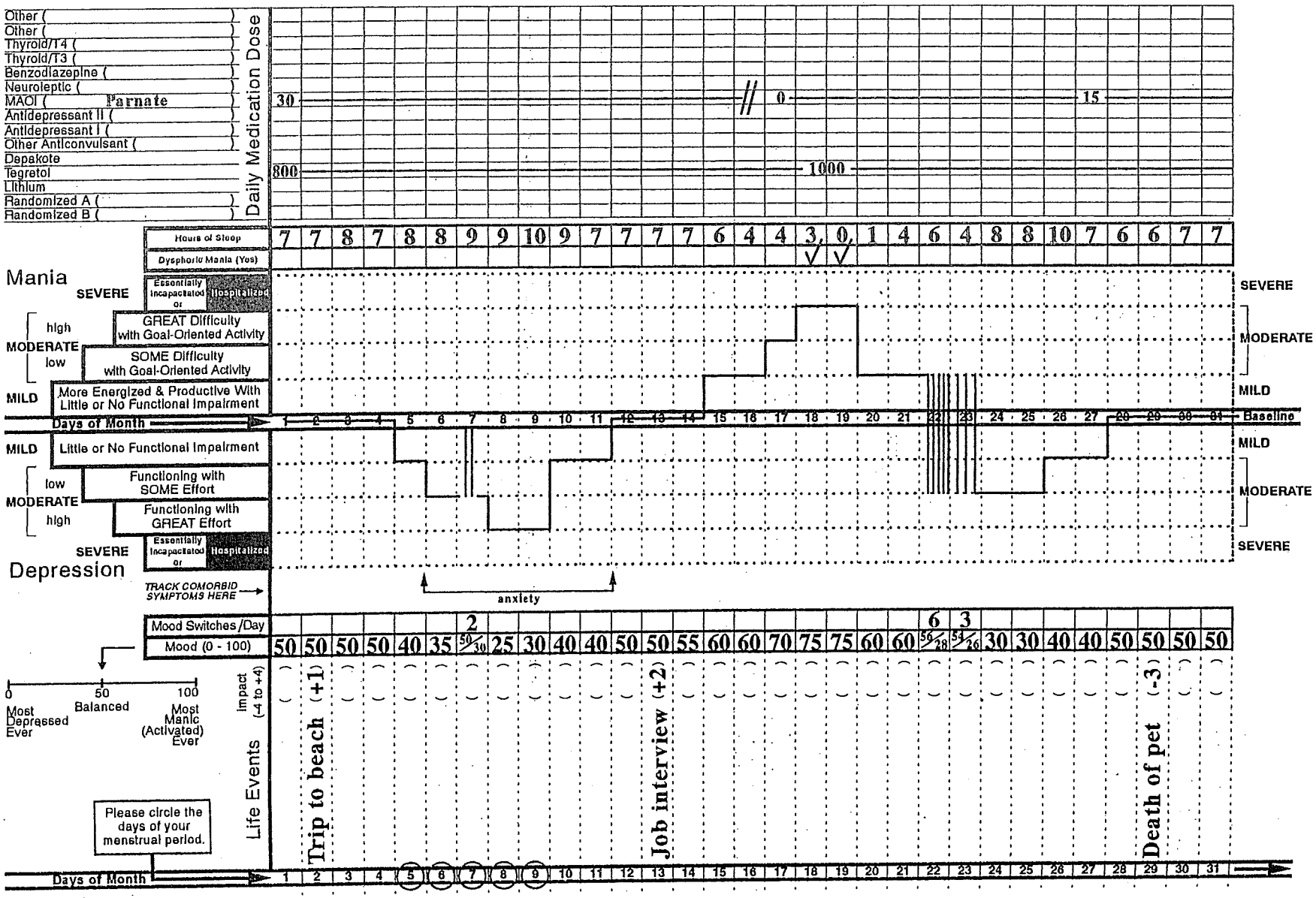

FIGURE 14.8-4 NIMH-LCM self ratings—prospective.

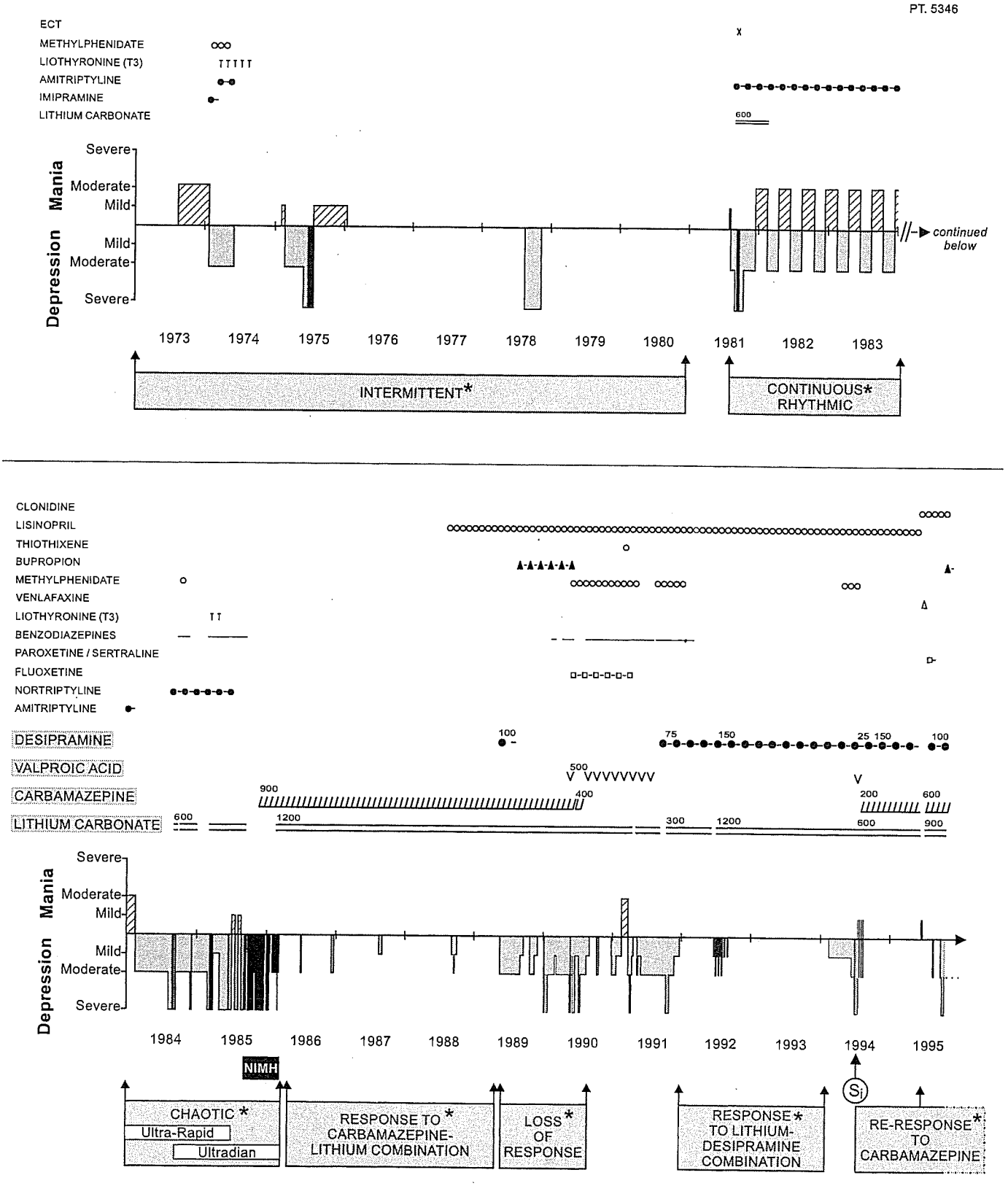

FIGURE 14.8-5 Phases of illness evolution and treatment response in a woman with bipolar II disorder.

so that their impact on the illness and patient satisfaction can be assessed. As illustrated in Figures 14.8-1 and 14.8-3, important psychosocial events (e.g., significant anniversaries, suicide attempts) and notes about adverse effects (e.g., dosage, reasons for discontinuation of medications) can be entered below the mood graph.

Descriptive Symptoms The anamnestic account of specific symptoms and their associated dysfunction also provides the basis for following clinical improvement during an acute episode and during future possible episodes. In particular, one should try to determine the best descriptors and early predictors of an individual patient's episode. For some patients it may be impaired sleep with early morning awakening; for others it may be an inability to concentrate. Still others may experience decreased energy or increased agitation, isolation, anxiety, appetite, or weight gain. The sequential ebbing of symptomatology during a treated episode may also help delineate the need for continued augmentation treatment or reciprocally yield clues to the earliest symptoms of a recurrence. Should these or other residual symptoms break through during prophylaxis or emerge while tapering medication, they can be used to indicate roughening and the need for renewed, more aggressive management of a potential episode.

Similarly, clinicians should contract with their patients in advance about specific symptoms that may herald depressive or manic episodes and require additional monitoring and intervention. Early signs of the emergence of the patients' typical symptoms—such as increased energy or religiosity or decreased sleep—that may be welcomed, may actually presage more consequential manic symptoms. Attention to these early warning signs while insight is still preserved and denial manageable may save patients and their families from a more prolonged or catastrophic episode. A specific contract such as "call if you should have two nights with less than 5 hours of sleep" is often more helpful than a more general suggestion to call if needed.

Prospective Charting For the bipolar patient with several episodes, the author suggests that some elements of this life chart process be continued prospectively, preferably on a daily basis. This can be accomplished quite easily in a number of ways, including having the patient keep a nightly calendar and write a number on a visual analog scale from 0 (worst ever felt) to 50 (normal or balanced) to 100 (most energized or manic ever). Following discussion with the clinician, this score can be converted to life-charted episodes based on functional incapacity.

In this fashion or with a more complete daily prospective mood chart such as the NIMH-LCM-p patients can track their mood fluctuations in a systematic manner that is unobtrusive and takes only seconds to complete. Pocket life charts and computer graphics packages are now available. Mood rating, like self-assessment of urine glucose concentration by the diabetic patient, may provide an important measure of how well the patient's illness is responding to a given treatment modality, and its dosage adverse-to-effect efficacy ratios and titration. The morbidity and mortality of the mood disorders can be as severe as those of many medical illnesses for which a great deal more attention is paid to the longitudinal and systematic monitoring of fluctuations in symptomatology, biochemistry, and underlying pathology. Patients should be encouraged to help in this life-chart process if they are amenable to it. The completed retrospective and ongoing prospective charts may also help in any future transfers of medical care, orientation of hospital staff, or consultation request should the patient move or suffer future episodes requiring review and revision of treatment.

Subjective and Objective Differences Finally, asking patients to make a calendar, rate their moods (with a specific number on the 100-mm line), and assess illness-driven functional incapacity, may have other secondary benefits. Patients can become better attuned to possible subjective versus objective differences in illness assessment. Some depressed patients can detect mood changes and adverse effects before therapist observation, but many bipolar depressed patients can show remarkable improvement in major aspects of their symptomatology, including sleep, appetite, energy, spontaneity, and sociability, without any subjective sense of mood improvement. If patients do not recognize that their depression is improving despite objective signs, it may lead to further therapeutic pessimism and also may increase the possibility of suicide, as they now may have more energy to carry out such a plan. Moreover, return to previous optimal social and occupational function may lag even further behind objective and subjective appreciation of symptomatic improvement, so that the patient requires additional support, encouragement, and possible retraining during this time frame.

TIME FRAME OF EDUCATION

Although a hopeful perspective about the treatability of a patient's episode should be maintained, a series of drug trials may be needed before the best treatment regimen is found. Evaluation of an acute antidepressant treatment response often requires 3 to 6 weeks, and a given agent's lack of efficacy should be treated as additional information about the patient's illness rather than an indication that the illness is not responsive. Several recent studies in unipolar depression suggest that a lack of some improvement after 4 weeks is a very poor prognostic sign for eventual response with further continuation into 5 and 6 weeks.

Thus, augmentation approaches, in particular, should be triggered at these early times rather than after several months, particularly if high doses or adequate blood concentrations of a given compound have been achieved. In the treatment of acute mania, in which response is typically more rapid (days to weeks), one should consider additional and alternative approaches if improvement is not observed over much shorter periods (days to a week). At the outset of treatment the availability of different effective treatments, with many drugs in each class, should be brought to the patient's attention. This puts possible treatment sequences in their proper perspective and emphasizes that a lack of response to, or an intolerance of, one drug does not portend an ultimate negative therapeutic outcome.

These points should be reemphasized throughout the entire therapeutic process, particularly in light of the different time frames available to the therapist and the patient. The therapist is aware of the many treatment alternatives and the extended treatment course sometimes required to achieve optimal efficacy. The patient (and perhaps even the family) may be overwhelmed by a sense of immediacy and desperation about the current mood-disordered state. Particularly for the depressed patient, this feeling of pain and hopelessness can too easily overtake the realities of the situation and increase the risk of suicide before a positive treatment outcome is achieved.

Reassurance without overpromising immediate therapeutic effects thus appears to be an important part of the treatment. 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 of these cases. Thus, supportive, interpersonal, cognitive, and behavioral approaches to the psychopharmacotherapy of the mood disorder may be essential. Patients should also be counseled not to make important long-term decisions

on the basis of a distorted view of themselves and their future during an acute depressive or manic episode.

Stressing the time needed to evaluate a given treatment may help maintain the patients' and families' morale and help obtain an adequate informed consent while avoiding malpractice litigation. In this regard, the patient must be told the possible adverse effects of each drug treatment, so that these effects are expected and not seen as dangerously unpredictable, or conversely, they can be recognized as something that merits closer attention, a call to the physician, or an extra visit when indicated.

HOSPITALIZATION

The decision to hospitalize severely depressed or manic patients depends on a variety of clinical and (disappointingly) economic issues. Hospitalization is often indicated for the acutely suicidal patient and may also be considered for the patient with associated medical problems or one who needs close management and monitoring of complicated or novel psychopharmacological regimens. For the knowledgeable patient and supportive family, one or more of a series of psychopharmacological approaches can often be accomplished on an outpatient basis, particularly if there is close coordination between the patient and physician regarding dosage, titration, adverse effects, and indicators of improvement. Despite many of the largely societal criticisms of the modern use of ECT, this modality should be given a higher priority when treating patients with extreme suicidality, associated medical illnesses, difficult adverse reactions to routine psychopharmacological agents, or other medical emergency situations (such as malignant catatonia or hyperthermia) that demand the most rapid treatment response available. For the recurrent manic patient who has refused voluntary hospitalization at the height of an episode or might be likely to do so, obtaining informed consent in advance (during a well interval) for future involuntary hospitalization and pharmacological treatment may avoid many cumbersome practical and medicolegal difficulties should another manic episode requiring hospitalization occur.

PSYCHOTHERAPY AND PHARMACOTHERAPY

Depression is a serious, potentially life-threatening medical illness, and patients and their families deserve much support. Combining psychosocial and pharmacological approaches is important for most because of their potential mutual interaction and support in the context of ongoing pharmacotherapy.

Cognitive-behavioral therapy may enhance medication compliance and provide support for the patient in the interval before psychopharmacological interventions are successful, especially if several agents are required before an effective regimen is found. Moreover, stress and other psychosocial issues may be involved in the onset and recurrence of some depressions and manias and may be indicators for more aggressive pharmacological management.

Frequent meetings with the patient may also help in assessing response to pharmacotherapy and suicide risk. In a depressed patient with severe pain and suffering, frequent meetings may facilitate the fastest maximal application of pharmacological leverage; regimens can be revised as quickly as possible (days to a week in mania, and several weeks in depression) if improvement is not forthcoming. Combined treatment may also be helpful in instances of partial response to monotherapy, a protracted episode, poor interepisode recovery of function, an associated personality disorder, or the presence of acute psychosocial stressors.

NEUROTRANSMITTER THEORIES

Because most of the effective treatments for mood disorders were discovered by serendipity, pharmacological agents have propelled theoretical formulations rather than vice versa. Neurotransmitter theories of the basis of depression have included serotonergic, noradrenergic, cholinergic, dopaminergic, γ-aminobutyric acid GABAergic, and, most recently, glutamatergic, each based on presumed mechanisms of effective pharmacotherapeutic interventions. For example, finding that several drugs that acutely potentiated catecholamines and indolamines were antidepressants and that reserpine (which depleted these neurotransmitters) could exacerbate depression and treat mania led to the amine hypotheses of deficiencies in depression and excesses in mania.

Relatively selective manipulations of each of several different neurotransmitter systems (serotonin, noradrenergic, and dopaminergic) now seem to be associated with antidepressant effects (Tables 14.8-2 and 14.8-3), which raises a critical psychopharmacological question, whether an individual may respond to one type of treatment with a postulated mechanism of action targeting one neurotransmitter

Table 14.8-2
Targets of Action of Antidepressants and Mood Stabilizers

ANTIMANIC					
High-potency Benzodiazepines		Typical neuroleptic agents		Atypical neuroleptic agents	
↑ Cl^- influx		Block D_2 receptors		Block mesolimbic dopamine D_1, D_2, D_4 receptors and 5-HT_2 receptors	
MOOD STABILIZERS					
↓ 2nd messenger and G protein	↑ GABA	↓ Glutamate	↓ Calcium	↑ Thyroid	Atypical
Lithium	Valproate	Carbamazepine	Nimodipine		Clozapine
Carbamazepine	Gabapentin	Lamotrigine	Isradipine	T_3 (25 μg)	(Risperidone)
Valproate	Tiagabine	Topiramate	(Amlodipine)	↑↑ T_4 (150%)	Olanzapine

ANTIDEPRESSANTS				
Dopamine	Serotonin (5-HT)	5-HT plus	Norepinephrine (NE)	5-HT and NE
Bupropion	Fluoxetine	Nefazodone	Desipramine	Clomipramine
	Sertraline	Mirtazapine	Nortriptyline	Venlafaxine
	Paroxetine		Maprotiline	
	Fluvoxamine			

Table 14.8-3
Adverse Effects of Biological Treatments Used to Treat Depression in Bipolar Disorder Patients

Antidepressants	Manic Switch	Sedation	Hypertension	Anticholinergic	NE/5-HT	Weight	Sexual Dysfunction	Lethality in OD	Comments
Bupropion (75–450 mg/day)	+	+/−	0	+/−	+/0	↓	0	Low	Seizures at high dosages
SSRIs	+	+/−	0	0	0/+++	↓, ↑	+++	Low	Insomnia, headache
SNRIs Venlafaxine (37.5–250 mg/day)	+?	+	—	+/−	++++/++++	0	+/−	Low	↑ BP, few mm Hg
MAOIs	++?	+	+++	0		↑	++	High	Diet to avoid tyramine
RIMAs Moclobemide (150–1600 mg/day)	+?	+	+	0	++/++	(↑)?	?	?	Not need diet? Less effective than MAOIs
Trazodone (50–600 mg/day)	?	+++	+++	0	0/++	⇈	+/−	Low	Priapism
Nefazodone (100–600 mg/day)	?	++	0	0	0/+++		+/−	?	Insomnia vs. increase in slow-wave sleep
Mirtazapine (15–45 mg/day)	?	+++			++/+++	⇈	++	?	α_2-Blocker
Alprazolam (2–6 mg/day)	+++	++	0	0	?	0	0	? moderate	Short half-life ↑ switch
Buspirone (5–35 mg/day)	? ++	+	(+)?	?	/++ agonist	?	—	?	Premature ejaculation
Amitriptyline (75–300 mg/day)	++	+++	+++	+++	±/+++	⇈	+	High	Avoid these relative to second- and third-generation antidepressants; high variability in drug levels
Imipramine (75–300 mg/day)	++	++	+++	+++	++/+++	⇈	+	High	
Desipramine (75–300 mg/day)	+++	+	+++	+	+++/0	↓, 0	+/−	High	Switch rate more than bupropion
Nortriptyline (50–150 mg/day)	++	++	++	++	+++/++	0, ↑	+/−	High	Possible inverted U type blood concentration clinical response
Lithium (600–1500 mg/day)	0	+/−	0	0	−/+	⇈	0	Moderate	Especially for augmentation may require thyroid supplementation
ECT (6–12 Treatments)	+	+	−	++ (atropine)	++/++	0	0	Low N/A	Anesthesia; seizure memory loss

Abbreviations: NE, noradrenergic; OD, overdose; SNRIs, serotonin and noradrenaline reuptake inhibitors; BP, blood pressure; RIMAs, reversible inhibitors of monamine oxidase type A.
Ratings: 0, None; +/−, equivocal; +, mild; ++, moderate; +++, marked; ++++, very marked.

system, but not to another (Fig. 14.8-5). In the absence of definitive studies of this question, one is tempted to recommend the sequential use of drugs that act differently within or among classes of agents (e.g., changing from a relatively more serotonergic to a relatively more noradrenergic tricyclic reuptake inhibitor or from a tricyclic drug to an MAOI to lithium). Few validated clinical or biological markers of response to given treatment agents exist, so one must move through the various treatments or adjuncts for the refractory patient until an effective one is found, largely through trial and error. An MAOI trial should be considered for a patient who has failed to respond to multiple previous antidepressants, as response rates remain 50 to 60 percent with this agent. A similar strategy of using agents with different mechanisms of action sequentially or concurrently in mania may also be warranted (Tables 14.8-4 and 14.8-5).

Since 1 month must elapse between treatment with serotonin-active compounds and an MAOI, a transition may be achieved with bupropion, a noradrenergic-selective agent, lithium, or an anticonvulsant. With increasing levels of refractoriness, one should reevaluate the diagnosis (especially with a careful assessment of possible physical, psychological, or drug abuse comorbidity) and consider consultation, psychotherapy revision, as well as more complex combination treatment approaches.

Lithium, valproate, and carbamazepine each alter dopamine and noradrenergic function and upregulate γ-aminobutyric acid (GABA)

Table 14.8-4
Putative Psychotropic and Mechanistic Effects of the Anticonvulsants

Treatment (abbreviation) (close mg/day)	Target Symptoms			Mechanisms			Comments
	Mania	Depression	Anxiety	Amines and Amino Acids	Peptides	Electrolytes	
ECT (6–9 treatments)	+++	+++	?	↑ NE, DA	↑ TRH, ↑ CRH		Anesthesia, seizures, and memory loss
Phenytoin	(+/−)	(+/−)	(+/−)	↓ Glucose release	↓ SRIF	↓ Na_+ type II, Ca_{2+}	
Carbamazepine (4–1800)	+++	+	+	↓ P-type benzodiazepine receptors, ↓ adenosine A_1; ↓ glutamate release	↑ TRH, ↑ Sub P, ↓ SRIF, ↓ NPY	↓ Na_+ type II, ↑ K_+, ↓ NMDA-Ca_{2+}	Individual dose titration; autoinduction; CYP 3A4 interactions
Clonazepam (0.5–4)	(++)	(+)	+++	↑ 5-HT		↑ Cl_-	Helps sleep and panic
Alprazolam (0.5–4)	−−	++	+++			↑ Cl_-	May precipitate mania
Barbiturates	(−)	−−	++			↑ Cl_-	Behavior dyscontrol (avoid)
Nimodipine (90–480)	++	(++)	(+)	↓ DA	↑ SRIF (↑TRH)	↓ L-type Ca_{2+}	Dihydropyridines more effective than phenylalkylamine?
Isradapine (10–20)							
Amlodipine (5–15)							
Verapamil (240–480)	++	0	+	0 − DA		↓ L-type Ca_{2+}	
Valproate (250–3000)	+++	(+)	+	↑ GABA via multiple mechanisms	↓ SRIF	↓ T-type Ca_{2+}, ↓ Na_+, ↑ K_+	Zinc and selenium may help prevent alopecia
Vigabatrin	?	(− −)	?	↑ GABA via ↓ metabolism			Depressogenic in epilepsy?
Gabapentin (400–4800)	(+)	(+)	(+)	↑ GABA via transporter effect	No Δ SRIF	↓ Ca_{2+}	Mood stabilizing?
Treatment of pain, tremor, parkinsonism							
Tiagabine (TIA)	?	?	?	↑ GABA via reuptake block			Psychotropic?
Lamotrigine (25–500)	(++)	(++)	?	↓ Glutamate release; 5-HT_3 block 5-HT reuptake		↓ Na_+ type II	Likely antidepressant
Felbamate	?	?	(− −)	↓ $Glutamate_R$ ↑ GABA			↑ Aplastic anemia ↑ Hepatic failure
Topiramate	?	?	?	Blocks AMPA glutamate receptors			↓ Weight ↓ Renal stones

Abbreviations: ECT, electroconvulsive therapy; Ne, noradrenergic; DA, dopaminergic; TRH, thyrotropin-releasing hormone; CRH, corticotropin-releasing hormone; SRIF, Somatostatin releasing inhibiting factor; Sub P, substance P; NPY, neuropeptide Y; NMDA, *N*-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid.
Ratings: − −, Worse; 0, absent; +/−, minimal; +, somewhat effective; ++, effective; +++, very effective; (), equivocal findings or weak or inconsistent database.

type B ($GABA_B$) receptors in the hippocampus (Fig. 14.8-6). They also target G protein systems, decrease protein kinase C activity, and inhibit calcium influx through the glutamate *N*-methyl-D-aspartate (NMDA) receptor. Lithium and valproate increase myristoylated alanine-rich C kinase substrate (MARCKS) and activator protein–1 (AP-1) binding, as well as messenger ribonucleic acid (mRNA) levels for BCL-2, and brain-derived neurotrophic factor, the latter two of which may be involved in the prevention of apoptosis. GABAergic effects are enhanced by valproate and gabapentin, whereas topiramate, carbamazepine, and lamotrigine decrease excitatory amino acid release or function in part via blockade of sodium ion channels.

TREATMENT OF ACUTE MANIA

Lithium Lithium has been the paradigmatic treatment for acute and prophylactic treatment of mania. In comparative studies with antipsychotic agents, it yields better overall improvement in most aspects of manic symptomatology, including psychomotor activity, grandiosity, manic thought disorder, insomnia, and irritability. However, the onset of antimanic action with lithium can be rather slow (Fig. 14.8-7), even with aggressive dosing; thus acutely deteriorating aggressive or psychotic manic patients may require supplementation of lithium in the early phases of treatment. Until recently, this was traditionally accomplished with the typical neuroleptic drugs, including the phenothiazines, thiothixines, or butyrophenones such as haloperidol (Haldol). Because of the rapidly growing evidence for the parallel acute antimanic efficacy of the mood-stabilizing anticonvulsants carbamazepine (Fig. 14.8-7) and valproic acid, it is suggested that these alternative agents or the more recently available atypical serotonin dopamine antagonists be used as initial supplements rather than in place of the conventional antipsychotics for a variety of rea-

Table 14.8-5
Algorithm for Augmentation and Switching Strategies, Treatment of Bipolar Disorder, Manic Phase, Dysphoric Type

First mood stabilizer LIFE chart

Valproic acid (mood stabilizer III) (if euphoric, start with lithium)

A. *Breakthrough hypomania or mania*
   1. *Insomnia*
   2. *Hypomania*
   3. *Full-blown mania*
      Clonazepam or
      Lithium or adjunctive use of clonazepam or lorazepam for sleep disturbance
      Lithium or antipsychotic if psychosis remains problematic with double or triple mood stabilizer (typical → atypical)

B. *Breakthrough depression* (check thyroid)
   1. *Isolated depression*
      a. Bupropion
      b. SSRI
      c. Venlafaxine
         +
         i. Potentiation with liothyronine, or Lithium
         ii. Crossover or MAOI
   2. *Recurrent depression*
      d. Add second mood stabilizer (Li or CBZ) then a, b, c
         +
         i. Potentiation with liothyronine or Lithium
         ii. Crossover or MAOI
   3. *Recurrent psychotic*
      e. ECT
      f. Atypical antipsychotic (SDA)
      g. Clonazepam or lorazepam.

C. *Breakthrough cycling*
   1. *Rapid Cycling*
      a. Very mild hypomania—antidepressants listed above
      b. Bipolar I or II disorder—add second mood stabilizer
   2. *Ultrarapid/ultradian*
      c. Add second mood stabilizer (Li/CBZ)
      d. Add third mood stabilizer (Li/CBZ) + thyroid augmentation
      e. Calcium channel blocker (nimodipine/isradipine)
      f. Putative anticonvulsant mood stabilizer—watch literature ??gabapentin ??lamotrigine
      g. High-dosage thyroid hormone
      h. SDA
         Risperidone
         Clozapine
         ?Trimipramine
      i. Clonazepam or lorazepam
      j. Typical antipsychotics
      k. ECT
         If depression predominates after "Add second mood stabilizer," then antidepressant series ("Isolated depression")*

D. Tolerance pattern
   1. Maximize dosage
   2. Augmentation strategies for predominant symptoms
   3. Switch drug class or mechanism of action
   4. Time off drug (or another or ECT) then restart

* Bupropion, SSRI, venlafaxine.

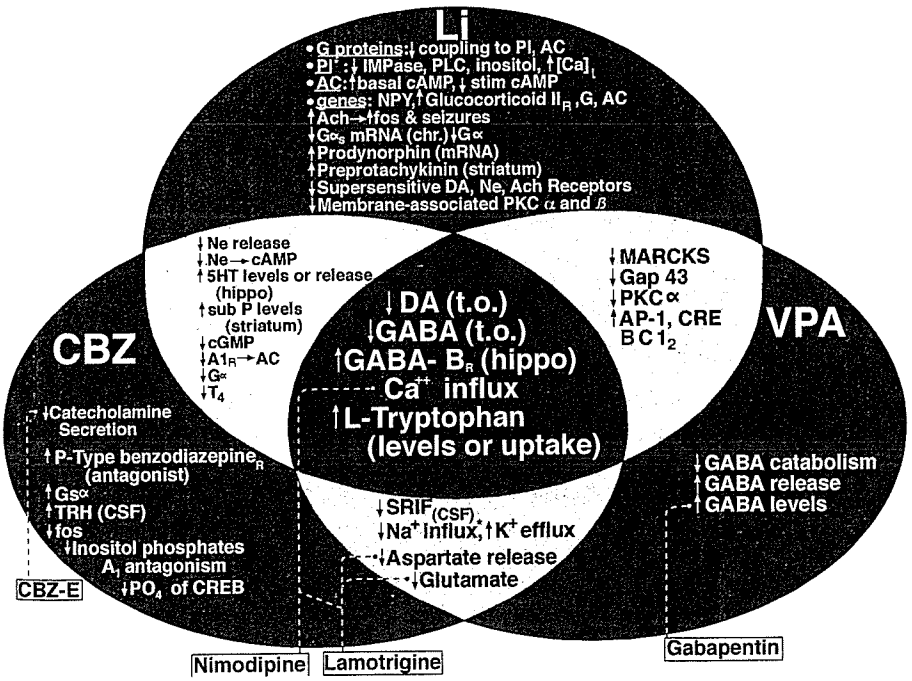

FIGURE 14.8-6 Common and different mechanism of mood stabilizers. PI, phosphoinositol; AC, adenylate cyclase; IMPase, inositol monophosphatase; PLC, phospholipase C; cAMP, cyclic adenosine monophosphate; NPY, neuropeptide y; ACh, acetylcholine; DA, dopaminergic; Ne, noradrenergic; PKC, protein kinase C; $A1_R$, adenosine A1 receptors; T_4, thyroxine; CRE, cyclic response element; CBZ, carbamazepine; TRH, thyrotropin-releasing hormone; CREB, cyclic response element binding protein; VPA, valproate; SRIF, somatostatin; t.o., turnover.

sons related to their adverse effect profiles and the risk of tardive dyskinesia.

Double-blind controlled evaluations in many different laboratories have indicated that the onset of antimanic efficacy with carbamazepine is as rapid, or almost as rapid, as it is with traditional antipsychotic drugs, including chlorpromazine (Thorazine), thioridazine (Mellaril), haloperidol, and pimozide (Orap) (Fig. 14.8-7). As of 1998 19 double-blind studies of carbamazepine in acute mania indicated clinical efficacy. Fewer controlled studies have been performed with valproate, but they represent the largest placebo-controlled studies of both lithium and valproate, and they also indicate acute antimanic efficacy. Because initial acute antimanic response

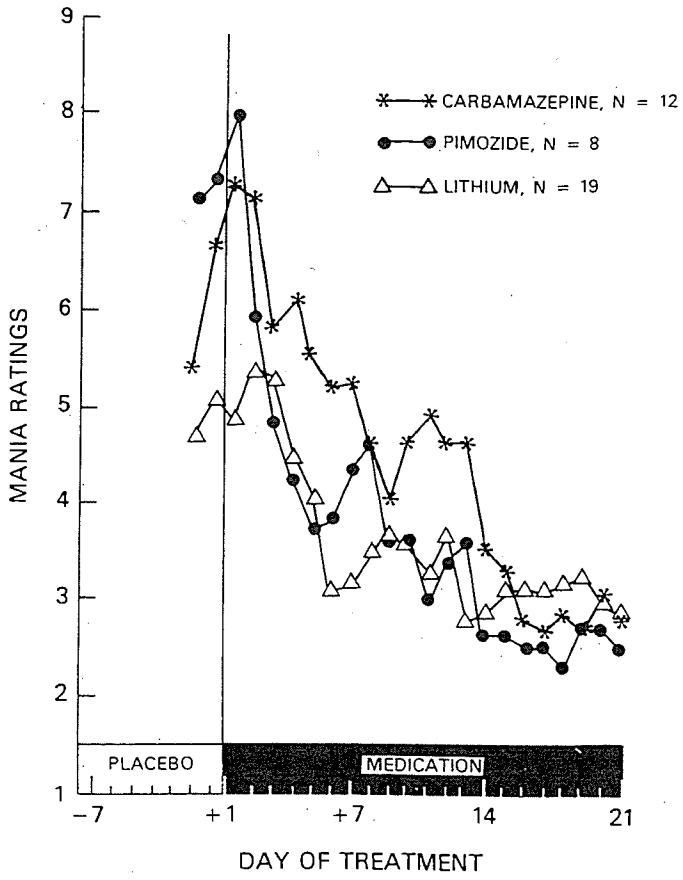

FIGURE 14.8-7 The time course of onset of antimanic response to blind administration of carbamazepine in 12 patients is compared with other similarly diagnosed and rated patients treated with pimozide ($N = 8$) or lithium ($N = 19$).

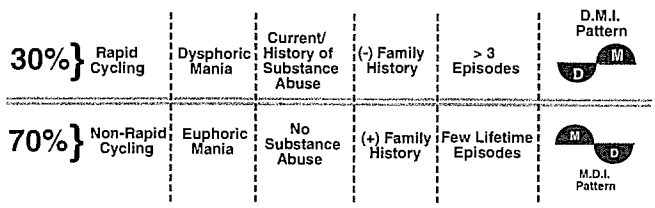

FIGURE 14.8-8 Variable lithium-response rate based on bipolar disorder subtype. D.M.I., depression, mania, well interval; M.D.I., mania, depression, well interval.

may be a guide to subsequent prophylaxis (the major focus of therapeutics of bipolar illness), the author also encourages the investigation of an individual's acute response to these anticonvulsant agents as adjuncts. Antipsychotic agents can always be used later in the sequence if dictated by a lack of clinical response to the mood stabilizers and the adjunctive high-potency benzodiazepines.

Lithium Response The typical clinical profile of the manic patient most responsive to lithium carbonate is one with a classic presentation and euphoric mania, rather than severe or dysphoric mania with paranoid or destructive trends; a pattern of mania followed by a depression and then a well interval rather than a pattern of depression, mania, well interval or continuous cycling; a history of fewer prior episodes and no rapid cycling (i.e., four episodes a year); a positive family history of primary mood disorder in first-degree relatives; and a lack of substance abuse and other comorbidities such as panic disorder. These characteristics can make the difference between a 70 and a 30 percent response rate (Fig. 14.8-8).

Lithium doses should be administered to achieve concentrations in serum between 0.6 and 1.2 mEq per liter. Although a high-dose strategy is advocated by some investigators (concentrations of 1.5 or above), the author has not seen many patients who fail to respond at more typical lithium blood concentrations and respond well when pushed to higher levels that are associated with greater side effects. Dose-limiting adverse effects may include gastrointestinal disturbances (particularly diarrhea) as well as neuropsychiatric syndromes including tremor, subjective sense of cognitive slowing, confusion, and myoclonic twitches. Concentrations of lithium in blood achieved at a given dosage may increase further if the patient switches from mania to depression, leading to greater adverse effects. For the inadequate responder to lithium at levels associated with few side effects, the author recommends potentiation with other agents, rather than discontinuing lithium and requiring a new agent to treat any additional withdrawal emergent symptoms.

The most recent and largest placebo-controlled study of lithium indicated that only 50 percent of patients achieved a 50 percent or greater improvement by 3 weeks. Those with a prior anecdotal history of lithium nonresponse by self-report were particularly at risk for nonresponse in this controlled study. However, even in the responsive group, many symptoms remained at the end of 3 weeks. Thus, even without the increased pressures from managed care for rapid discharge from the hospital, most full-blown manic patients require adjunctive treatment to achieve a timely and adequate antimanic response. A broad range of such options are now available (Table 14.8-6).

Valproic Acid Typical dosages of valproic acid are 750 to 2000 mg a day, achieving blood concentrations between 50 and 120 μg/mL. Rapid oral loading with divalproex using 15 to 20 mg/kg from day 1 of treatment, has been well tolerated and associated with a rapid onset of response. Blood concentrations above 45 μg/mL have also been associated with earlier response. In several case series, patients with more-typical manic syndromes and fewer schizoaffective symptoms appeared to show a high frequency of response. In contrast to lithium, those with a history of lithium nonresponse, dysphoric mania, or rapid cycling are not less likely to respond to valproate (Table 14.8-6).

Carbamazepine Several preliminary studies have suggested that some of the variables associated with a poor response to or intolerance of lithium may be associated with a good antimanic response to carbamazepine. Thus, the drug may be considered for lithium-nonresponsive manic patients (Fig. 14.8-5).

Typical dosages of carbamazepine to treat mania have ranged between 600 and 1800 mg per day associated with blood concentrations between 4 and 12 μg/mL. However, within this dosage and blood-concentration 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 adverse effects are likely dose related. Dosage administration with this anticonvulsant must be individualized, as there is wide variability in the dosage and blood concentration at which adverse effects occur. Increasing the dosage to achieve a clinical effect and titrating the increases against the emergence of adverse effects is the appropriate strategy for such wide

Table 14.8-6
Speculative Differential Approaches to Bipolar Disorder Subtypes

Euphoric Mania	Dysphoric	Rapid Cycling	Ultradian Cycling	Substance Abuse
1 Lithium (mood stabilizer I)	Valproate (mood stabilizer II) or carbamazepine (mood stabilizer III) clonazepam or lorazepam	Valproate (mood stabilizer II)	Major mood stabilizer combination	Carbamazepine or valproate (mood stabilizer III, mood stabilizer II)
2 Clonazepam or lorazepam	Lithium potentiation	Valproate + lithium	Plus Ca_{2+} blocker	Plus lithium
3 Adjunct with second mood stabilizer carbamazepine or valproate (mood stabilizer III, mood stabilizer II)	Other mood stabilizer: carbamazepine or valproate	Carbamazepine + lithium	Ca_{2+} blocker + carbamazepine (mood stabilizer III)	Valproate or carbamazepine (mood stabilizer II, mood stabilizer III)
4 Augment with other (mood stabilizer II, mood stabilizer III)	Lithium potentiation	Triple mood stabilizer I–III (lithium, carbamazepine, valproate)	Triple mood stabilizer I–III (lithium, carbamazepine, valproate)	Plus lithium
5 Triple (mood stabilizer I–III) plus clonazepam	Clonazepam or lorazepam	Add liothyronine or levothyroxine	Add liothyronine or levothyroxine	Lithium and adjuncts
6 Antipsychotic	Gabapentin? Typical Atypical	Lamotrigine	Lamotrigine	*Consider*: + Naltrexone for alcohol craving
7 Calcium	Olanzapine			*Consider*: + Coping skills therapy for type II alcoholism (early-onset men) with sociopathy or conduct disorders
8 Gabapentin	ECT			*Consider*: + Interpersonal therapy for type I alcoholism (late-onset men and all women) with predominant anxiety
9	Clozapine	Clozapine	Clozapine	
10	(Trimipramine)	(Trimipramine)	(Trimipramine)	

individual variability. After several weeks carbamazepine induces hepatic enzymes that lower its levels and may require additional upward dose titration.

Carbamazepine and valproic acid have been used in combination to treat epilepsy, but only preliminary evidence for the efficacy of this combination in acute and prophylactic management of the refractory bipolar patient is available. Valproate may increase concentrations of carbamazepine and its active 10,11-epoxide metabolite, indicating a need for lower carbamazepine dosage when both drugs are used in combination. Typical adverse effects of carbamazepine and other antimanic drugs are listed in Table 14.8-7.

Clonazepam and Lorazepam The high-potency benzodiazepine anticonvulsants studied in acute mania include clonazepam (Klonopin) and lorazepam (Ativan). Both appear effective and are widely used for adjunctive treatment of acute manic insomnia, agitation, aggression, and dysphoria as well as panic. As noted above, the benign adverse-effect profiles of these agents render them ideal adjuncts to lithium, carbamazepine, or valproate and preferable to the dopamine receptor antagonists (typical antipsychotics) for first-line augmentation. The sedating effects of clonazepam may be problematic in some outpatients, but this property of the drug may be used for bedtime medication for severely insomniac manic patients.

Both of these two high-potency benzodiazepines work rather selectively at the central-type benzodiazepine receptor; in contrast, carbamazepine is not active at this receptor and appears to act at the so-called peripheral-type benzodiazepine receptor (Table 14.8-4). Classic central-type benzodiazepine receptors modulate GABA receptors that facilitate chloride influx and neuronal inhibition (Fig. 14.8-9). In contrast, the peripheral-type benzodiazepine receptor appears to be more closely associated with mitochondrial neurosteroid biosynthesis and calcium channels. These findings are noteworthy in regard to possible differential psychotropic responsiveness between these two classes of anticonvulsants.

Table 14.8-7
Comparative Clinical and Adverse-Effect Profiles of Lithium, Nimodipine, and the Putative Mood-Stabilizing Anticonvulsants (Preliminary Clinical Impressions)

	Lithium (0.5–1.2 mEq/L)	Carbamazepine (4–12 μg/mL)	Valproate (50–120 μg/mL)	Nimodipine (12 ng/mL)	Lamotrigine	Gabapentin	Topiramate
Clinical profile							
▶ Acute episodes							
Mania	++	++	++	+	(+)	(++)	±
Dysphoric mania	+	(++)	++	+	?	(+)	±
Family history negative	±	++	±	?	?	?	?
Depression	+	+	±	+	(++)	(+)	()
▶ Prophylaxis							
Mania	++	++	++	+	(+)	+	(+)
Depression	++	++	+	+	(++)	+	(±)
Rapid cycling	+	+	++	+	(++)	(++)	+
Continuous cycling	++	++	(++)	(++)	?	?	+
▶ Seizures							
Generalized, complex, partial absence	0	++	++	±	++	++	++
▶ Paroxysmal pain syndromes	0	——	++	?	++	——	——
Migraine	±	++	+	—	?	(+)	?
▶ Adverse effect profiles	±	±	++	+	?	(+)	?
White blood count	⇈*	⇊	(↓)	—	—	—	—
Diabetes insipidus	⇈*	↓	—	—	—	—	—
Thyroid hormones, T_3, T_4	⇊	⇊	↓	—	?	(↑)?	?
Thyroid-stimulating hormone	⇈*	—	?	—	—	—	?
Serum calcium	↑	↓	?	?	?	?	—
Weight gain	⇈	(↑)	⇈†	—	—	↑	—
Tremor	⇈	—	⇈	—	↑	↑	—
Memory disturbances	(↑)	(↑)	(↑)	——	(↑)	↑	↑
Diarrhea, gastrointestinal distress	⇈	(↑)	↑	(↓)	—	(↑)	
Teratogenesis	(↑)	↑	↑	—	—	—	?
Psoriasis	↑	——	—	—	—	—	—
Pruritic rash	——	⇈	(↑)	(↑)	⇈	(↑)	—
Alopecia	(↑)	—	↑†	—	—	—	—
Agranulocytosis, aplastic anemia	——	↑	—	—	—	—	—
Thrombocytopenia	—	(↑)	↑	—	—	—	—
Hepatitis	—	↑	↑	—	↑	—	(↑)?
Hyponatremia, water intoxication	—	↑	—	—	—	—	
Dizziness, ataxia, diplopia	—	↑	(↑)	—	↑	↑	↑
Hypercortisolemia, escape from dexamethasone suppression	—	⇈	?	—	—	—	—

Clinical efficacy: 0, none; ±, equivocal; +, effective; ++, very effective; (), very weak data; ?, unknown; ——, exacerbation.
Side effects: ↑, increase; ↓, decrease; (), inconsistent or rare; —, absent; ——, worse.
* Effect of lithium predominates over that of carbamazepine when used in combination.
† About 3 months after onset of valproic acid; prevent alopecia with zinc and selenium?

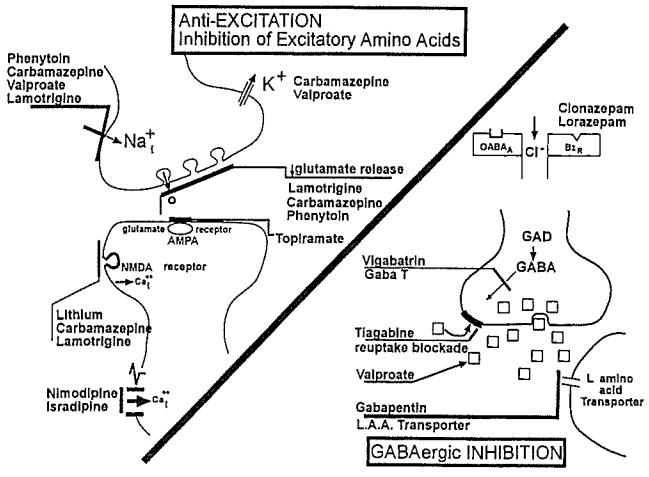

FIGURE 14.8-9 Dual targets of mood stabilizers. Bz_R, benzodiazepine type R receptors, AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionate; GAD, glutamic acid decarboxylase; L.A.A., L amino acids.

Dopamine Receptor Antagonists Studies indicate that short-term use of conventional antipsychotics (Table 14.8-8) in the treatment of mania results in unintended and often unneeded persistence of antipsychotic use 6 months or more after the acute episode. Such intermittent to chronic maintenance treatment with traditional neuroleptic drugs should be avoided, if possible, since bipolar disorder patients are reported to be at high risk for tardive dyskinesia (20 to 40 percent of those exposed), equal to or greater than that of patients with schizophrenia.

Thus, the author recommends exploring potential mood-stabilizing alternatives to lithium (e.g., valproate and carbamazepine), short-term adjuncts (e.g., clonazepine or lorazepam), or serotonin-dopamine antagonists before using dopamine receptor antagonists in bipolar disorder. Intermittent neuroleptic drug use, rather than being a protective factor may actually increase the risk of tardive dyskinesia, according to both clinical and preclinical studies.

The strategy of rapid tranquilization with suprathreshold doses of antipsychotic agents should be avoided. Many double-blind evaluations of this strategy in acutely psychotic schizophrenia patients and one trial in manic patients have shown that the high-dosage strategy (40 to 60 mg a day of haloperidol) is no more efficacious than traditional dosage regimens (10 mg a day) and is associated with greater adverse effects. Particularly for extremely manic patients,

Table 14.8-8
Antipsychotic Drug Use in Mania

Drug (Database) (dosage range, mg/day) (trade name)	Mechanism	Assets (+)	Liabilities (−)	Comment	Relative Chlorpromazine Equivalents
Typical Antipsychotics					
(Dopamine Receptor Antagonists)					
Chlorpromazine (+ + +) (200–600) (Thorazine)	↓ D_2, ↓ α_1	+ Sedating + IM availability	− Hypotension − Akathisia		100
Haloperidol (+ + +) (5–20) (Haldol)	↓ D_2	+ Less hypotension + Less sedating + IM available	− Akathisia − Extrapyramidol side effects (EPS)	▶ Widely used ▶ Normal daily dosage (10mg) better than high dosage (40 mg) for efficacy and adverse effects	2
Pimozide (+ +) (1–8) (Orap)	↓ D_2, ↓ Ca_{2+} channels	+ Ca_{2+} blocker + Low doses + Not sedating	− Arrhythmias reported		
Atypical Antipsychotics					
(Serotonin-Dopamine Antagonists)					
Risperidone (+) (2–10) (Risperdal)	↓ D_1 (+ +) ↓ D_2 (+ + + +) ↓ 5-HT_2, α_1, α_2	+ Few EPS in low doses	− EPS in ↑ dosages − Antimanic? − Hypotension − ↑ Prolactin − Tachycardia − Sexual dysfunction	▶ Reports of exacerbation of mania with dosages over 6–8 mg/day ▶ Can ↑ obsessions and compulsion	1.5
Clozapine (+ + +) (300–900) (Clozaril)	↓ D_1 (+ +) ↓ D_2 (+ +) ↓ D_4, 5-HT_2 ↓ α_1, α_2 ↓ H_1, M_1	+ No risk of tardive dyskinesia + Well studied and effective in dysphoric mania and rapid cycling	− Weekly blood monitoring − Sedation − Hypotension − Sialorrhea − Weight gain − Seizures	▶ Blood monitoring for agranulocytosis inconvenient and expensive ▶ Do not exceed ↑ 50 mg every 2 days ▶ Can ↑ obsessions and compulsions ▶ 5-HT block 10 times > D_2 block	100
Trimipramine (±)?? (50–300) (Surmontil)	↓ D_2, D_4 ↓ M_1	+ Proved antidepressant	− Sedating − Unproved antipsychotic properties	▶ D_2, D_4 blocker and antidepressant ▶ ? Mood stabilizer	
Olanzapine (+) (7.5–20) (Zyprexa)	↓ D_1 (+ + +) ↓ D_2 (+ + +) ↓ D_3, D_4, 5-HT_2 ↓ α_1, α_2 ↓ H_1, M_1	+ No blood monitoring + Proved antimanic + Fewer EPS	− Sedation − Weight gain − Nausea/ dyspepsia − Orthostatic hypotension	▶ Most similar biochemical profile to clozapine ▶ Most widely used atypical agent	4
Quetiapine (Seroquel)	↓ D_1 (+) ↓ D_2 (+ +) ↓ α_1 ↓ H_1, M_1	+ No ↑ prolactin	− Somnolence − Alopecia − Constipation − Weight gain − Hypotension	▶ Limbic selective ▶ Few anticholinergic adverse effects	100
Ziprasidone (Zeldox)	↓ D_1 (+) ↓ D_2 (+ + + +) ↓ 5-HT_2, α_1	+ No weight gain	− Somnolence − Dizziness − Nausea − Hypotension		50

Key: (+) to (+ + + +), relative strength of evidence.

the use of heroic antipsychotic dosages to decrease psychomotor activation may not be justifiable considering the added risk of ordinary toxicities, the risk for neuroleptic malignant syndrome, and the sporadic reports of reversible and irreversible organic impairments when used in conjunction with lithium.

Serotonin-Dopamine Antagonists The availability of new atypical antipsychotics with their presumed equal efficacy but superior adverse effect profiles (Tables 14.8-9 and 14.8-10) may change the algorithm for the treatment of acute mania. A minority of patients appear to require antipsychotics for short- and long-term mood stabilization. Not only can the typical neuroleptic drugs predispose to a variety of acute extrapyramidal effects and long-term tardive dyskinesia, they can also exacerbate the depressive phases of bipolar illness, increasing the frequency or duration of depression or both. These potential liabilities should lead one to use the newer atypical neuroleptic agents if additional antipsychotic treatment is required.

Clozapine appears to be particularly efficacious in refractory bipolar I disorder characterized by either dysphoric mania or rapid cycling. Its efficacy in bipolar disorders equals or betters that in schizoaffective disorder and schizophrenia as well. However, it has

Table 14.8-9
Receptor Activities of Atypical Antipsychotics Relative to Haloperidol

Effects Mediated by Receptor Mechanism	↓ Motor Activity ↓ Enabling	EPS (Relative to 5-HT_2); ↑ prolactin	Antidepressant Anxiolytic	Antidepressant	Reflex Tachycardia Hypotension Dizziness	Block BP effects of clonidine Panic attacks	Sedation Drowsiness Weight gain	Blurred vision Sinus tachycardia Dry mouth Constipation Attacks of glaucoma
Drug (class) Receptor	**D_1**	**D_2**	**5-HT_{1A}**	**5-HT_{2B}**	**α_1**	**α_2**	**H_1**	**M_1**
Haloperidol (butyrophenone)	+ + +	+ + + +	NA	+	+ +	NA	NA	NA
Clozapine (dibenzodiazepine)	+ +	+ +	+	+ + +	+ + +	+ + +	+ + + + +	+ + + + +
Risperidone (benzisoxazole)	+ +	+ + + +	+ +	+ + + + +	+ + +	+ + +	+ +	NA
Olanzapine (thienobenzodiazepine)	+ + +	+ + +	NA	+ + + +	+ + +	NA	+ + + +	+ + + +
Remoxipride	NA	+	NA	NA	NA	NA	NA	NA
Seroquel (dibenzothiazepine)	+	+ +	NA	+	+ + + +	+	+ + + + ?*	+ + + ?*
Sertindole	+ + +	+ + + + +	+ +	+ + + +	+ + +	NA	+	+
Ziprasidone	+	+ + + +	NA	+ + + +	+ +	NA	+	NA

Adapted from Pickar D: Prospects for pharmacotherapy of schizophrenia. Lancet *345*:557, 1995.
Ratings: +, weak; + +, mild; + + +, moderate; + + + +, strong; + + + + +, very strong; NA, not available.
* vs. weak effects.

Table 14.8-10
Clinical Profiles of the Atypical Antipsychotics Relative to Haloperidol

Drug (Trade Name)	Relative Potency, Chlorpromazine Equivalents	Weight Increase	Sedation	Autonomic	Extrapyramidal Effects	Increased Prolactin	Clinical Dosage (mg/day)	Half-Life
Haloperidol (Haldol)	2	+	+	+	+ + +	+ + +	5–20	3 wk
Clozapine (Clozaril)	100	+ + +	+ + +	+ + +	+/−	0	100–600*	8 h
Risperidone (Risperdol)	1.5	+ + +	+ +	+ +	+ +	+ + +	4–12†	20 h
Olanzapine (Zyprexa)	4	+ + +	+	+	+	+	10–25	35 h
Remoxipride	NA							
Seroquel (Quetiapine)	100	+ +	+ +	+ +	+	0	300–900 (limbic selective)	6.9 h (but overdose feasible)
Ziprasidone (Zeldox)	50	±	+ +	+ +	+ +	+	80–200	5 h

Ratings: 0, none; ±, equivocal; +, mild; + +, moderate, + + +, severe.
Adapted from Gerlach J, Peacock L: New antipsychotics: The present status. Int Clin Psychopharmacol *10*(Suppl 3):39, 1995.
* Modification from Richelson E: Preclinical pharmacology of neuroleptics: Focus on new generation compounds. J Clin Psychiatry *57*(Suppl):4, 1996.

considerable liabilities: inconvenience, cost, and risk of agranulocytosis, which requires weekly blood monitoring. Olanzapine has a biochemical profile similar to that of clozapine, and preliminary evidence suggests that this newly approved agent will assume a similar role in the treatment of refractory bipolar disorder patients. Initial trials of olanzapine in acute mania yielded positive results, and the drug appears to be generally well tolerated, except for substantial weight gain in some patients.

The use of low dosages of risperidone appears promising, although there are several case reports of depressed patients switching into mania when treated with high dosages of this agent. Low dosages are associated with increased prolactin, and dosages over 8 mg a day are associated with both extrapyramidal effects and weight gain.

Other atypical agents should be watched for their spectrum of efficacy in acute mania and prophylaxis, as they may have beneficial profiles in the treatment of mania such as relative lack of sedation (olanzapine and sertindole); lack of prolactin increases (clozapine, quetiapine, and sertindole); fewer anticholinergic adverse effects (seroquel and sertindole); and less weight gain (ziprasidone). The possible antidepressant aspects of these putative mood stabilizers, perhaps related to their positive effects in the negative symptoms of schizophrenia, also deserve close scrutiny. Tables 14.8-9 and 14.8-10 summarize preliminary data on the mechanisms of action, adverse effects, and potential efficacies of the serotonin-dopamine antagonist.

A potentially unique approach to the dopamine system might be attained with the tricyclic drug trimipramine (Surmontil). This long-approved antidepressant had an unknown mechanism of action, since it was not a potent reuptake blocker of any of the amine systems. It was recently shown to be a moderately potent antagonist of type 2 dopamine (D_2) and D_4 receptors, somewhat similar to clozapine. It has also been reported in open studies to be effective in monotherapy for acute schizophrenic episodes and psychotic depression. Therefore, in light of its D_2 and D_4 blocking properties as well as its efficacy as an antidepressant, some have recommended using trimipramine in bipolar patients with refractory rapid cycling depressions.

L-Type Calcium Channel Inhibitors A series of preliminary reports suggest that the calcium channel inhibitor verapamil (Calan, Isoptin) has acute antimanic efficacy. Whereas a number of controlled studies suggest the antimanic utility of verapamil, several recent studies suggest the superiority of lithium. Moreover, one randomized study in acute depression indicated that verapamil is no more effective than placebo and less effective than routine antidepressant treatment. These data led to a search for a more effective calcium channel blocker that might have better spectrum of antidepressant and prophylactic effects than verapamil.

Several groups chose to study the dihydropyridine L-type calcium channel inhibitor nimodipine (Nimotop) because of its (1) ability to penetrate the CNS, (2) relative lack of tolerance development in the treatment of migraine (in contrast to many other calcium channel inhibitors, (3) better profile in many types of animal seizure models than verapamil, and (4) greater ability to block cocaine-induced hyperactivity and associated dopamine overflow. One study reported that 10 of the first 30 evaluable treatment-refractory patients had a clinically relevant response to nimodipine, including patients with rapid and ultradian cycling frequencies (Figs. 14.8-10 and 14.8-11). Responsivity was confirmed and reconfirmed in some of these patients in a double-blind, off-on-off-on design. Almost all of these patients needed their regimens further supplemented with another agent such as lithium or carbamazepine for a more complete response, however. Carbamazepine augmentation of nimodipine was effective (moderate or marked response on the Clinical Global Impression Scale) in only 5 of 14 patients treated with the combination.

Of considerable interest were several patients who clearly responded to either monotherapy or combination therapy with nimodipine and transitioned from nimodipine on a double-blind basis to maximally tolerated doses of verapamil, without maintaining response (Fig. 14.8-11). They later either reresponded to nimodipine or to another dihydropyridine L-type calcium channel inhibitor such as isradapine (Dynacirc) further confirming the initial responsivity to this drug class but also suggesting that responsivity might be better conferred by the dihydropyridine subtype of L-type calcium channel inhibitor (with the binding site deep inside the calcium channel) than the phenylalkylamine verapamil (which blocks at the outside of the channel) (Fig. 14.8-10).

Although there is some evidence that patients with extremely rapid cycling fluctuations within a 24-hour period (ultra-ultra rapid

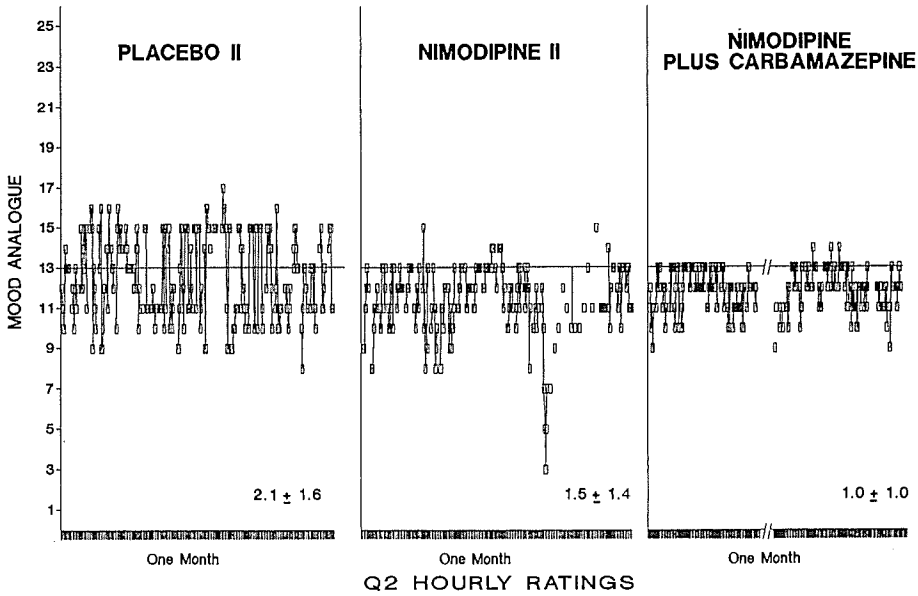

FIGURE 14.8-10 Efficacy of Nimodipine plus carbamazepine combination in a bipolar II female with ultradian cycling.

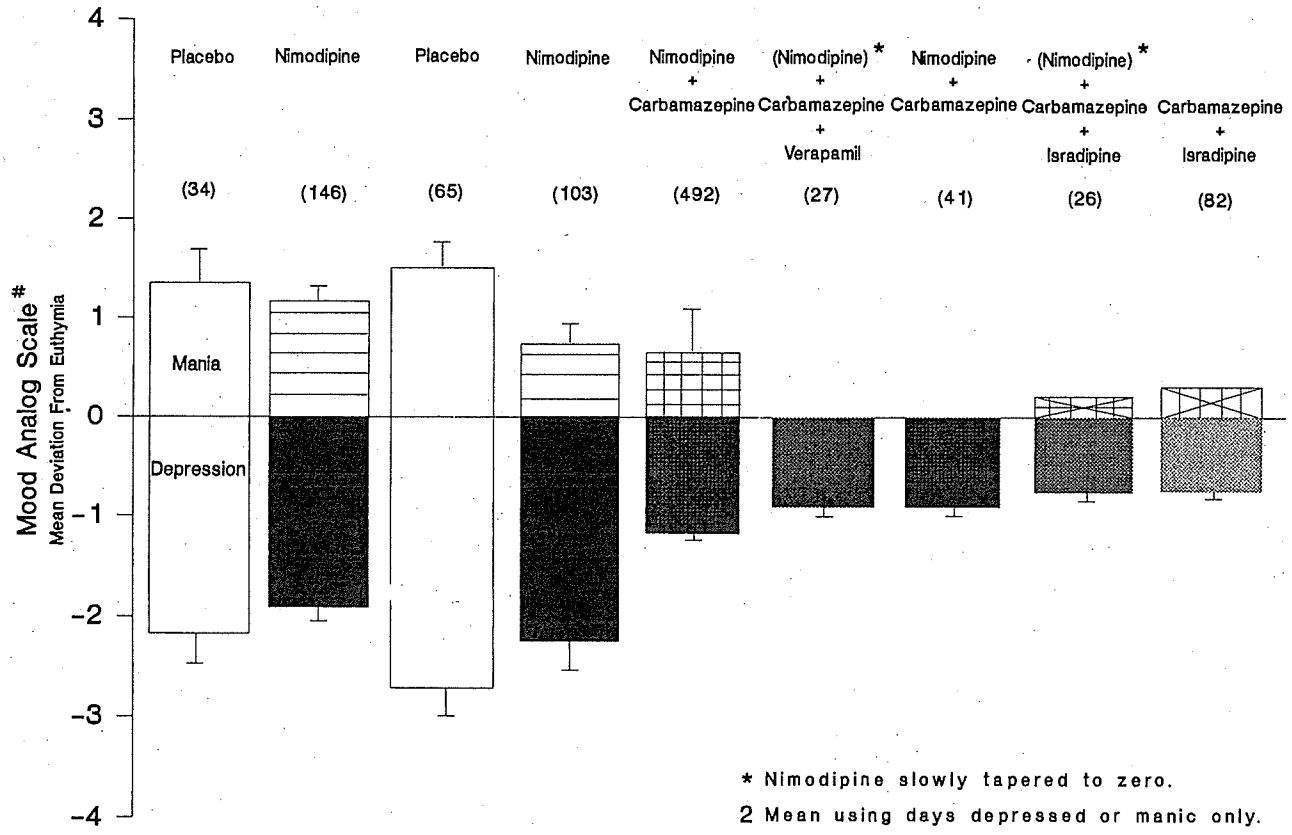

FIGURE 14.8-11 Nurse ratings of the efficacy of dihyropyridine L-type calcium channel inhibitors in a woman with bipolar II disorder.

cycling) are among those who respond best to the dihydropyridines, the question of whether this subgroup is selectively targeted remains open. Depressed patients with the more classical pattern of global and frontal hypometabolism on positron emission tomography (PET) were among those who responded best to nimodipine. In contrast, those with a hyperactive metabolic pattern were more likely to respond to carbamazepine. Much work remains to define the precise role of the calcium channel blockers in the treatment of bipolar refractory depression (Tables 14.8-5 and 14.8-6).

Lamotrigine A series of preliminary reports and two controlled trials suggest that lamotrigine, the newly approved anticonvulsant for add-on therapy, has antidepressant and possibly mood-stabilizing properties. In an open study 67 patients were studied usually with the drug as an adjunct to previously ineffective treatment regimens; 27 of 39 (69 percent) who presented in the depressed phase and 19 of 25 (76 percent) in the manic phase showed moderate-to-marked improvement.

A randomized, double-blind study at the NIMH found a significantly greater incidence of good response to blind lamotrigine monotherapy (17 of the first 3 patients [52 percent] than to (9 of 33 gabapentin [27 percent]) or placebo (7 of 32 [22 percent] placebo ($P < .05$). Many patients with refractory depression profiles were among those who showed a good response. Patients with bipolar I disorder depression showed a non-significantly better response than those with bipolar disorder II or a depressive disorder. Another large multicenter study indicated that both 50 and 200 mg a day of lamotrigine were superior to placebo in a 7-week trial in depressed bipolar I disorder patients.

Lamotrigine treatment should be initiated slowly in monotherapy with one 25-mg pill for the first 2 weeks and then 50 mg for 2 weeks, with slow increases thereafter to avoid a moderately high incidence of rash. The rate of increase should be halved if patients are on a regimen including valproate, which can markedly increase lamotrigine blood concentrations and the propensity for rash and more serious dermatologic complications. Conversely, carbamazepine decreases lamotrigine concentrations by approximately 50 percent, and one can start with higher dosages.

The precise anticonvulsant or psychotropic mechanisms of action of lamotrigine remain to be delineated. However, lamotrigine, like valproate, is a broad-spectrum anticonvulsant, effective not only in complex partial and generalized seizures, but also in absence and atonic seizures, in contrast to carbamazepine, which can exacerbate absence seizures. This is important because recent studies have suggested that carbamazepine, lamotrigine, and phenytoin have highly similar properties in the blockade of type 2 sodium channels and consequent inhibition of release of excitatory amino acids such as aspartate and glutamate (Figs. 14.8-9 and 14.8-12). However, the differential clinical profiles of these drugs in epilepsy and the preliminary evidence that lamotrigine may be effective in some patients who respond inadequately to carbamazepine suggest that lamotrigine has additional mechanisms not shared by carbamazepine. Recent evidence suggests that lamotrigine affects different types of calcium channels (N-type and P-type) and blocks serotonin reuptake and is active at serotonin (5-hydroxytryptamine [5-HT]) type 3 (5-HT_3) receptors, but the high concentrations at which these serotonergic effects are observed suggest that they are not clinically relevant. Preliminary data suggest that depressed patients with the more classi-

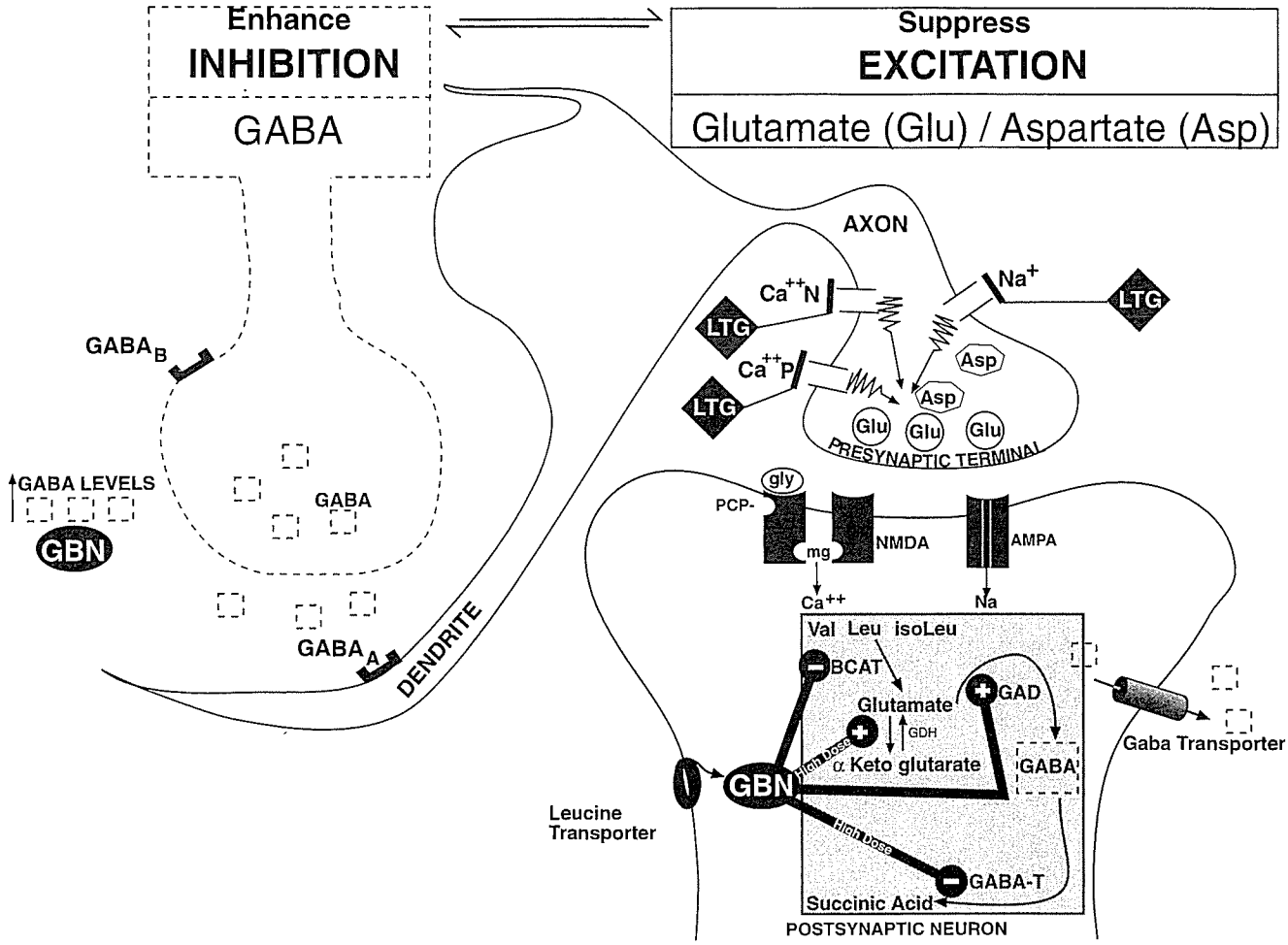

FIGURE 14.8-12 Targets of action of lamotrigine (LTG) and gabapentin (GBN). AMPA, α-amino-3-hydroxy-5-methyl-4-isoxalone propionate; GAD, glutamic acid decarboxylase; GDH, glutamate dehydrogenase; PCP, phencyclidine.

cal topographic pattern of frontal hypoperfusion on PET studies are likely to respond to lamotrigine.

Gabapentin Open adjunctive studies indicate that gabapentin, a newly approved anticonvulsant for adjunctive therapy may also have some mood-stabilizing effects in bipolar patients. The drug appears to have positive effects on sleep and anxiety. However, two double-blind studies of monotherapy, one in acute mania and the other in refractory affectively ill patients showed no benefit over placebo. Whether gabapentin's prominent effects on the L–amino acid transport mechanism (Fig. 14.8-9) and resulting increases in brain GABA concentrations (Fig. 14.8-11) are related to its anticonvulsant or putative psychotropic properties remains to be determined.

Topiramate A recently approved add-on agent for treatment of refractory epilepsy, topiramate, is just beginning to be studied in bipolar disorders (Table 14.8-7). Preliminary uncontrolled data suggest it may have mood-stabilizing properties in rapid-cycling patients, with better antimanic than antidepressant effects. A major asset of topiramate is its positive effect of weight loss in contrast to lithium, valproate, gabapentin, many antidepressants, and most antipsychotic drugs. As a carbonic acid inhibitor it has a 1 percent risk of renal calculi (virtually all occurred in males); the calculi are made of calcium and respond well to emergency lithotripsy. Cognitive slowing and difficulty with word finding, may appear with rapid dosage escalation or in combination therapy. Topiramate is a selective inhibitor of glutamate α-amino-3-hydroxy-5-methyl-4-isoxalone-propionate (AMPA) receptors (Fig. 14.8-9) that also has GABAergic actions and blocks sodium ion channels.

Other Anticonvulsants The clinical utility of other GABA-active anticonvulsants, such as the GABA reuptake inhibitor tiagabine (the transamine inhibitor γ-vinyl GABA (vigabatrin [Sabril]) and the agonist progabide (all remain to be further explored, as does the older anticonvulsant phenytoin (Dilantin). Acetazolamide (Diamox) has been reported to be effective for atypical psychoses associated with dreamy, confusional states as well as those occurring premenstrually or in the puerperium. Whether this profile is shared by other carbonic acid inhibitors such as topiramate remains to be determined.

Electroconvulsive Therapy Older clinical observations and recent controlled clinical trials continue to document the efficacy of ECT in acute mania. Bilateral treatments appear to be required; unilateral, nondominant treatments have been reported to be ineffective or to exacerbate manic symptoms in some studies. In light of the many effective pharmacological treatments noted above, and the

utility of using the assessment of their acute antimanic efficacy as a surrogate marker for putative efficacy in long-term prophylaxis, ECT may be reserved for the very rare refractory manic patient or one with medical complications, as well as extreme exhaustion (lethal catatonia) or malignant hyperthermia (Table 14.8-6). Antimanic effects of a brief course of repeated transcranial magnetic stimulation (rTMS) of the brain at 20 Hz over the right but not left frontal cortex or 1 Hz rTMS bifrontally have been observed; whether this well-tolerated nonconvulsive strategy will eventually have a role in clinical therapeutics remains open.

OTHER THEORETICAL AND MECHANISTIC CONSIDERATIONS

Antiadrenergic Drugs A series of other nonanticonvulsant compounds with some neurotransmitter selectivity has been reported to be efficacious in treating mania. Clonidine (Catapres) an α_2-adrenergic agonist, is used to treat hypertension. It acutely inhibits the firing of the noradrenergic locus coeruleus and has been reported to show short-term antimanic efficacy in some (but not all) controlled trials. Response in the first few days of treatment may not be associated with an ultimate long-term response, however. Another agent that inhibits noradrenergic function is the β-adrenergic receptor antagonist propranolol (Inderal). Because very high dosages of either the dextrorotatory or levorotatory of this agent isomer form have been effective, it is questionable whether the β-antagonist properties or the membrane-stabilizing effects of this drug account for its short-term antimanic efficacy.

Cholinomimetics One open study reported that high dosages of choline (3 to 8 grams per day) possess antimanic and anticycling effects in refractory bipolar patients. Intravenous administration of the indirect cholinergic agonist physostigmine (Antilirium) has been demonstrated to have an almost immediate antimanic effect. Physostigmine inhibits acetylcholine esterase function, making more acetylcholine available at the synapse. Although this strategy can rapidly decrease manic symptomatology, it also has a rapid half-life and can be associated with rather marked increases in dysphoria and other adverse effects, such that its long-term utility is doubtful. The success of attempts to increase cholinergic function in the long term through other methods (e.g., 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 (an acetylcholinesterase inhibitor) suggests that given appropriate pharmacological intervention and pharmacokinetics, there is no theoretical reason why an acute antimanic response cannot be achieved extremely rapidly, even though most antimanic treatments have a moderate delay in onset. Manipulations of a variety of neurotransmitter systems (inhibition of nonadrenergic and dopaminergic and potentiation of the cholinergic, benzodiazepine, GABA, and perhaps serotonergic systems) all can induce antimanic effects. The antipsychotic agents block dopamine receptors; clonidine and propranolol appear to decrease α- and β-noradrenergic function, respectively. Reserpine (Diupres) which depletes catecholamines and indoleamines, has also been reported to have antipsychotic and antimanic effects.

As noted in Tables 14.8-2 and 14.8-3, awareness of the multiple neurotransmitter approaches to the treatment of mania may be clinically useful in both changing and combining treatments that target different systems in nonresponsive patients. Alterations in endogenous neuropeptide function also have been postulated in mania. Although manipulations of opioids or cholecystokinin have not yielded consistent results in psychotic schizophrenia patients, isolated reports that thyrotropin-releasing hormone (TRH) or calcitonin were successful in treating excited psychotic states, including mania, deserve replication. The potential efficacy of peptide interventions in mania is mentioned because peptides could represent the next generation of antimanic treatments, particularly in light of the evidence of peptide neurotransmitters coexisting in neurons with more classical neurotransmitter substances that have been indirectly linked to the manic syndromes and the early reports of the antidepressant effects of a substance P antagonist.

Preliminary evidence indicates that the L-type calcium channel inhibitors that inhibit calcium influx through voltage-dependent channels may be effective in treating acute mania. New data indicate that lithium, carbamazepine, lamotrigine, and valproate all block calcium cation (Ca_{2+}) influx through the glutamate NMDA receptor (Fig. 14.8-9), which raises the theoretical rationale of using different mechanisms of blockade of Ca_{2+} influx for more effective or complete effects in refractory patients. Multiple studies of platelets and lymphocytes of bipolar disorder patients indicate increased baseline levels of, or serotonin- or thrombin-stimulated rise in, intracellular calcium.

A new approach examining common effects of chronic lithium and valproate has revealed inhibition of protein kinase C as a putative target for antimanic effects. This idea of H. Manji received preliminary support from the observations of rapid-onset acute antimanic effects in six of nine patients treated with the protein kinase C inhibitor tamoxifen (Nolvadex).

Many of the principles of treating unipolar depression are applicable to the treatment of depression in bipolar disorders, but the critical role of concomitant treatment with mood stabilizers and targeting the symptoms most characteristic of bipolar disorder depression—such as its atypicality, and reverse vegetative symptoms of hypersomnia, increased appetite, weight, lethargy, and psychomotor retardation—require emphasis. Antidepressant drugs that are particularly useful in bipolar disorder patients are listed in Table 14.8-2.

MAINTENANCE TREATMENT OF BIPOLAR DISORDERS

Lithium Prophylaxis Lithium originally appeared to be effective in some 70 to 80 percent of bipolar disorder patients, but current estimates suggest that even with adjunctive use of antidepressants and antipsychotics, a response rate of 40 percent or less in many lithium clinics is more accurate (Fig. 14.8-13).

Although initial studies indicated the need for blood concentrations between 0.8 and 1.2 mEq per liter, some series have suggested that concentrations of 0.5 to 0.8 mEq per liter might be effective in maintenance treatment. However, a recent controlled study indicated that the lower levels of adverse effects are achieved at a cost; the relapse rate with a low lithium concentration range (0.4 to 0.6 mg/L) is three times that at higher concentrations (0.8 to 1.0 mg/L). Monitoring of trough levels (performed in the early morning with the AM dose withheld) at 1- to 2-month intervals (or more frequently if the patient's course is unstable) is recommended. A 1-year controlled study reported that the greater the lithium-induced decreases in plasma free thyroxine (T_4) concentration, (but not lithium blood levels) the greater the severity of depression and cycling.

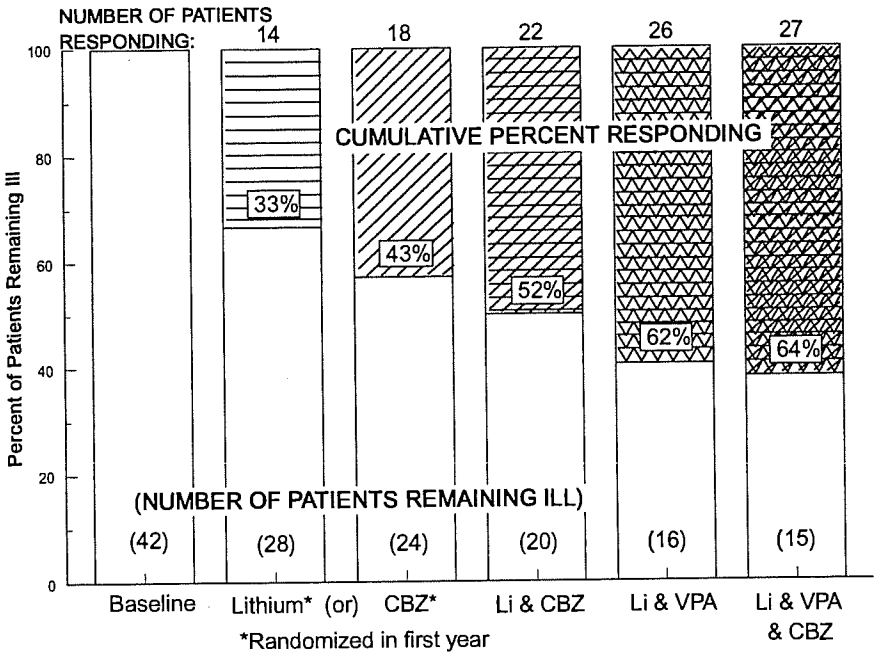

FIGURE 14.8-13 Cumulative response and failure rates on mood-stabilizing regimens. CBZ, carbamazepine; VPA, valproate.

Because of the substantial data on long-term efficacy and prevention of suicide with lithium treatment, preventive treatment should be considered after one or two manic episodes and after a single severe episode of mania, particularly if there is a positive family history of bipolar disorder. The development of a life chart, 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—socially incapacitating and requiring hospitalization—or associated with extremely adverse events for the patient and family, one would be more likely to consider prophylaxis earlier rather than later, despite moderately long well intervals between episodes. These factors should be discussed with the patient during a euthymic interval so that the appropriate risk-benefit ratios can be weighed carefully with adequate informed consent. Data from numerous studies indicate that greater numbers of prior episodes (more than three or four) are associated with a poor response to lithium prophylaxis, so delayed prophylaxis may have negative consequences not only for the increased morbidity during these recurrences, but also for ultimate treatment response. Whether greater numbers of prior episodes also predispose to the development of tolerance (Fig. 14.8-14) or lithium discontinuation-induced refractoriness (Fig. 14.8-15) remains to be studied.

Carbamazepine and Other Mood Stabilizers One alternative to traditional unimodal antidepressants for depressive breakthroughs is the addition of first-generation anticonvulsant mood stabilizers such as carbamazepine or valproate, or putative second-generation anticonvulsants such as lamotrigine (Table 14.8-11). Although the controlled evidence concerning the efficacy of carbamazepine used as monotherapy for primary depression is inadequate those findings taken with the more substantial emerging literature on the efficacy of carbamazepine prophylaxis for both manic and depressive episodes, raise the priority of using this agent to supplement lithium in depressive breakthroughs, particularly those of the rapid-cycling variety. Although only one-third of refractory depressed patients responded in one study, the responders tended to be the patients with greater initial severity of depression and clearer prior histories of discrete episodes rather than chronic depression.

When antidepressant response to carbamazepine was observed, it tended to occur with the typical lag observed with other agents, so that only minor improvement was noted in the first and second weeks of treatment, but considerable improvement was observed after the third and fourth weeks. Surprisingly, the degree of antidepressant response was correlated with the degree of decrease in T_4 and free T_4. An abnormal EEG or increased psychosensory symptoms did not predict an acute response to carbamazepine in one series, but did in another when carbamazepine was used for augmentation, and a 53 percent response was observed compared with an even higher rate for lithium augmentation.

More than a dozen controlled studies support the comparative efficacy of carbamazepine and lithium in the prophylaxis of both manic and depressive episodes. One study reported lower antimanic effects of carbamazepine than with lithium as did another study in patients with classic euphoric mania. However, the latter study indicated a better response to carbamazepine in those with atypical presentations (i.e., dysphoric mania, schizoaffective disorder, rapid cycling and comorbidities).

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 help a substantial subgroup of otherwise refractory patients (Fig. 14.8-5). In one randomized study in bipolar outpatients with a high incidence of rapid cycling, response rates were under 25 percent with either lithium or carbamazepine monotherapy for 1 year, even when adjunctive antidepressants and antipsychotic drugs were allowed, but over 50 percent with both drugs in combination (Fig. 14.8-16). Thus, one might consider combination mood stabilizer treatment from the outset in this rapid-cycling subgroup.

Carbamazepine has been reported effective in some patients failing multiple traditional antidepressant trials, especially in those with a history of head trauma or EEG abnormalities, in one series. As

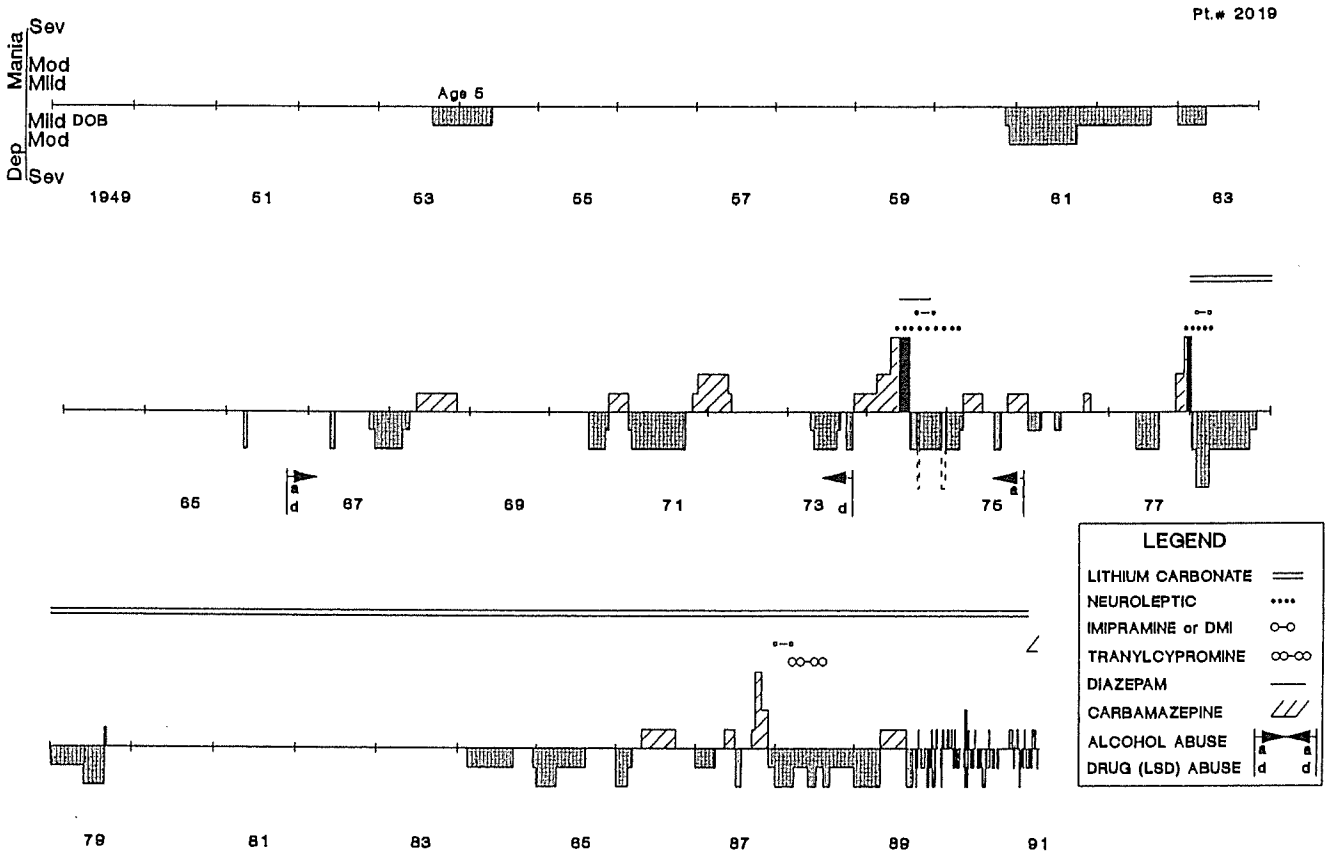

FIGURE 14.8-14 Development of refractoriness to lithium in the course of malignant progression of mood disorder. DMI, desipramine; LSD, lysergic acid diethylamide; DOB, date of birth.

noted for refractory bipolar disorder patients discussed below, the anticonvulsants carbamazepine and valproate may be used in combination with unimodal antidepressants, and the role of these and other combination treatments for the refractory depressed patient deserves much further systematic research to provide adequate statistical and sequence-ordering guidance for the clinician.

Valproic Acid In many open series, valproic acid alone or in addition to lithium has been reported to be successful in the long-term treatment of a substantial subgroup of previously lithium- or carbamazepine-refractory patients. The acute antidepressant efficacy of valproic acid is much less well delineated than its antimanic efficacy, and the utility of this treatment for an acute depressive episode remains to be further elucidated. Nonetheless, the combination of lithium and valproate offers another excellent option in the long-term management of bipolar patients who do not respond to lithium alone. A response to one anticonvulsant may not predict a response to another, and positive long-term effects of valproic acid plus lithium have been noted in patients who did not respond to lithium or carbamazepine prophylaxis (Figs. 14.8-17 and 14.8-18).

Lamotrigine A series of open studies suggests the possibility of mood stabilizer effects of lamotrigine, in many instances in those not responsive to conventional treatments. One double-blind, controlled study of short-term prophylaxis in ultrarapid-cycling patients revealed significant antidepressant and antimanic effects over those of either gabapentin or placebo. These data, taken with the large controlled trial of lamotrigine in bipolar I disorder depression suggest that the addition of lamotrigine to lithium or another mood stabilizer is an alternative option to the addition of a unimodal antidepressant. Response rates of 60 to 70 percent were observed in open studies when lamotrigine was used adjunctively.

Calcium Channel Inhibitors The few uncontrolled studies of calcium channel inhibitors suggest their promise as prophylactic treatments, but they may be less effective for depressive breakthroughs than for manias. One study reported better prophylactic efficacy of 1 year of the combination of lithium and nimodipine compared with 1 year of either drug alone. Further controlled studies of prophylaxis are sorely needed. Although data are limited to just one double-blind series at the NIMH, in the several patients crossed over blindly from one L-type calcium channel inhibitors to another, agents in the dihydropyridine class (nimodipine and isradapine) had better antidepressant and mood-stabilizing effects than the phenylalkylamine verapamil (Figs. 14.8-10 and 14.8-11).

Gabapentin Gabapentin may show positive effects on mood, anxiety, and sleep in 30 to 40 percent of refractory bipolar disorder patients, but much higher rates of response are reported in open studies when gabapentin is used as add-on treatment. The mood-stabilizing anticonvulsants (carbamazepine, valproate, lamotrigine, and gabapentin) certainly also deserve more consideration for a pa-

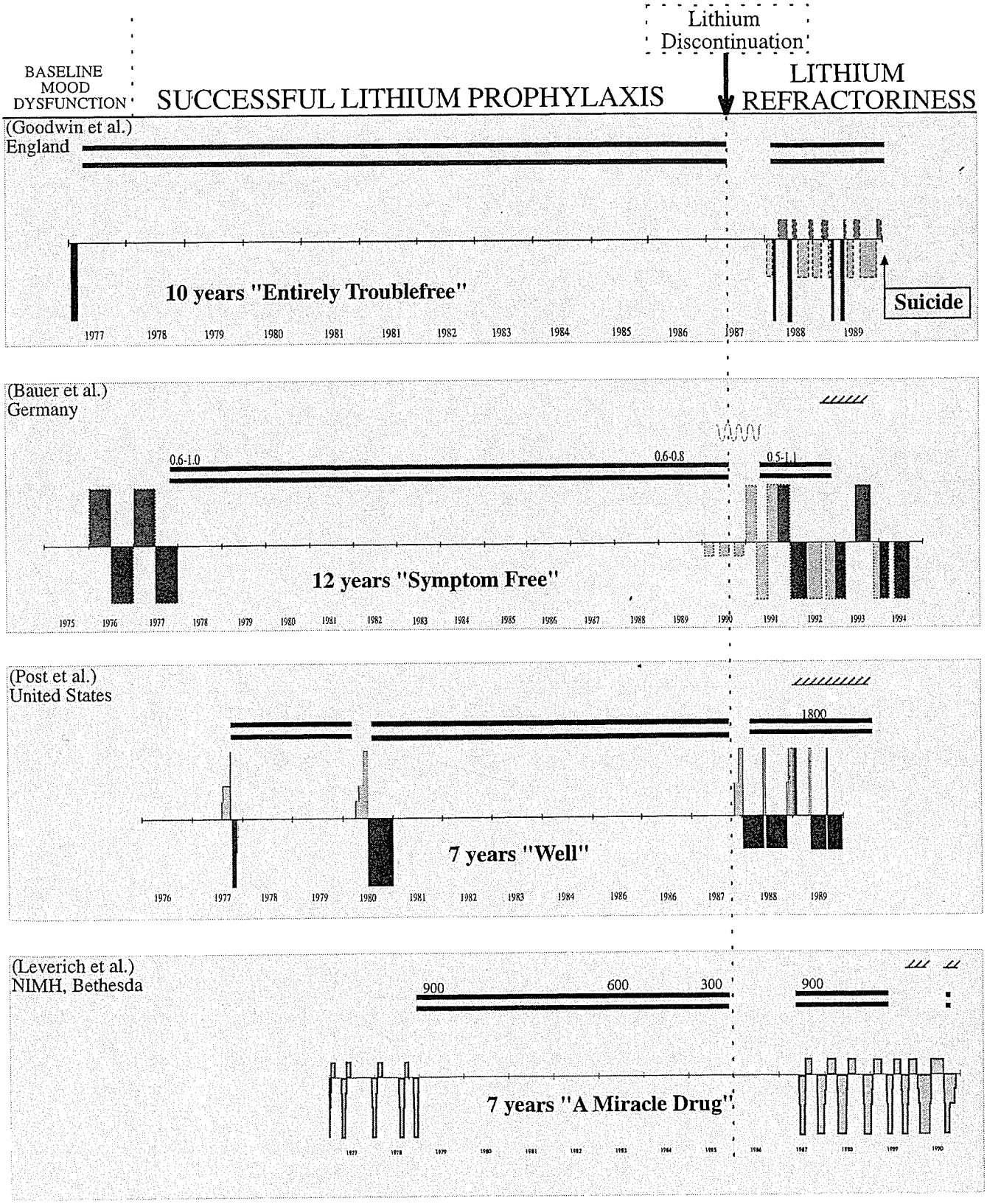

FIGURE 14.8-15 Lithium discontinuation–induced refractory illness.

Table 14.8-11
Drugs in the Prevention of Manic Depressive Episodes and Cycling

Primary Drug (putative mood stabilizer [MS])	Adjunctive Drugs: Manic (M)	Adjunctive Drugs: Bipolar-Depression (D)
MS # first-line for mania (M) or cycling (C)	*First line* - Mania (M)	D-1 Bupropion + +
MS I. Lithium + + + +	M-1. Benzodiazepines (high potency)	D-2 SSRIs
MS II. Valproate + +	a. Clonazepam + + +	a. Fluoxetine + +
MS III. Carbamazepine + + +	b. Lorazepam + +	b. Sertraline + +
Second line	M-2. Typical Neuroleptics + + + +	c. Paroxetine + +
MS IV. Ca_{2+} blocker + +	a. Butyrophenone	d. Fluvoxamine ±
A. Dihydropyridine	b. Phenothiazine	D-3 SNRI
1. Nimodipine + + +	c. Thiothixene	Venlafaxine + +
2. Isradipine + +	d. Molindone	D-4 MAOI + + +
3. Amlodipine ±	M-3. Atypical neuroleptic antipsychotics (M & C)	a. Typical
B. Phenylalkylamine	a. Clozapine	1. Tranylcypromine + +
1. Verapamil + +	b. Risperidone	2. Phenelzine +
C. Diltiazam	c. Olanzapine	b. RIMA—maclobemide
MS VI. Risperidone +	*Second line* (M, D, & C)	D-5 Nefazodone ±
MS VII. Clozapine + +	MS V/D. T_3 (replacement) 25–37.5 μg + +	D-6 NSRI
Olanzapine ±	T_4 (replacement) 75–150 μg +	a. DMI ± desipramine
Second/third line	MS VIII/D. T_4 (hypermetabolic) + free thyroxine index > 150% (T_4 150–400 μg)	b. Maprotiline ±
MS IX. Gabapentin +	*Third line*	D-7 Tricyclic serotonin reuptake inhibitor
MS X. Lamotrigine + +	M-4. Choline ±	Clomipramine ±
MS XI. ECT + + + +	Acetazolamide ±	D-8 α_2 antagonist
MS XII. Trimipramine (±)	*Fourth line*	Mirtazapine ±
Fourth line	M-5. Folate ± *	D-9 Tricyclic drugs–secondary amine
Omega-3 fatty acids + (9 grams)	M-6. Ascorbate + *	a. DMI
Calcitonin +	M-7. Methylene blue +	b. Nortriptyline
Clonidine ±	M-8. Smoking cessation ()*	D-10 Dopamine active
Propranolol (high dose)		a. Trimipramine ±
Mysoline ±		b. Amoxapine ±
Phenytoin ±		c. Bromocriptine +
Spironolactone		D-11 rTMS ±
		D-12 Precursors
		a. Inositol + +
		b. Tyrosine ±
		c. Tryptophan ±
		D-13 Psychostimulants
		a. Methylphenidate ±
		b. Amphetamine ±
		c. Pemoline ±
		D-14 High-intensity light ± 10,000 lux (esp. in AM)
		D-15 Sleep deprivation + +
		D-16 TRH ±
		D-17 Antiglucocorticoid
		a. Ketoconazole + +
		b. Aminoglutethimide
		D-18 Glucocorticoids
		a. Prednisone ±
		b. Dexamethazone ±
		D-19 Inositol, 12–14 grams

Ratings-established, + + + + multiple controlled trials; solid, + + + some controlled trials; substantial, + + multiple studies or one controlled study; weak, + few studies; equivocal, ± cases only; no data, () speculative.
* Relatively benign adverse effects dictate greater use.
Abbreviations: SNRI, serotonin-noradrenaline reuptake inhibitor; RIMA, reversible inhibitor of monamine oxidase type A; rTMS, repeated transcranial magnetic stimulation; TCA-SRI, tricyclic antidepressant-serotonin reuptake inhibitor.

tient's profound sleep disturbance, with or without associated posttraumatic stress disorder, especially if the patient has comorbid alcoholism or bipolar disorder depression and benzodiazepines are to be avoided.

Thyroid Although thyroid potentiation similar to that observed in unipolar depression can be attempted, treatment with dosages above suppressive doses should be approached with caution. Several investigators found associated medical toxicities with high-dosage thyroid treatment and inadequate maintenance of long-term prophylaxis unless other routine agents were used concurrently. Thus liothyronine (Cytomel), the levoratatory isomer of triiodothyronine (T_3), is recommended for short-term augmentation strategies because of its short half-life, and levothyroxine (Levoxyl, Synthroid) the levorotatory

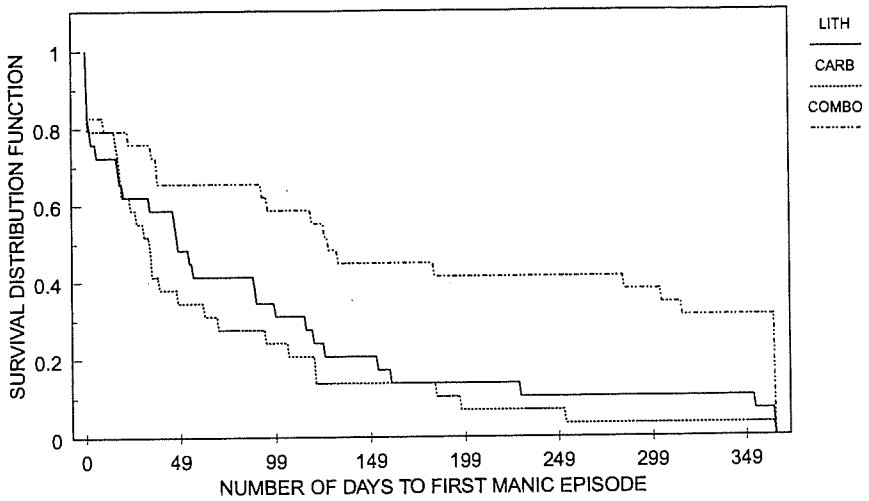

FIGURE 14.8-16 Mean survival time to first manic episode is longer on the combination of lithium and carbamazepine than with either lithium and carbamazepine alone ($N = 29$).

Lithium & Carbamazepine: mean survival time = 179.3 days
Lithium: mean survival time = 89.8 days
Carbamazepine: mean survival time = 66.2 days
Generalized Wilcoxon (Breslow): chi-square = 7.50, df = 2, p = 0.024

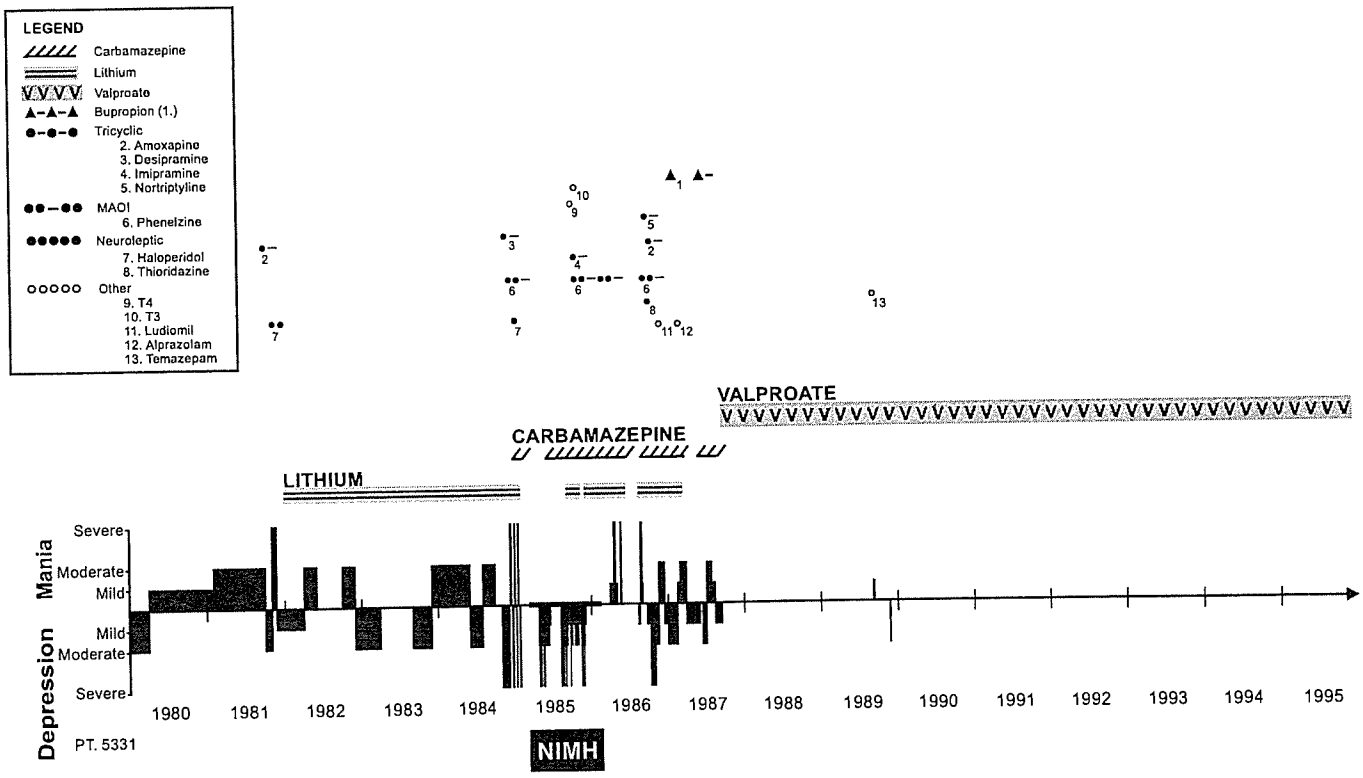

FIGURE 14.8-17 Prophylactic response to valproate in a nonresponder to lithium and carbamazepine.

isomer of T_4 is recommended by some as more appropriate for long-term maintenance during prophylaxis. As noted above, addition of liothyronine to levothyroxine has been reported to benefit nonresponders.

Hypermetabolic Dosages of Levothyroxine Recent data indicate that high-dosage levothyroxine treatment—μg a day targeted toward achieving a free thyroxin index 150 percent of normal—may be helpful as an adjunctive treatment in rapid-cycling patients. Another report further suggests that this high-dosage augmentation strategy may benefit patients with persistent refractory depression. The data indicating improvement in both manic and depressive phases with hypermetabolic levothyroxine augmenting strategies speaks to the potential importance of this modality for

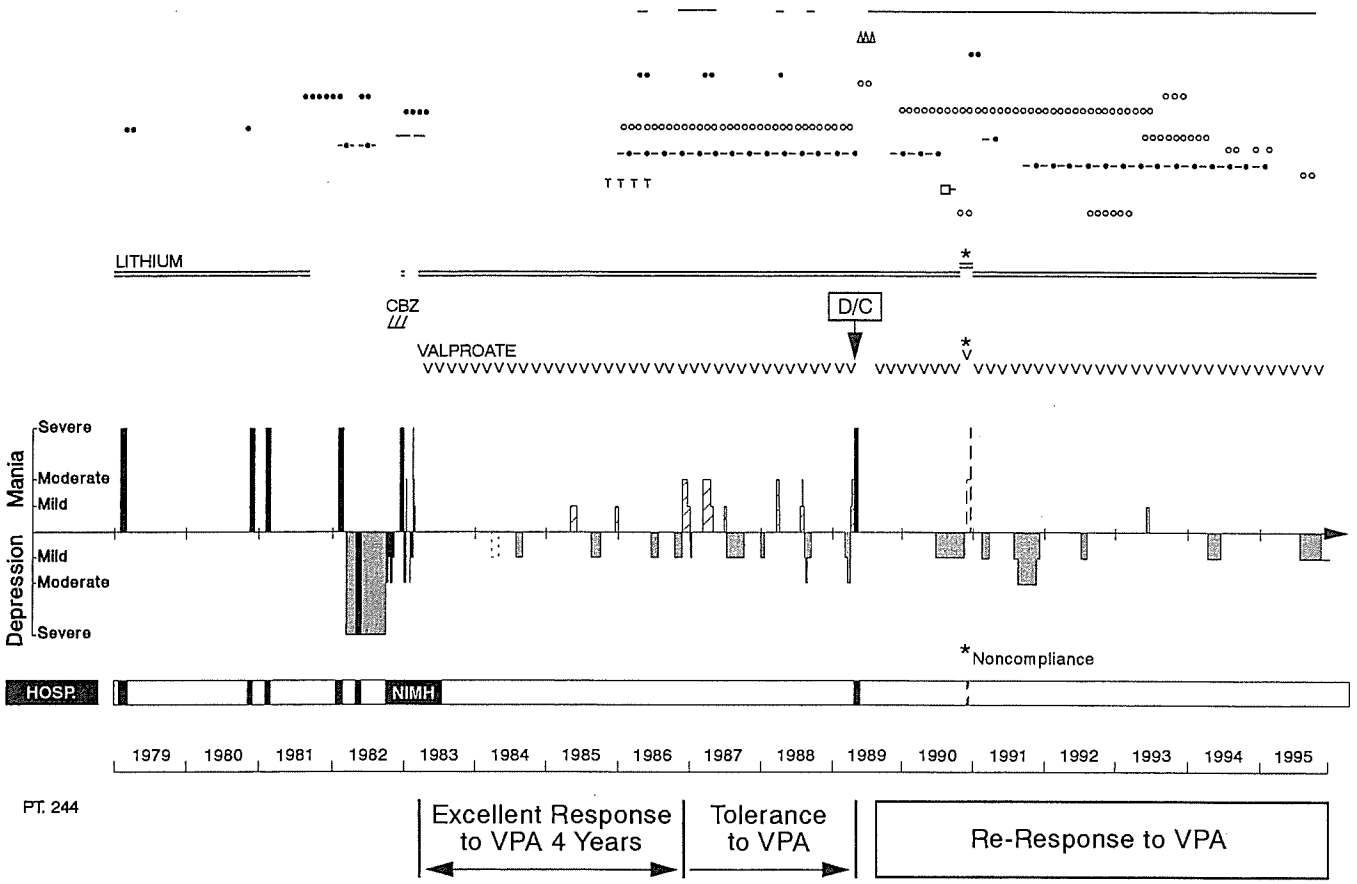

FIGURE 14.8-18 Tolerance and reresponse to the prophylactic effects of valproate (VPA). CBZ, carbamazepine; D/C, discontinuation.

bipolar disorders. However, systematic long-term trials must be conducted, and the issue of whether some patients lose responsivity to such thyroid augmentation strategies with the development of tolerance requires further exploration.

Serotonin-Dopamine Antagonists Given their short-term antimanic and longer-term antipsychotic effects against the positive and negative symptoms of schizophrenia, the serotonin-dopamine antagonists are becoming increasingly important in prophylaxis of mood and schizoaffective disorders. Their better profile of acceptability (Table 14.8-8) and safety than the conventional antipsychotics impels their use instead of these conventional antipsychotics even before adequate data on long-term efficacy become available.

POTENTIAL CORRELATES OF RESPONSE TO THE MOOD STABILIZERS

From a clinical and theoretical perspective it would be valuable to know whether the efficacy of carbamazepine, valproate, or the other putative mood-stabilizing anticonvulsants is related to their ability to stabilize neural excitability in temporal lobe and limbic structures (independent of whether or not a seizure disorder underlies the mood disorder) (Figs. 14.8-8 and 14.8-19). Only a minimum of evidence is available indicating that carbamazepine, for example, acts via its effects on temporal lobe or limbic substrates. However, the approximate rank ordering of carbamazepine, valproate, and phenytoin according to their degree of limbic selectivity is roughly related to their psychotropic efficacy and provides at least indirect support for the limbic hypothesis.

An indirect marker of limbic dysfunction—degree of psychosensory symptoms—is not related to carbamazepine response in primary affective disorder, although others disagree. Recent PET data, however, suggest that patients with initial baseline hypermetabolism, particularly in the left insula, are among those who respond best to carbamazepine, whereas those with a pattern of baseline frontal hypometabolism respond best to nimodipine. These preliminary data are among the first to provide suggestive evidence that increased metabolism in mesiotemporal structures could be associated with the therapeutic response to carbamazepine. Patients with relative hypoperfusion at baseline show normalization upon successful treatment with lamotrigine or gabapentin, whereas nonresponders tend to be closer to normal at baseline and decrease significantly with treatment with these agents. Some preliminary data also link baseline hypometabolism with response to high-frequency rTMS, which normalizes this pattern. Those with relative hypermetabolism at baseline respond to low-frequency (1 Hz) rTMS in association with normalization of this pattern. Although not clinically useful at present, one can only hope that replication and extension of these studies will assist in better matching individual treatments to individual patients.

A number of studies suggest an equally good response to valproate in dysphoric compared to euphoric mania, in contrast to the relatively poor response to lithium in the dysphoric subtype. One

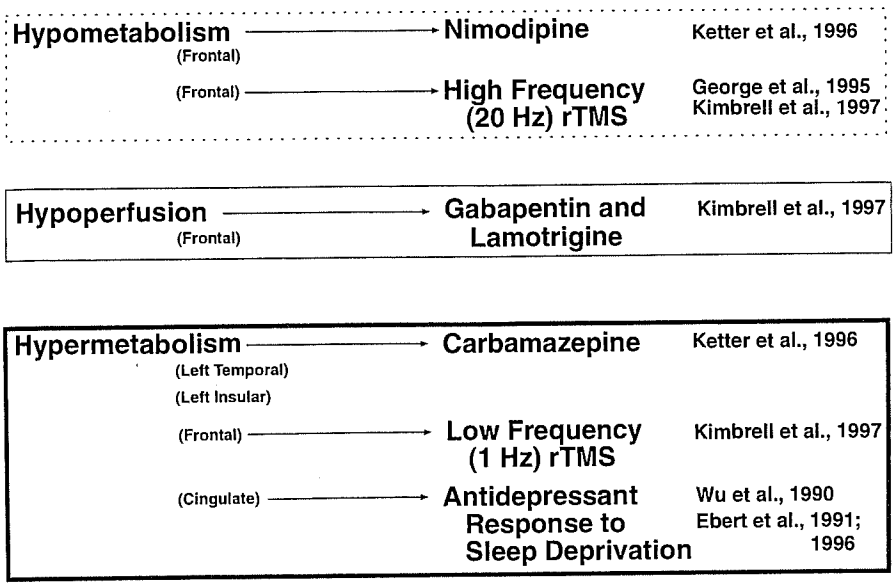

FIGURE 14.8-19 Preliminary predictors of clinical response—functional brain imaging. rTMS, repeated transcraneal magnetic stimulation.

small study suggested that carbamazepine responders tended to be more dysphoric at baseline than nonresponders.

More than 15 studies have reported a relatively poor response to lithium in rapid-cycling patients; only 2 studies have reported a good response, and 4 have reported no differential response. The relation of carbamazepine response to rapid cycling is less clear. In one acute mania study and several prophylaxis studies, a high response percentage was observed in rapid-cycling patients. However, when rapid-cycling patients were compared with non-rapid-cycling patients in two studies, both found a higher prophylactic response rate to carbamazepine in non-rapid-cycling patients. Data from Japan are revealing in that the 53 percent response rate to carbamazepine in patients with a history of rapid cycling (compared with 76 percent in those without) is still substantially higher than the 30 percent response rate observed for lithium in patients with a history of rapid cycling (compared with 64 percent in those without such a history).

Taken together, these data suggest that rapid cycling is a poor prognostic indicator for both carbamazepine and lithium treatment, although some patients with rapid cycling respond positively to carbamazepine. NIMH data suggest the potential utility of treatment of rapid-cycling patients on the combination of lithium and carbamazepine from the outset (with its 53 percent response rate) in light of the poor response to either monotherapy in these patients (28 percent response to lithium and 19 percent response to carbamazepine).

Rapid cycling and prediction of response to valproate is less well studied, but initial indications from a large double-blind collaborative study are that the short-term antimanic response is robust in these individuals, which agrees with other data from open studies indicating an excellent acute and prophylactic response in several large cohorts of rapid-cycling patients treated with either monotherapy or combination treatment. However, one study reported that an accelerating course of illness was a poor prognosis factor for predicting valproate response. Initiating treatment with valproate (Fig. 14.8-17) or lithium and valproate in rapid-cycling or dysphoric manic patients from the outset may thus be a particularly useful alternative to lithium and carbamazepine for this subgroup.

Some evidence suggests that a negative family history of mood disorders may be associated with a good response to carbamazepine; seven of eight studies reported that a positive family history of affective illness in first-degree relatives is associated with a positive response to lithium. These data, in conjunction with clinical case reports illustrating that patients with evidence of delirium, dementia, and other cognitive disorders show a relatively poor response to lithium, a high potential for toxicity, and a potentially good response to the anticonvulsants carbamazepine or valproate, suggest that the familial genetic subtype of mood disorders may be more responsive to lithium than the subtype mediated through other nonhereditary pathophysiological mechanisms, which may be better targeted with the mood-stabilizing anticonvulsants. These possible mechanisms include neuronal and environmental insult related to birth trauma, infection, secondary mood disorder, and substance abuse. Further study of this issue is clearly required.

The mood-stabilizing anticonvulsants (carbamazepine, valproate, and possibly lamotrigine and gabapentin) certainly also deserve higher consideration for a patient's profound sleep disturbance (with or without associated posttraumatic stress disorder), especially if the patient has a comorbid alcohol use disorder or a bipolar disorder, and benzodiazepines are to be avoided.

RELATIVE ADVERSE-EFFECT PROFILES OF LITHIUM AND THE MOOD-STABILIZER ANTICONVULSANTS

Since only a modicum of data suggests clinical or biological predictors of response to the mood stabilizers (Figs. 14.8-8 and 14.8-19), adverse effect profiles and tolerability in long-term prophylaxis (Table 14.8-7) as well as mechanisms of action (Table 14.8-4, Figs. 14.8-6 and 14.8-9) become potential selection factors.

The general profile of lithium-induced side effects has proven to be relatively benign in the long-term maintenance treatment of bipolar patients. However, several of lithium's more prominent adverse effects deserve comment, as do the relative comparisons with and among the mood-stabilizing anticonvulsants.

Thyroid Function Lithium clearly can impair thyroid function by several different mechanisms; it has even been used to treat hyperthyroidism. Lithium uniformly lowers T_3 and T_4 concentrations in the

plasma and, in some patients, increases thyroid-stimulating hormone (TSH). TSH concentrations above normal can be taken to indicate that the hypothalamic-pituitary-axis is working overtime to maintain normal levels of thyroid hormones. Lower free T_4 concentrations during lithium prophylaxis in one study were associated with more-severe depression and more-rapid mood fluctuation. Thus, one might consider thyroid replacement with levothyroxine when levels of TSH are elevated, even when thyroid hormone indexes are still within their normal lower limits. Occasional checks of thyroid function at 6-month to 1-year intervals are wise, as is an earlier check if there is a breakthrough of depressive symptomatology during otherwise adequate lithium maintenance treatment. In these instances, treatment of underlying hypothyroidism can help alleviate a depression that is linked to this hormonal deficit. Whereas levothyroxine is generally used for suppression of TSH and replacement, anecdotal evidence suggests that addition of liothyronine to the levothyroxine replacement may help some patients with refractory depression or cycling.

Carbamazepine tends to decrease T_4, free T_4, and T_3 concentrations (as does lithium), and in combination, the decreases are additive. 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. When the two drugs are used in combination, however, the lithium effect on TSH may override that of carbamazepine, and the patient may then require thyroid supplementation.

Renal Function By the late 1980s the fear 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 with elevated creatinine and low clearance originally attributed to lithium were, in part, related to the absence of an age-matched control group of psychiatric patients not treated with lithium. Thus, although lithium rather consistently 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, although isolated case reports persist. Preliminary data suggest that less renal toxicity may occur in patients using single nighttime dosing (producing higher peaks, but lower nadirs) than occurs with conventional dosing regimens. Single nighttime dosing may also facilitate compliance.

Current practice suggests that frequent monitoring of renal function during lithium treatment is not generally indicated; however, baseline measures of renal function including creatinine clearance should be obtained before beginning lithium treatment in patients with a history of some renal alterations. Patients must have adequate fluid intake to maintain an appropriate fluid and electrolyte balance because of the induction of diabetes insipidus syndrome related to the blockade of antidiuretic hormone actions. Several patients have been reported in whom 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 (e.g., during extreme athletic stress or during gastrointestinal illnesses with 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 thiazides) are used, lower dosages of lithium are indicated because these agents will increase lithium concentrations.

Because carbamazepine appears to act as a vasopressin agonist either directly or by potentiating vasopressin effects at the receptor, it will not suffice to reverse lithium-induced diabetes insipidus, which occurs by an action of lithium below the receptor level at the adenylate cyclase second-messenger system. Demeclocycline (Declomycin) and doxycycline (Vibramycin) may counter the hyponatremic effects of carbamazepine, as may lithium. The hyponatremic effects of the ketoderivative oxcarbazepine may be more prominent than those of carbamazepine. To the extent that the minor cognitive impairments of lithium are in part related to its ability to impair vasopressin function in the brain, these data suggest that not only would carbamazepine be less likely to cause this adverse effect, but also during combination treatment, the adverse effects of lithium might 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 concentration.

Tremor Tremor can be problematic for a small but substantial percentage of patients treated with lithium. The tremor is frequently exacerbated by social stress. When the tremor persists at doses near 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 4 to 6 hours. Valproate also has dose-related tremorogenic effects. Gabapentin, in contrast, has been used to treat essential tremor. The dihydropyridine L-type calcium channel inhibitors may provide a nontremorogenic adjunct or alternative to lithium.

Gastrointestinal Effects Gastrointestinal adverse effects (diarrhea and indigestion) can also be problematic for many patients on lithium and valproate but may be attenuated by reducing the dose or giving it at mealtimes (for indigestion). Antidiarrheal agents should be restricted to short-term treatment. The calcium channel blockers (which may be constipating) may substitute for lithium or partially counter its adverse effects when used in combination. Histamine type 2 receptor (H_2) inhibitors may help counter valproate's gastrointestinal adverse effects.

Cognitive Effects Patients may express concern about the effects of lithium on their memory, spontaneity, or creativity. Although some impairment can be objectively delineated in some, but not all, types of detailed neuropsychological testing, most patients either do not experience this 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 phases. Although no adequate approach to the subjective cognitive effects of lithium has been demonstrated (other than reducing the dose), associated causes for cognitive impairment must be ruled out, including possible hypothyroidism or an inadequately treated coexistent depression. Donepezil (Aricept) has been reported helpful in isolated case reports and deserves further exploration and study.

Many so-called drug-related adverse effects are also evident during placebo treatment phases and thus appear to be more closely associated with illness-related variables than with a particular psychopharmacological treatment. This perspective on lithium maintenance treatment clearly needs to be explored with the patient to avoid premature discontinuation of treatment or noncompliance. Carbamazepine and valproate are noted for their benign cognitive side effects in the epilepsies and may be better tolerated than lithium in some instances, although they, too, can be associated with subjective

complaints and word-finding difficulties. Lamotrigine does not appear to have lithium's occasional liability of stabilizing mood slightly below baseline, and some patients may be stabilized at a mood or energy level slightly over baseline (i.e., above 50 millimeters on the mood analogue scale). Topiramate clearly causes cognitive motor slowing, speech, or word-finding difficulties in a small percentage of patients, particularly with high initial doses, rapid upward titration or in combination therapy. Valproate has been associated with a reversible organic brain syndrome with EEG slowing and a dementia-like presentation in isolated patients with epilepsy.

Weight Gain Lithium-induced weight gain can be a vexing problem for a moderate percentage of patients, and in one study was a correlate of better mood-stabilizing response. Thyroid indexes should be rechecked, and the patient reminded not to use calorie-containing beverages when maintaining the necessary increased fluid intake associated with diabetes insipidus.

Weight gain can also be problematic with valproate. Whether this is a correlate or causal link in the reported occurrence of polycystic ovary syndrome in epileptic patients taking valproate remains for further study.

Like most dopamine receptor antagonists (with the possible exception of molindone [Moban]), the serotonin-dopamine antagonists are also associated with weight gain; clozapine, olanzapine, and risperidone are particularly problematic for some patients. One should watch for replication of one anecdotal report of the antidiabetic drug troglitazone (Rezulin) which helped to cause substantial weight loss in a patient who gained considerable weight on olanzapine. Topiramate has a strong tendency to help with weight loss, apparently by both decreasing carbohydrate craving and possibly increasing metabolism as well. Early clinical vignettes suggest it may help overcome lithium or valproate weight increases when used in combination with them. Carbamazepine and gabapentin are less problematic, and, L-type calcium channel inhibitors are relatively weight neutral. Patients lost about 2 pounds in 6 weeks on lamotrigine in one controlled study, compared with a gain of about 2 pounds on gabapentin.

Headache Many mood stabilizers, such as lithium, valproate, and the L-type calcium channel inhibitors are reported to be effective in migraine prophylaxis. Carbamazepine increases substance P concentrations and sensitivity and may treat cluster headaches but can exacerbate migraine. Lamotrigine, with its weak serotonin reuptake effects, may either ameliorate or exacerbate headaches. Lamotrigine and gabapentin have apparent antipain long-term effects in some syndromes.

Rash Lithium may precipitate or exacerbate psoriasis and acne. Lamotrigine treatment must be started extremely slowly to help avoid the otherwise high incidence of rash (10 percent); some estimates suggest that 1 in 500 patients progresses to severe, potentially lethal extremes of Stevens-Johnson or Lyell's syndromes. Risk factors, in addition to rate of titration, include use with valproate (requiring a halving of the lamotrigine dose) and a history of multiple or severe rash on other medications.

Carbamazepine may also produce a common pruritic rash (10 to 15 percent), but severe deterioration to Stevens-Johnson syndrome may be less common than during lamotrigine treatment. Nonetheless, in most instances, carbamazepine treatment should be discontinued with the onset of a rash. However, when patients respond to carbamazepine and other effective treatments are not available, prednisone has reportedly suppressed uncomplicated carbamazepine-induced rashes (i.e., those without evidence of systemic involvement with fever or lymphadenopathy) in a very high percentage of patients. Whether a similar strategy would be effective for lamotrigine remains unstudied.

Hepatitis Valproate has been associated with reports of severe hepatitis in the neurological literature; most of the fatalities have been in children under the age of 2 years, particularly those on polytherapy. Few serious hepatic adverse effects have been reported in adult psychiatric patients on valproic acid, but liver function might be monitored periodically when using this agent, and patients should be warned to report symptoms that might be referable to hepatitis such as fever, right upper quadrant pain, malaise, nausea, anorexia, Coca-Cola–colored urine, and jaundice. Benign elevation of liver function test (LFT) results to two or three times normal are not uncommon in patients taking valproate, carbamazepine, and other anticonvulsants, and LFTs can be followed without drug discontinuation. Zinc and selenium supplements are recommended with valproate, since they are reported anecdotally to decrease the incidence of hepatitis, pancreatitis, and alopecia. Rare cases of carbamazepine-induced hepatitis have been reported, but routine monitoring for this adverse effect does not appear to be indicated. Since lithium and gabapentin are excreted by the kidney, they have no liability in those with evidence of liver pathology or toxicity.

Hematological Effects The side-effect profile of carbamazepine tends to be quite different from that of lithium or valproate (Table 14.8-7). Whenever lithium and carbamazepine act on a common target system, the effects of lithium tend to override those of carbamazepine. In other instances this is a clinical disadvantage, except for the ability of lithium to increase the white count (via increases in colony stimulating factor) which will override the white count-suppressing effects of carbamazepine (via decreasing colony-stimulating factor), and may thus be clinically useful. However, lithium is effective in this regard only against carbamazepine's benign suppression of the white count, and its effects are doubtful if there is evidence of more problematic interference by carbamazepine in hematological function manifest in other cell lines, such as platelets or red cells (RBCs), indicating a possible pancytopenic or aplastic process. The risk of agranulocytosis or aplastic anemia in patients taking carbamazepine has been estimated to be from 1 in 10,000 to 1 in 100,000. If there are normal levels of other blood elements (platelets and RBCs), potentiation with lithium will likely reverse the benign white-count suppression of carbamazepine. Valproate has been associated with thrombocytopenia; the potential impact of lithium on this syndrome has not been reported.

Teratogenic Effects Cardiac (Ebstein's) anomalies of great vessels have been reported to occur with a higher frequency than expected in patients treated with lithium during pregnancy, although recent studies suggest the risk may not be much greater than that in the general population. Thus, the previous prohibition against use of lithium during pregnancy is being reevaluated. In some instances in which the discontinuation of lithium treatment would put the mother at high risk for a severe depression or mania, continuing lithium treatment may be appropriate, especially with increased ability for fetal monitoring.

An increased risk (several percent) of spina bifida has been reported for valproate (which may be dose-related) as well as a slightly

smaller risk for carbamazepine, and use of these agents should be avoided in pregnancy if possible. Folate supplements should be used. Persisting biochemical alterations have been found in some animal studies of fetal exposure to typical antipsychotics but have not been assessed systematically in human follow-up studies. Few data are available for lamotrigine and gabapentin, but no specific teratogenic effects have been described. Topiramate causes some bone deformity in animals, but the risk for humans has not been systematically evaluated. ECT may have the lowest risk to the fetus among the somatic treatments, but the effect of maternal seizures has also not been systematically evaluated. The calcium channel blockers have a benign record for fetal abnormalities, and these agents remain among the better candidates for continuation of a putative mood stabilizer during pregnancy. As needed, short-term augmentation with minimal dosages of antipsychotics or high-potency benzodiazepines may be tolerated.

Approaches to Adverse Effects: Dosage Reduction, Adjunctive, Alternative Treatment Dosage reduction may be a first maneuver in treating a variety of lithium-induced problems (tremor, weight gain, thirst, urinary frequency, diarrhea, or psychomotor slowing). If these lower dosages are not adequate for prophylaxis, combination or alternative treatment, especially with carbamazepine or a dihydropyridine calcium channel adverse blocker (which have different side-effect profiles), or other putative mood stabilizers such as valproate may be indicated (Fig. 14.8-5). The renal clearance of lithium appears to decrease with age, so that a lower dose may be necessary and adequate in the older patient on lithium maintenance.

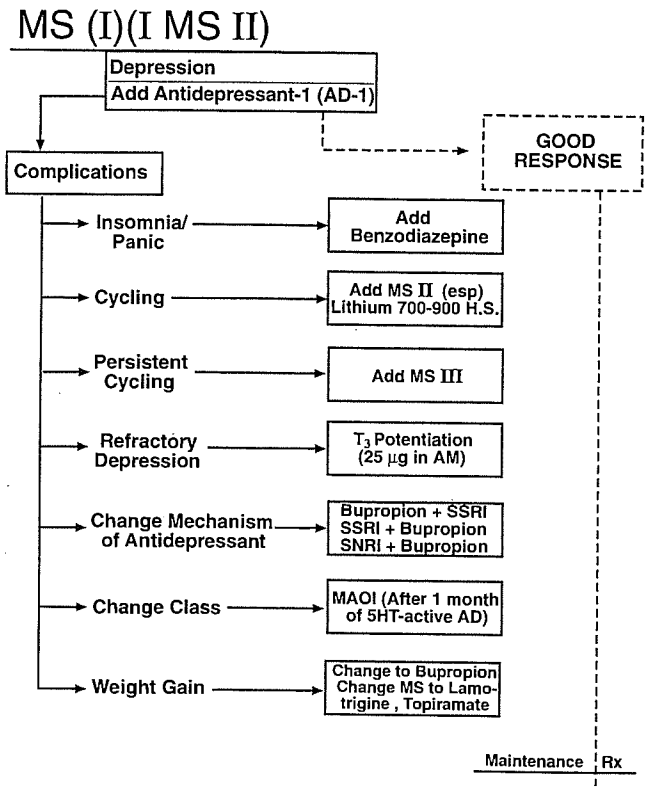

FIGURE 14.8-20 Algorithm for treating bipolar depression and treatment complications. MS I, first mood stabilizer; MS II second mood stabilizer

TREATMENT OF BREAKTHROUGH DEPRESSIVE EPISODES DURING LITHIUM AND OTHER MOOD-STABILIZER PROPHYLAXIS

Antidepressant Augmentation Approaches to a depression in an untreated bipolar patient or during an episode emerging during lithium prophylaxis differs from that in a unipolar depressive disorder patient, and few antidepressants have been systematically evaluated in bipolar disorders. The author emphasizes possible choices of agents based on adverse-effect profiles (Table 14.8-3), the differential presenting symptom clusters and comorbid syndromes (Fig. 14.8-20), and mechanisms of action (Table 14.8-2). However, a strong empirical database for these recommendations is lacking. Moreover, given the necessity for protracted clinical trials (of many weeks) to evaluate the clinical efficacy of each individual drug, attempting to potentiate a specific drug treatment once adequate dosages or blood concentration have been reached is recommended before switching treatment modalities. Thus, thyroid or lithium potentiation deserves emphasis in the treatment sequence before multiple trials with single alternative agents. Figure 14.8-21 illustrates a possible treatment algorithm for a depressed patient with a bipolar disorder.

Potentiation of the Antidepressant Given the long time frame that may be required to evaluate the adequacy of an antidepressant response, antidepressant potentiation should be considered in either the first or second antidepressant trial before switching antidepressants, even to a new category of agents. Thus, when a patient appears to be at either maximally tolerated dosages (or adequate blood concentration of the drug) and has not responded adequately, one might consider adding thyroid hormones or lithium (Table 14.8-5, Fig. 14.8-20).

A sizable but mixed literature exists regarding the efficacy of thyroid potentiation in converting (20 to 50 percent) antidepressant nonresponders to responders. This effect appears to be independent of initial clinical thyroid status or any evidence of hypothyroidism. A response to the addition of liothyronine (25 to 37.5 μg per day in the morning) may occur within days and usually occurs within the first week or two of treatment. Therefore, if there is no response in this time frame, the clinical trial of liothyronine potentiation can be exchanged for other options. Adverse effects are very unusual but could include tachycardia, hypertension, anxiety, or flushing.

A second option is potentiation with lithium. An extensive literature, particularly in unipolar depressions, reveals that addition of lithium carbonate to a variety of antidepressant modalities, including tricyclic drugs, heterocyclic drugs, MAOI, or even carbamazepine, often yields clinical improvement (40 to 60 percent). Response may begin within 24 to 48 hours but may be slower in onset and stretch over 1 to 3 weeks. Dosages of lithium slightly below those conventionally used for monotherapy are generally effective (i.e., 750 to 900 mg in a single dose at bedtime may suffice to reach a target of 0.75 mg/L, which is the concentration reported to be needed for potentiation in unipolar depression). When used in this fashion, the adverse-effect profile of lithium appears quite benign. Lithium potentiation may be effective for all subtypes of depression.

New data suggest that concurrent treatment of acute depression with lithium and antidepressants from the outset also results in more

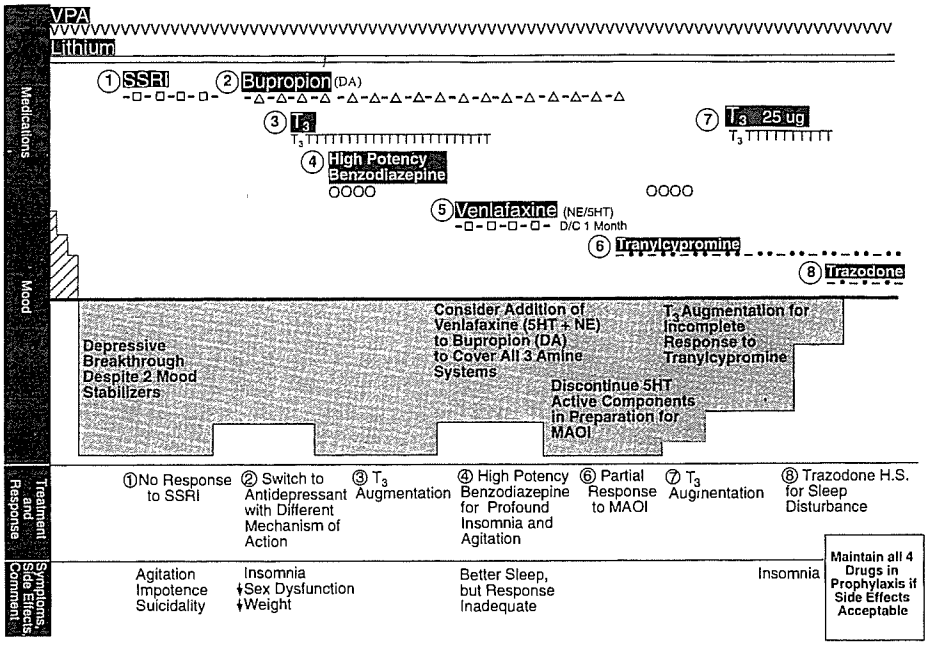

FIGURE 14.8-21 Possible sequential algorithm for the bipolar disorder patient with refractory depression. DA, dopaminergic; NE, noradrenergic.

rapid response than with an antidepressant alone. Thus, for the untreated bipolar disorder patient presenting with a depressive episode, the combination of an antidepressant and a mood stabilizer such as lithium is highly recommended. The initial reports of estrogen potentiation of antidepressant response do not appear as promising as those of either thyroid or lithium potentiation but may be considered for postmenopausal women.

Shifting Antidepressant Classes: MAOIs One might consider shifting treatment from one type of antidepressant to another if unacceptable adverse effects appear before adequate blood concentrations or a clinical response has been achieved. If adequate dosages and blood concentrations have been achieved without antidepressant effect, one may switch to a drug with a different biochemical profile within the same class or to a different class, such as an MAOI, but only after a 2- to 4-week period off agents with high potency in blocking serotonin reuptake (Table 14.8-5, Fig. 14.8-20). Problems with orthostatic hypotension may become more prominent in the second and third weeks of MAOI treatment. Salt loading, pressure stockings, and fludrocortisone (Florinef) or the peripherally acting α_1 agonist midodrine may prove effective in the treatment of MAOI-induced hypotension. MAOIs can be given in single morning doses or in divided doses. If marked insomnia occurs, nighttime doses of trazadone (Desyrel) have been recommended by some authorities. Bouts of daytime drowsiness and sedation may also become a problem. One might attempt to titrate the dosage against adverse effects, as variations in dosage or timing 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. These crises may be clinically manifested as explosive headaches, flushing, palpitations, perspiration, and nausea. Immediate treatment with a slow infusion of phentolamine (Regitine) (5 mg intravenously) in an emergency room is recommended. Most authorities suggest that the patient carry a 10-mg nifedipine (Adalat, Procardia) capsule with them that they could use sublingually or bite and swallow in the event of a presumptive hypertensive crisis.

Although tricyclic and heterocyclic drugs, SSRIs, serotonin-noradrenaline reuptake inhibitors (SNRIs), and MAOIs are central treatments for the unipolar depressed patient, there is reason for caution in their use for the bipolar patient. Some but not all studies have reported an increased incidence of switches into hypomania or mania during tricyclic or MAOI therapy, higher than expected for the patient's natural course of illness, particularly in previous rapid cyclers (Fig. 14.8-22). Whether this increased incidence of switching or cycle acceleration is sufficient to avoid the initial use of antidepressants in favor of mood stabilizers remains controversial. Thus, a shorter depression may occur at the cost of the more rapid onset of the following manic episode, whereas withdrawal of tricyclic drugs and MAOIs has also been shown to slow this cycle acceleration in a small number of patients.

Uncontrolled observations suggest that tricyclic antidepressants and related compounds may be implicated in the development of continuous cycling phases (i.e., successive episodes without a well interval) (Fig. 14.8-23). This phase of the illness becomes difficult to treat and tends to be relatively lithium refractory. Anecdotal evidence and one double-blind, randomized study indicate that bupropion may not be associated with the same switching tendency as the tricyclic antidepressant desipramine (Norpramine). SSRIs may be less involved in the switch phenomenon and in cycle induction than the tricyclic drugs, but this too requires further investigation, since the commencement of rapid or continuous cycling coincident with the use of SSRIs has been observed anecdotally.

Once a switch has been observed with an MAOI, reexposure to even a different MAOI may also lead to an earlier onset of a switch, as observed in one controlled study, perhaps reflecting a sensitization phenomenon. Naturalistic data, however, raise questions about whether antidepressant-induced switches occur on each exposure to these drugs. Moreover, it is unclear whether a drug-induced switch appears only in those predestined to have spontaneous switches or whether this occurrence actually predisposes the patient to develop further spontaneous manic episodes. Women and those with rapid cycling may be at higher risk for tricyclic-induced switching or cycle acceleration.

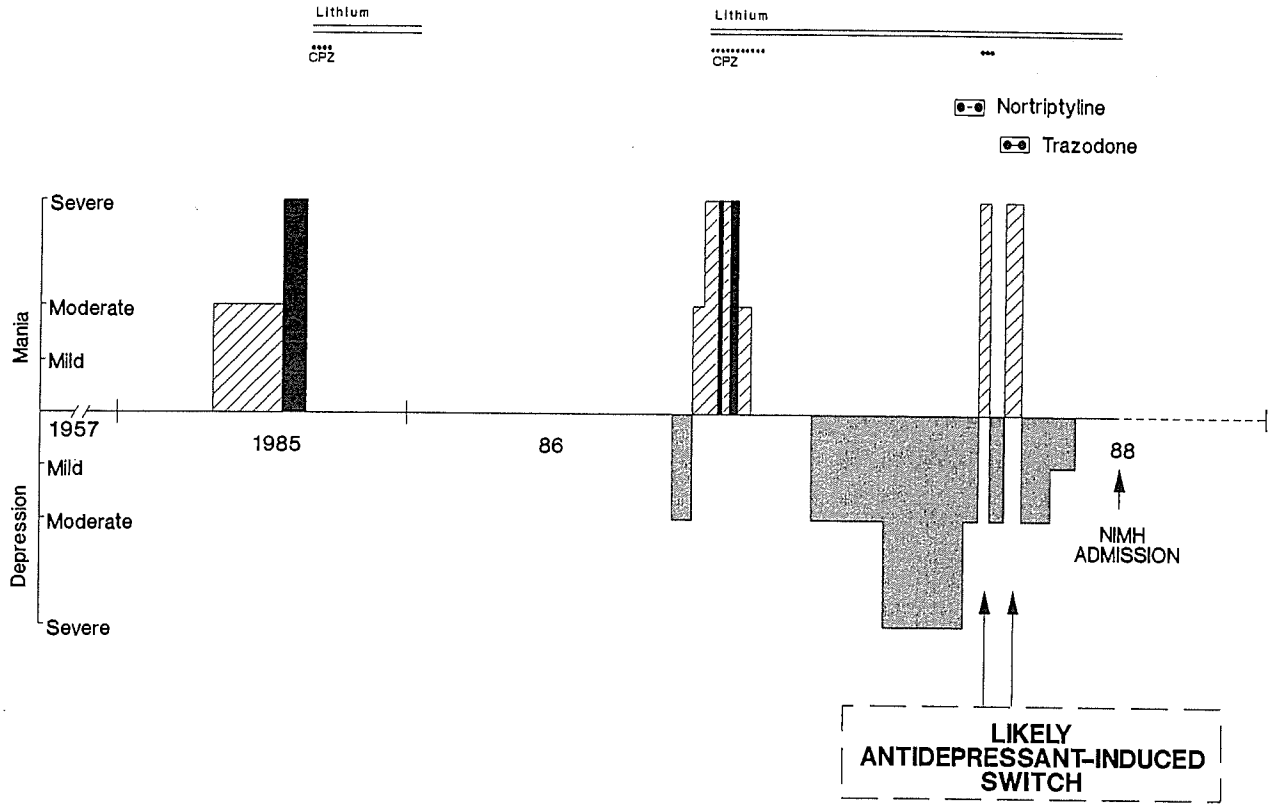

FIGURE 14.8-22 Antidepressant-induced mania in a male patient with bipolar I disorder. CPZ, chlorpromazine.

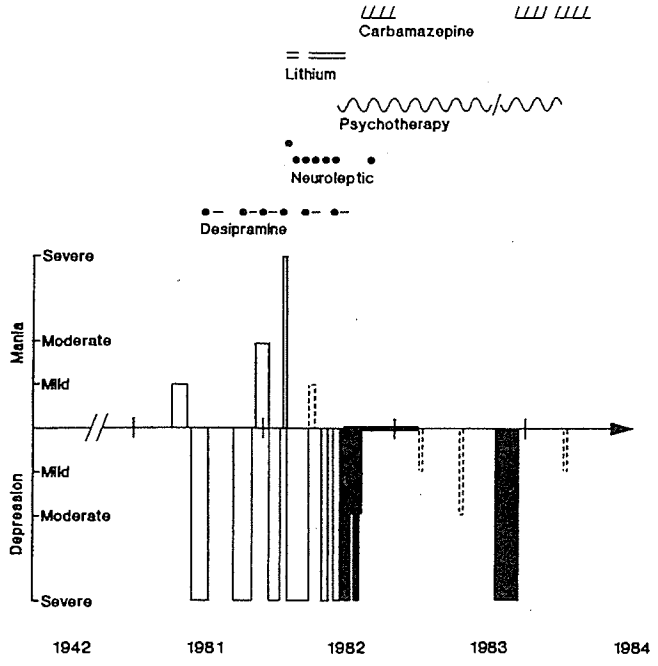

FIGURE 14.8-23 Life chart of a patient rated likely to have had antidepressant-induced cycle acceleration. *Solid black shading* indicates patient was hospitalized.

Adding a Second Mood Stabilizer The unimodal antidepressants should be used cautiously and in conjunction with mood stabilizers for bipolar disorder depressive episodes, and particularly if there is a prior history of drug-induced switches, other options should be considered. There is much to recommend adding a second or even a third mood stabilizer (lithium, lamotrigine, carbamazepine, valproate, or a dihydropyridine L-type calcium channel inhibitor) in the rapidly (or ultrarapidly or ultradian) cycling depressed bipolar disorder patient prior to the use of a unimodal antidepressant (Table 14.8-5, Fig. 14.8-24).

If unimodal antidepressants are used for a bipolar disorder depression, clinical lore suggested that they should be tapered and discontinued as soon as possible, to avoid the potential for drug-induced switches and cycle acceleration, especially since lithium may not be able to prevent these phenomena. However, maintenance therapy with bupropion and lithium has been reported to be effective in rapid-cycling patients, and use of unimodal antidepressants in conjunction with the new putative mood stabilizers deserves study. Several case reports suggest that alprazolam (Xanax) may, like the tricyclic drugs, also induce switches into hypomania and mania (even in unpredisposed patients) and this high-potency benzodiazepine should be avoided in favor of the long half-life compounds clonazepam and lorazepam, which do not appear to share the proclivity of the triazolobenzodiazepine compounds for the induction of mania. These high-potency benzodiazepines may be useful adjuncts to the mood stabilizers; however, the rare patient may experience these classical benzodiazepines as mood destabilizing or even depressogenic.

Some evidence suggests that the MAOIs, in general, may be less prone than tricyclic drugs to induce switches. The MAOIs should

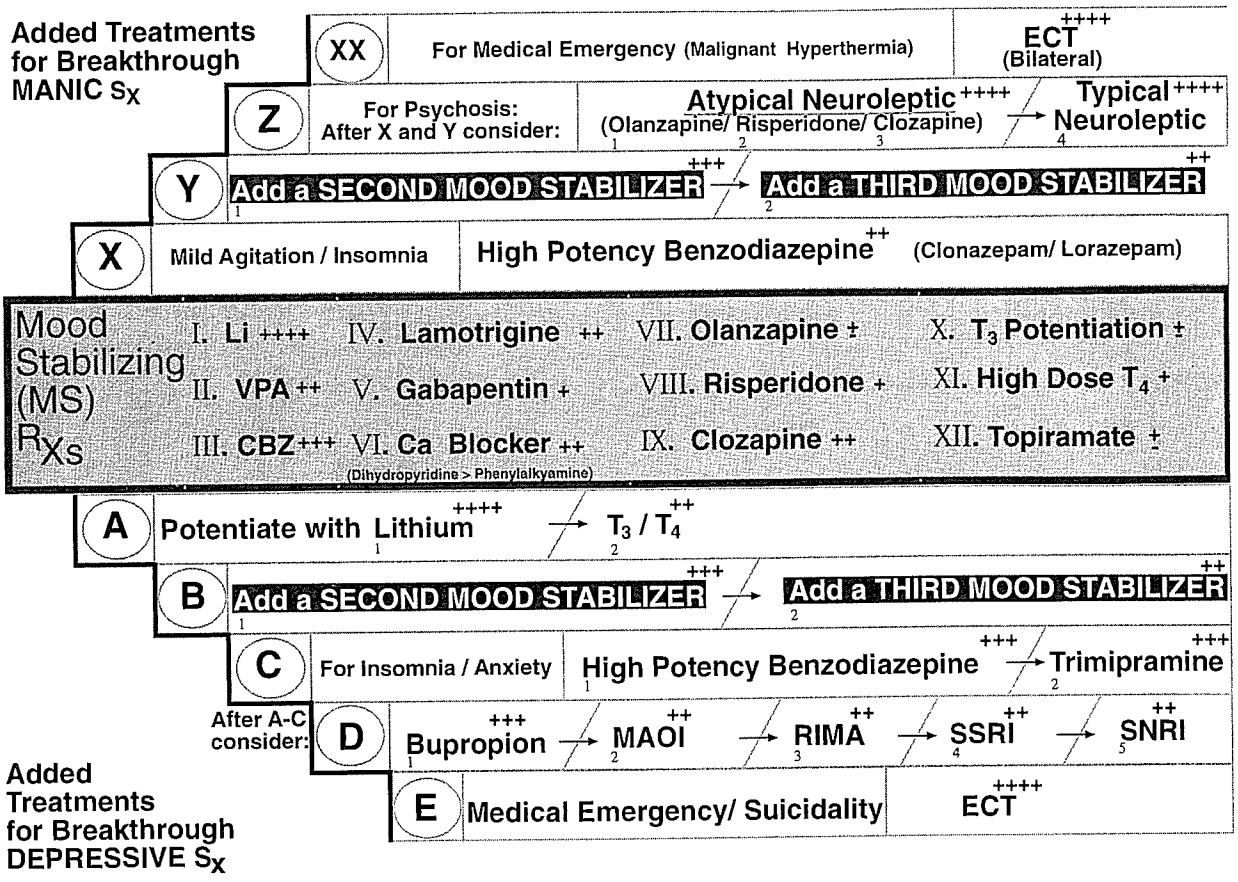

FIGURE 14.8-24 Treatment algorithm for bipolar disorder patients with rapid and ultrarapid cycling. VPA, valproate; CBZ, carbamazepine.

be given relatively greater consideration, especially for the reversal of vegetative (anergic, hypersonic, or hyperphagic) states in the bipolar patient. A substantially higher rate of antidepressant response was reported in one controlled series for tranylcypromine (Parnate) (81 percent) compared with imipramine (Tofranil) (48 percent) in bipolar disorder patients. Clorgyline, a selective *MAO type A* inhibitor not yet clinically available has been reported to slow cycling frequency. The reversible inhibitor of monoamine exiduse type A (RIMA) moclobemide (Aurorix) (Table 14.8-3) is widely available in Europe and Canada but not in the United States; this drug is not believed to be as effective an antidepressant as the nonselective MAOIs, such as tranylcypromine and phenelzine (Nardil); however, these MAOIs are unique in potentiating all three amine systems (serotonin, noradrenaline, and dopamine). One could attempt such an equivalent effect by using venlafaxine (for its serotonergic and noradrenergic effects) in combination with bupropion (for its dopaminergic effects).

It is possible that the anticholinergic rather than the noradrenergic effects of the tricyclic drugs makes them prone to cause switches or cycle acceleration. A comparison of SSRIs with the noradrenaline selective agents (desipramine, nortriptyline [Aventyl], and maprotiline [Ludiomil]), or to the SNRI venlafaxine would clarify the putative role of norepinephrine reuptake blockade in inducing these phenomena.

Dopamine-Active Compounds and Other Treatments

Bupropion Bupropion in conjunction with a mood stabilizer has shown promise in short-term and prophylactic management of bipolar disorder patients, including rapid cyclers. Although it may be added to lithium or valproate prophylaxis without pharmacokinetic interactions, when used with carbamazepine its blood concentrations are markedly decreased and those of an active metabolite increased (Fig. 14.8-25).

Psychostimulants The role of psychostimulants as short-term augmentation has not been systematically explored, although it is apparently widely used by some experts in the field. However, one investigator has indicated that this is not a useful long-term strategy, since many patients appear to develop tolerance to this modality. This strategy should perhaps be reserved for temporary augmentation while awaiting more-effective antidepressant response to other modalities.

The same investigator also observed that tolerance does not appear to develop when the psychomotor stimulants are combined with MAOIs. This strategy should be reserved for only the most refractory patients, since the *Physician's Desk Reference* (PDR) lists an absolute contraindication to combining stimulants and MAOIs. Nonetheless, this appears to be effective and tolerated by most patients in many small case series.

Dopamine Agonists Small clinical series have also suggested some antidepressant efficacy of the direct dopamine agonist bromocriptine, which is used to treat parkinsonian patients. One double-blind study indicated that it was as effective as imipramine. A related dopamine agonist, piribedil (Trivastal), has been effective for

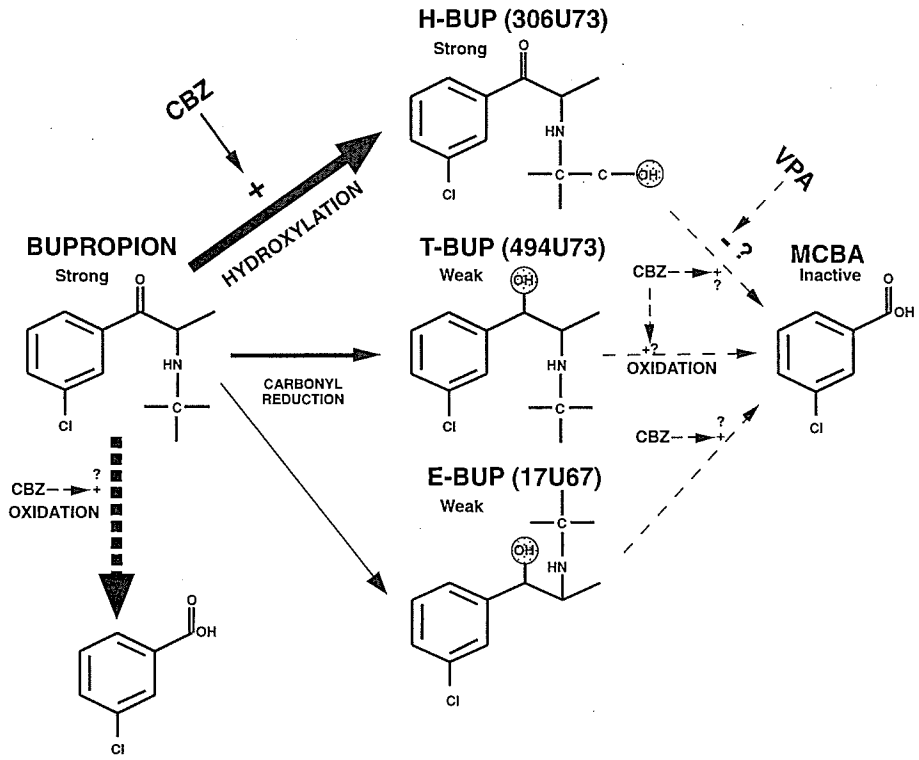

FIGURE 14.8-25 Bupropion metabolism. CBZ, carbamazepine; VPA, valproate; MCBA, metachlorobenzoic acid.

the occasional refractory depressive patient. Pergolide (Permax) was reported to be an effective augmenting agent in one series on refractory depression but not in another.

Pramipexole, a potent D_3 as well as D_2 agonist recently approved for use in parkinsonism, is reported (at 1 mg a day or higher) to have antidepressant effects equivalent to those of fluoxetine (Prozac). Treatment should be started at low dosages and titrated toward 1 mg a day very slowly to avoid adverse effects such as nausea and orthostatic hypotension.

Dopamine-active drugs has been reported to be more effective in patients with low concentrations of the dopamine metabolite homovanillic acid in their cerebrospinal fluid (CSF). A similar relation to low concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) and a better response to the serotonin active compounds clomipramine (Anafranil) and sertraline (Zoloft) have been reported. The results are inconclusive as to whether urinary concentrations of the noradrenergic metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) can predict the response to noradrenergically active antidepressants. Consistent biochemical markers of antidepressant response have not yet been identified.

Light in Morning and Melatonin at Night Systematic trials of augmentation with bright light (more than 7500 lux) may also be worth considering in patients with marked disruption of circadian rhythmicity and the typical bipolar disorder hypersomnia. In these instances, high-intensity light might be more useful in the morning, although this issue needs to be reexamined with more-systematic prospective randomized studies.

An additional approach to altering sleep activity cycles (which are common in bipolar disorder patients) might be to use melatonin adjunctively at night, although this, too, requires caution and prospective studies. In addition, isolated reports exist of exacerbation of sleep or mood in some patients when using melatonin supplementation.

Sleep Deprivation as a Short-Term Antidepressant Paradoxically, sleep deprivation may be an adjunctive procedure to hasten antidepressant response (Fig. 14.8-26). A rapid, transient, antidepressant response to 1 night of sleep deprivation has been reported consistently in studies from many different laboratories. Preliminary evidence suggests that sleep deprivation in the last half of the night (from 3 to 7 AM) may be just as effective as total sleep deprivation and may thus be more convenient for clinical use and outpatient treatment.

Although most responsive patients relapse after 1 night's recovery sleep, some modalities (especially lithium) may help sustain the sleep deprivation response. One recent report also indicates that progressive changes in the hours of sleep (from 5 PM on the sleep deprivation day to 6 PM the next, and so forth toward an 11 PM bedtime) also help hold a sleep deprivation response.

The rapid onset (overnight) effects achieved differs from the slower but sustained effects following selective deprivation of rapid eye movement (REM) sleep, that is, a modality that is not readily amenable to clinical use. Response to sleep deprivation may be related to phase or duration of a bipolar disorder depressive episode, with less responsivity early in the episode and a greater responsivity late in the episode. Several, but not all, studies indicate that the degree of antidepressant response to sleep deprivation is correlated with the degree of increase in morning plasma TSH concentration, presumably driven by endogenous increases in TRH. Parenteral TRH administration (500 mg intravenously) has also been reported to have rapid-onset effects, and two case reports suggest more-sustained effects with low dosage (50 μg a day at bedtime).

Inositol Inositol (12 to 16 grams a day) has recently been reported to have antidepressant, antianxiety, and antiobsessive-compulsive effects. This remains to be more systematically explored in bipolar disorder patients (in light of no reports of patients switching in one series reporting a 50 percent response rate in patients who

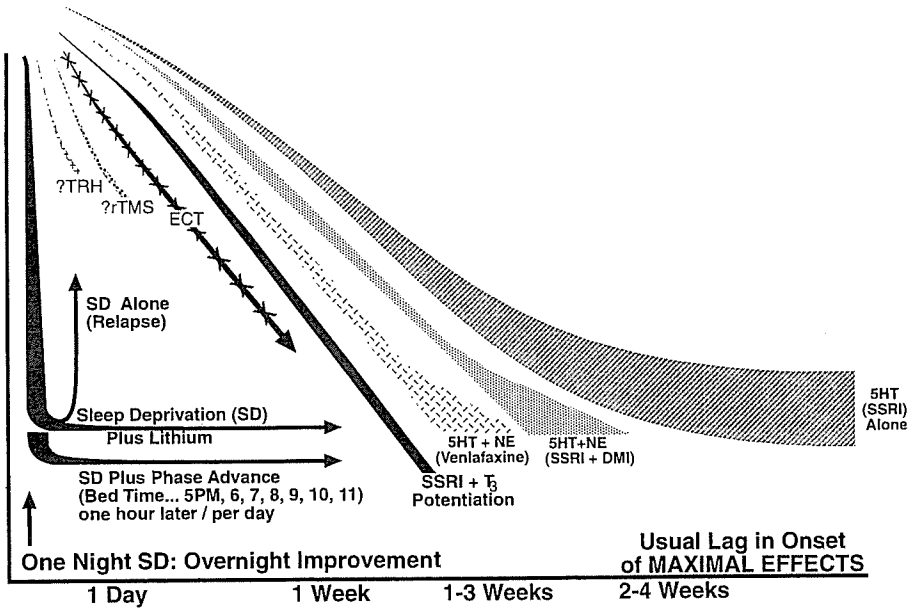

FIGURE 14.8-26 Nine potential clinical approaches to rapid-onset antidepressant effects. rTMS, repeated transcranial magnetic stimulation; NE, noradrenergic; DMI, desipramine.

were concomitantly treated with lithium, carbamazepine, or valproate. Theoretically, inositol should not only relieve some lithium-induced adverse effects, but could potentially reverse its therapeutic efficacy to the extent that inositol depletion from reduced phosphoinositide (PI) turnover is related to lithium's mechanism of action. This has not been reported, however. Myoinositol measured by magnetic resonance spectroscopy (MRS) has been reported to be low in brains of bipolar disorder patients (in proportion to the severity of their depression); and lithium lowers it further. One would then predict that inositol augmentation might make carbamazepine even more effective, because carbamazepine has effects opposite to that of lithium, and increases the inositol-1 phosphatase enzyme, which should increase inositol. Lithium, carbamazepine, and valproate are all reported to downregulate the transporter for inositol that has recently been isolated and cloned.

Choline One open study reported that potentiation with choline (3 to 8 grams a day) may be helpful in stabilizing mood in refractory cyclers, and this approach, too, requires further systematic study.

Folate and Ascorbate In two single, randomized, placebo-controlled studies, the vitamins folate (300 to 400 mg a day) and ascorbate (3 grams a day) have each been reported to have some beneficial effects on amelioration of mood in long-term prophylaxis of bipolar disorder patients and, in light of their benign side-effect profiles, might be worthy of consideration in the treatment regimen of the refractory bipolar disorder patient.

Omega-3 Fatty Acids One randomized double-blind study comparing the addition of omega-3 fatty acids (9 grams a day) or an olive oil placebo in bipolar disorder patients poorly controlled on mood stabilizers was terminated early because of the marked superiority of the omega-3 fatty acid to the control. Virtually all of the breakthrough depressive episodes occurred in the placebo control group.

APPROACHES TO SUICIDALITY

Regular psychiatric visits during the prophylactic well phase are recommended on an interval ranging from weekly to biweekly in unstable patients to 1 to 4 months in better stabilized patients, depending on a variety of ancillary circumstances including completeness of response, lack of psychosocial crises, history of compliance, insight into the illness and its treatment, absence of adverse effects, financial constraints, and the wishes of the patient. In addition to periodic assessment of all of these issues, regular treatment visits are recommended to assess the potential risks of suicide independently of the occurrence of discrete episodes. This is particularly important when there is a positive family history of suicide or other risk factors, including male sex, older age, comorbid alcohol abuse, high levels of anxiety, and prior suicide attempts (particularly if they have been severe).

Suicidal impulses and acts may not always vary directly with either severity of depression or reemergence of a full-blown episode requiring hospitalization and should be part of the careful ongoing clinical assessment of patients in all phases of their illness and treatment. Severe overwhelming psychic anxiety and agitation are predictors of completed suicide, and with the high comorbidity of panic disorder with either phase of bipolar disorder, one should be particularly alert to this and other high-risk factors. Specific contracting for communication with the clinician upon remergence or escalation of suicidal thoughts should be considered in high risk patients (Table 14.8-12).

Electroconvulsive Therapy ECT may benefit bipolar depressed patients who do not respond to lithium or other mood stabilizers and their adjuncts. This is particularly true when intense suicidality presents as a medical emergency. Whether ECT would continue to help abbreviate each bout of recurrent depressive episodes in rapid-cycling patients or whether it would be useful in long-term prophylaxis must be further investigated. The author has observed several instances in which tolerance appeared to develop to the therapeutic effects of repeated series of ECT. Moreover, concern about cognitive adverse effects remains, and the author has recently seen a number of otherwise healthy individuals with rather profound and sustained retrograde memory loss.

TREATMENT OF MANIC BREAKTHROUGHS

A wide range of drugs is available for breakthrough manic episodes occurring during lithium or other prophylactic treatment, in-

Table 14.8-12
Principles in the Treatment of Bipolar Disorders

Dual treatment: Focus acute short-term and prophylaxis
Mania: Treat first, do chemistries later
Load valproate and lithium; slowly start lamotrigine treatment
Use second mood stabilizers over antipsychotics
Benzodiazepines instead of antipsychotics
Combination treatment decreases adverse effects
Chart illness
Augment rather than substitute
Simplify (for adverse effects)
Taper of lithium slowly, if at all
Educate the patient's family
Assess compliance and suicidality
Develop an early warning system
Develop specific contracts
Regular visits; monitor course and adverse effects
Phone contact (PRN) when needed
Develop a "fire drill"
Prevent comorbid alcohol and other substance abuse
Psychotherapy and medicalization of illness
Give statistics: 50% relapse in first 5 months off lithium treatment
Patient as a co-principal investigator
Conservative treatment, if successful
Radical treatment, if inadequate response

cluding the entire spectrum of drugs indicated for the treatment of acute mania (Tables 14.8-5 and 14.8-6; Fig. 14.8-24). Ranking high in these treatments are carbamazepine and valproic acid, because of their longer-term prophylactic efficacy. Lamotrigine, nimodipine, and topiramate all require further study. Clonazepam or lorazepam may also be useful acute alternatives to antipsychotic supplementation, even though the benzodiazepines (and antipsychotic agents) appear to have a less primary role in the long-term management of bipolar disorders than the mood stabilizers carbamazepine or valproic acid.

The use of clozapine for bipolar disorder and schizoaffective disorder patients refractory to lithium, carbamazepine, and valproate is now well documented in many case series, especially for those with rapid cycling and dysphoric mania. Its lack of ability to induce tardive dyskinesia makes it particularly attractive, and one looks forward to a possible similar role for other atypical antipsychotics (Tables 14.8-8 and 14.8-10) without clozapine's liability for agranulocytosis and the attendant need for weekly white blood count monitoring. Given the high liability of tardive dyskinesia even with intermittent use of typical antipsychotics, these drugs should be relatively avoided in favor of the atypical agents and other mood stabilizers whenever possible.

COMPLEX COMBINATION THERAPY

Data from the NIMH also support the notion that many depressed patients with refractory bipolar illness can be treated with a variety

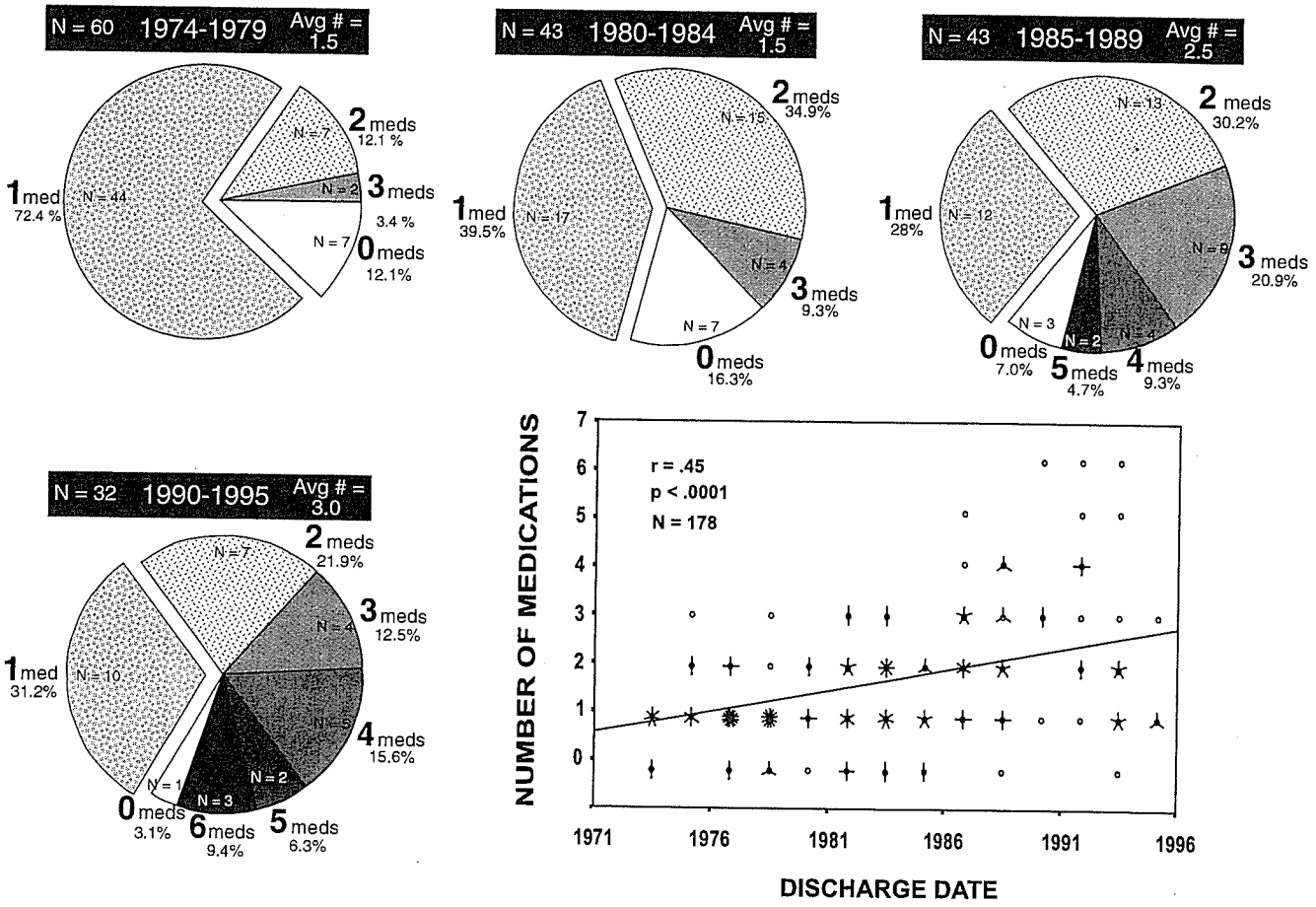

FIGURE 14.8-27 Increasing number of medications at discharge.

of approaches not typically involving the traditional unimodal antidepressant or typical antipsychotic modalities. Analysis of successive 5-year epochs in the tertiary-referral 3-West Clinical Research Unit of the Biological Psychiatry Branch showed that approximately the same high percentage (75 to 80 percent) of patients achieved marked or moderate improvement on the CGI at discharge in the past 25 years. However, patients in the years 1970 to 1974 required only monotherapy on discharge more than 75 percent of the time; this decreased to less than 25 percent in the most recent 5-year period, and the average number of medications on discharge increased from one to three per patient over the same time period (Fig. 14.8-27). Yet, unimodal antidepressants or antipsychotic drugs were used in

Table 14.8-13
Positive and Negative Selection Factors for Choice of Mood Stabilizer

	Lithium		Carbamazepine		Valproic Acid	
Target symptoms and anxillary responsive syndromes	Euphoric + + + + Family history positive + + + Mania-depression-well interval pattern + + + Steroid induced + + Suicidal + + +		Euphoric + + + Schizoaffective + + Secondary mood disorder + + + Aggressive + + + Dysphoric + Alcohol + + Cocaine ± Posttraumatic stress disorder + Steroid induced ± Pain syndromes + + + +		Dysphoric + + + Rapid cycling + + + Secondary mood disorder + + Panic + Migraine + + + + Alcohol ± Cocaine ± Posttraumatic stress disorder + Pain syndromes + +	
	Choose	**Avoid**	**Choose**	**Avoid**	**Choose**	**Avoid**
Adverse-effect profiles	↑ WBC (c)	Weight gain (c)	Minimal cognitive changes	Many drug interactions! (c)	Few drug interactions	Weight gain (c)
Positive → choose Negative → avoid	↑ Ca_{2+} (c)	Tremor (c)—DR	Little weight gain	↓ Potency of birth control pills (c)	Tolerated in overdose	GI distress (c) Tremor (c)—DR
	Renal excretion	Subjective (c)—DR cog. slowing	Tolerated in overdose		Minimal cognitive changes	Alopecia (r)—I Pancreatitis (yr)—I
(c), common	Nonsedating	↓ Thyroid (c)		Rash (10–15%) (c)		Polycystic ovaries (?)
(r), rare		↓ Renal		Ataxia/sedation (c)		↓ Platelets (c)
(vr), very rare		- ↑ D.I. (c) - ↑ GFR (r) Toxic in overdose - Cardiac (c)		Hyponatremia (c) Agranulocytosis (r)—I Aplastic anemia (vr)—I Allergy—I		Liver failure—(child < 2) (vr)
DR, dose-related		- Cerebellar (r)				
I, idiosyncratic		Poor in MS and neurological illness				
MS, multiple sclerosis		Pregnancy? - Ebstein's anomaly (vr)		Pregnancy - Spina bifida (1–3%) (r)		Pregnancy - Spina bifida (2–6%) (r)
	Lamotrigine		**Gabapentin**		**Topiramate**	
	Rapid cycling + + R Treatment refractory + + Pain syndromes + +		Parkinsonian symptoms + + Rapid cycling + + Insomnia + + Anxiety +		Bulimia + +	
	Choose	**Avoid-LTG**	**Choose**	**Avoid-GPN**	**Choose**	**Avoid**
	Nonsedating Weight neutral to weight loss	Rash (c): 5–10% Risk of severe rash: 1/500 (r)	Renal excretion Few interactions Helps essential tremor	Inhibits own uptake—requires t.i.d. or q.i.d. dosing	Weight loss (c) (sometimes sustained)	1% incidence of renal calculi Psychomotor slowing (c)
	Antidepressant; mood not set below baseline	Slow titration required				Difficulty with word finding (c) Possible insomnia
		↑ levels (× 2) with valproate ↓ levels (× 2) with carbamazepine				

less than 15 percent of the patients. Although these data based on sequential double-blind trials and augmentation strategies in this discharge phase of the hospitalization, did not involve a systematic randomized approach to therapeutics they nonetheless reveal that the vast majority of patients with refractory depressive and cycling presentations can be managed largely in the absence of the unimodal antidepressants or neuroleptic drugs. Multiple mood stabilizers in combination, often with thyroid augmentation, were used most of the time.

As in the late phases of other medical syndromes, complex combination treatment is often required for the treatment-refractory bipolar disorder patient. Although it may at first seem inappropriate to consider a regimen with four or five drugs for the treatment of refractory bipolar illness, this strategy is standard practice in many other areas of medicine such as the treatment of malignancies, tuberculosis, AIDS, or congestive heart failure. In these instances, multiple therapeutic modalities with different symptom targets and different mechanisms of action are often combined for optimal therapeutics.

With the availability of a variety of agents for bipolar disorders, it now befits the field to engage in more systematic clinical trial approaches to delineate the optimal strategies for achieving the most rapid response rates in the highest numbers of patients, so that even the most refractory bipolar disorder patients have an excellent chance at achieving and maintaining clinical remission.

Attempting to supplement the clinical effects of lithium and the mood-stabilizing anticonvulsants such as carbamazepine and valproic acid is often more effective than using lithium or the anticonvulsant alone. By augmenting rather than substituting a mood stabilizer, withdrawal-induced exacerbations will not confound the evaluation of the next agent, and time may be saved in the assessment of the combination in one clinical trial rather than two sequential trials (the anticonvulsant alone and then the combination). For patients who are unable to tolerate lithium carbonate, evidence does suggest that carbamazepine or valproate may be useful long-term maintenance treatments in preventing both manic and depressive episodes. A rather substantial literature on double-blind randomized studies provide evidence of carbamazepine's prophylactic efficacy. Most of the prophylactic data on valproate are based on clinical case series, however, with the exception of one randomized open trial showing efficacy equal to that of lithium and one blind trial showing that valproate has greater efficacy than placebo or lithium for recurrent depression. The choice of carbamazepine or valproate may depend on the future development of clinical predictors or on the current assessment of their relative side-effects profiles (Table 14.8-13). The data are even more preliminary for the L-type calcium channel inhibitor and the new putative mood-stabilizing agents such as lamotrigine and possibly topiramate and gabapentin.

All of these agents have differential presumptive biochemical mechanisms of action. One can begin to use augmenting strategies (Table 14.8-6), not only empirically (Fig. 14.8-5), but also based on combining agents with different actions (Table 14.8-2, Figs. 14.8-6 and 14.8-9), symptom targets (Table 14.8-4), side-effect profiles (Table 14.8-7), or benign pharmacokinetic and pharmacodynamic interactions. It is unclear whether using drugs with slightly different actions targeted to a single transmitter system such as GABA (i.e., enhancing GABA by reuptake blockade [tiagabine], transaminase inhibition [γ-vinyl GABA], transport effects [gabapentin], or multiple enzymatic actions [valproate]) will be more or less effective than simultaneously targeting two or more entirely different systems (e.g., enhancing GABA and inhibiting glutamate (Fig. 14.8-9).

Using several drugs in combination (Table 14.8-6) may actually help reduce the incidence of adverse effects by keeping each drug below its adverse-effects threshold (Table 14.8-7) rather than pushing one drug to maximum dosages for full therapeutic effect. Preclinical evidence indicates that such a combination strategy may also be less susceptible to the loss of effectiveness via tolerance. Optimally, one would like to use drugs with additive or synergistic therapeutic effects in the relative absence of adverse effects (Table 14.8-13); for this, knowledge of both pharmacokinetic and pharmacodynamic interactions is of considerable importance.

Pharmacokinetic Interactions There do not appear to be major pharmacokinetic interactions among lithium and the other mood stabilizers. There have been occasional reports of neurotoxicity when lithium and carbamazepine are used together. Because both agents can cause these adverse effects at or below clinically accepted

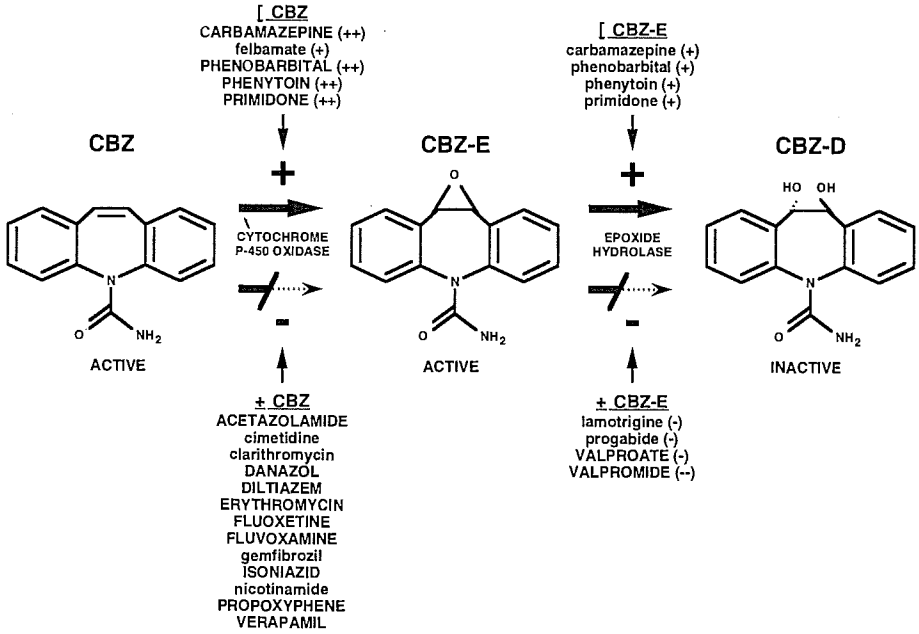

FIGURE 14.8-28 Carbamazepine (CBZ) metabolism.

dosage ranges, neurotoxicity may occasionally result from the combination treatment as well. In most instances the combination appears to be well tolerated. Many of the adverse effects reported in the literature appear to be caused by starting treatment with relatively large dosages of carbamazepine (rather than using slow increases) in combination with other agents, and assuming that the attendant adverse effects are related to the combination treatment rather than to carbamazepine alone. Carbamazepine enhances its own metabolism and that of other agents metabolized by the hepatic microsomal P450 system (CYP) isoenzyme CYP, 3A4 such as haloperidol or estrogen, and concentrations of these substances (as well as birth control pills) are markedly reduced by carbamazepine (Fig. 14.8-28). Despite this reduction in haloperidol blood concentrations, most studies report improvement with carbamazepine supplementation, suggesting that carbamazepine might potentiate antipsychotic effects because of actions other than dopamine receptor blockade.

Agents commonly used in medical practice can markedly increase carbamazepine concentrations and thus produce attendant toxicity (Table 14.8-14, Fig. 14.8-28). The most frequent dose-related toxic manifestations are dizziness, drowsiness, ataxia, diplopia, and confusion. These may occur in someone otherwise tolerating the drug well until other drugs are added. Erythromycin, triacetyloleandomycin (TAO), isoniazid (Nidrazid) (but apparently not other MAOIs), fluoxetine and fluvoxamine (Luvox), and the calcium channel inhibitors verapamil and diltiazem (Cardizem) (but not nifedipine, nimodipine, amlodipine [Norvasc], or isradipine) will increase carbamazepine concentrations. Less marked increases occur during cotreatment with propoxyphene (Darvon) and, transiently, with cimetidine (Tagamet). Carbamazepine will lower the blood concentrations of various agents (especially birth control pills) and interfere with some tests that depend on protein binding, including some pregnancy tests.

In contrast to the multiple pharmacokinetic interaction of carbamazepine with other drugs, based largely on its properties as an inducer of hepatic P450 enzymes, valproate has few problematic effects in this area. However, if carbamazepine and valproate are used together, one should consider reducing the carbamazepine dosage (because valproate increases concentrations of the 10,11-epoxide metabolite) as well as increasing the free fraction of carbamazepine (Fig. 14.8-28). Lithium and valproate are generally well tolerated in combination, but effects on tremor, weight gain, and gastrointestinal distress may be additive.

Carbamazepine markedly reduces the concentration of bupropion but increases that of its active hydroxy metabolite (Fig. 14.8-25), an action not shared by valproate. Valproate approximately doubles blood concentrations of lamotrigine and thus increases the likelihood of a severe lamotrigine rash; starting dosages of lamotrigine should be halved accordingly. If no rash occurs, lamotrigine and valproate have excellent tolerability and efficacy in epilepsy (and perhaps in affective illness) when used in combination. In contrast, carbamazepine decreases lamotrigine concentrations by about one-half, and these two drugs may be less useful in combination because of their similar adverse effects and pharmacodynamics.

Fluoxetine and paroxetine (Paxil) are inhibitors of CYP 2D6, and may increase concentrations of many agents such as desipramine and the secondary tricyclic antidepressants and phenothiazines (Table 14.8-15). Fluvoxamine is a potent inhibitor of CYP 1A2 (potentially producing theophylline toxicity) and CYP 2C19 (increasing warfarin [Coumadin] levels) as well as CYP 3A4. Nefazodone (Serzone) is also potent at CYP 3A4, producing cardiac arrhythmias with astemizole (Hismanal), cisapride (Propulsid), and terfenadine (Seldane), and likely increasing carbamazepine concentrations.

Table 14.8-14
Carbamazepine-Drug Interactions

Drugs whose concentrations are decreased by carbamazepine
- Alprazolam (?)
- Amitriptyline
- Azole antifungals (?)
- Bupropion
- Clobazam
- Clonazepam
- Clozapine†
- Cyclosporine (?)
- Dexamethasone (false-positive dexamethasone suppression test)
- **Dicumarol (?)**
- Doxacurium
- Doxepin
- **Doxycycline**
- Ethosuximide
- Felbamate
- Fentanyl
- Fluphenazine (?)
- **Haloperidol**
- **Hormonal contraceptives**
- Imipramine
- Lamotrigine
- **Methadone**
- Methylprednisolone
- Mianserin
- Nimodipine (?)
- Oxiracetam (?)
- **Pancuronium**
- Phenytoin (↑/↓/=)
- Prednisolone
- Primidone
- **Theophylline**
- Thiothixene (?)
- Valproate
- Vecuronium
- **Warfarin**

Drugs whose concentrations are increased by carbamazepine
- False-negative pregnancy tests
- Phenytoin (↑/↓/=)

Drugs that increase carbamazepine concentration
- **Acetazolamide***
- Baclofen (?)
- Cimetidine
- Clarithromycin
- **Danazol***
- **Dextropropoxyphene***
- **Diltiazem***
- **Erythromycin***
- **Fluoxetine***
- Flurithromycin
- **Fluvoxamine***
- Gemfibrozil
- **Isoniazid***
- Josamycin*
- Lamotrigine (↑ carbamazepine epoxide ?)
- Nicotinamide
- Ponsinomycin
- **Propoxyphene**
- Tefenadine (↑ free carbamazepine ?)
- **Triacetyloleandomycin***
- **Valproate** (↑ CBZ-E, ↑ free carbamazepine)
- **Verapamil***
- **Viloxazine***

Drugs that decrease carbamazepine concentration
- Adriamycin and cisplatin (?)
- Carbamazepine (autoinduction)
- Felbamate
- Isoretinoin (?)
- **Phenobarbital**
- **Primidone**
- Valproate (↑/↓/=carbamazepine)

Boldface indicates risk of important drug inefficacy or carbamazepine intoxication.
* Toxicity.
† Combination with carbamazepine not advised because of risk of agranulocyctosis.
(?)Slight or contradictory evidence.
↑, increased; ↓, decreased; =, unchanged.
Adapted from Keher TA, Post RM, Worthington K: Principles of clinically important drug interactions with carbamazepine. Part I. J Clin Psychopharmacol *11*:198, 1991.

SENSITIZATION EFFECTS ON THE MOOD DISORDERS AND IMPLICATIONS FOR PROPHYLAXIS

Early clinical observations and more-recent systematic controlled studies suggest that recurrent bipolar affective disorders may undergo a transition from initial episodes that are typically precipitated by psychosocial stressors to later episodes that tend to occur more spontaneously. This transition often occurs in the context of an overall pattern of cycle acceleration with a trend toward shorter well interval between successive episodes (Fig. 14.8-29). Both the effects of psychosocial stressors and recurrent mood episodes themselves may not only cause acute biological perturbations, but may also leave behind residual biological vulnerabilities, or memory traces, based on their

Table 14.8-15
Substrates, Inhibitors, and Inducers of Some Important Cytochrome P450 Isoforms

Parameter	CYP 1A2	CYP 2C19†	CYP 2D6†	CYP 2E1	CYP 3A3/4	
% of total CYP‡	13	20 (for all 2C)	2	7	30 (for all 3A)	
Substrates	Clozapine, caffeine, tacrine, tertiary amine tricyclic (*N*-demethylation) Propranolol, theophylline	Citalopram, diazepam (N-demethylation), hexobarbital, mephobarbital, moclobemide Tertiary amine tricyclic (N-demethylation) Omeprazole (5-hydroxylation), S-mephenytoin	Codeine (hydroxylation, O-demethylation), fluoxetine (in part), haloperidol (reduction), paroxetine Secondary and tertiary amine tricyclics (2-, 8-, 10-hydroxylation), venlafaxine (O-demethylation) Type IC antiarrhythmics, β-adrenergic receptor antagonists	Ethanol Acetaminophen, chlorzoxazone, halothane, isoflurane, methoxyflurane, sevoflurane	Alprazolam, carbamazepine, clonazepam, codeine (demethylation), diazepam (hydroxylation and N-demethylation), diltiazem, midazolam, nimodipine, sertraline, triazolam Tertiary amine tricyclics (N-demethylation), verapamil	Alfentanil, amiodarone, androgens, astemizole, cyclosporine, dexamethasone, disopyramide, erythromycin, estrogens, ethosuximide, lidocaine, loratadine, lovastatin, propafenone, quinidine, terfenadine
Inhibitors	Fluvoxamine Fluoroquinolines	Ketoconazole, omeprazole	Fluoxetine, haloperidol, moclobemide, norfluoxetine, paroxetine, perphenazine, sertraline (weak), thioridazine Quinidine	Diethyldithiocarbamate (disulfiram metabolite)	Diltiazem, fluoxetine, fluvoxamine, nefazodone, norfluoxetine, verapamil	Dexamethasone, erythromycin (macrolides), gestodene, itraconazole, ketoconazole, naringenin (grapefruit)
Inducers	Cigarettes Omeprazole	Rifampin		Ethanol Isoniazid	Carbamazepine, phenobarbital	Dexamethasone, phenytoin, rifampin

† Clinically significant polymorphism reported in humans.
‡ CYP percentages from Shimada T, Yamazaki H, Mimura M, Inui Y, Guengerich FP: Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: Studies with liver microsomes of 30 Japanese and 30 Caucasians. J Pharmacol Exp Ther *270*:414, 1994.

ability to alter gene expression (Fig. 14.8-30). Preliminary data from the Stanley Foundation Bipolar Treatment Outcome Network suggest that experiences of early verbal, physical, or sexual abuse are associated with a greater incidence of early-onset bipolar disorder and ultra-ultra-rapid (ultradian) cycling; physical abuse in childhood was associated with increased mania and sexual abuse with increased suicidality.

Following stress and episode-induced changes in neurotransmission, a cascade of neurobiological effects is thought to take place that includes not only short-term adaptations but also longer-lasting alterations initiated by a variety of transcription factors, including the immediate early genes, such as the transcription factors c-*fos* and c-*jun* as well as a variety of neurotrophic factors. These transcription factors can then induce changes in the long-term regulation of late effector genes (i.e., transmitters, receptors, and neuropeptides). This type of episode-related upregulation in transcript could account for the increase in corticotropine releasing hormone (CRH) in brain and CSF of depressed patients and its associated hypercortisolemia as well as the microstructural and synaptic organization of the brain revealed in many models of maternal deprivation and learning and memory.

If this conceptualization proves correct, it suggests the potential dual importance of preventing episodes of affective illness. Not only would episode-associated morbidity and potential mortality be prevented, but the longer-lasting neurobiological vulnerabilities associated with the experience of repeated affective episodes themselves (sensitization) might be attenuated as well. Although the mechanisms and direct causality have not been clarified, greater numbers of prior mood episodes are associated with greater degrees of cognitive dysfunction on a variety of neuropsychological tests in euthymic bipolar disorder outpatients.

Thus, given the increasing evidence that greater numbers of affective episodes are a poor prognostic sign and may be associated with resistance to effective treatment with lithium, both 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 recurrence.

Treatment efficacy may thus also vary as a function of the stage of illness evolution (Fig. 14.8-29). For example, pharmacotherapies such as lithium and unimodal antidepressants may be more effective in initial and midphases of the illness, but with the emergence of rapid and ultra-rapid cycling, adjunctive treatments with the anticonvulsants may be required, with the antidepressants used more sparingly. In the latest stages of illness, sometimes associated with ultradian cycling, dihydropyridine *L*-type calcium channel inhibitors augmented by mood-stabilizing anticonvulsants may be required.

Similar transitions may occur in psychotherapeutic approaches wherein psychotherapy may be effective in the early, milder forms

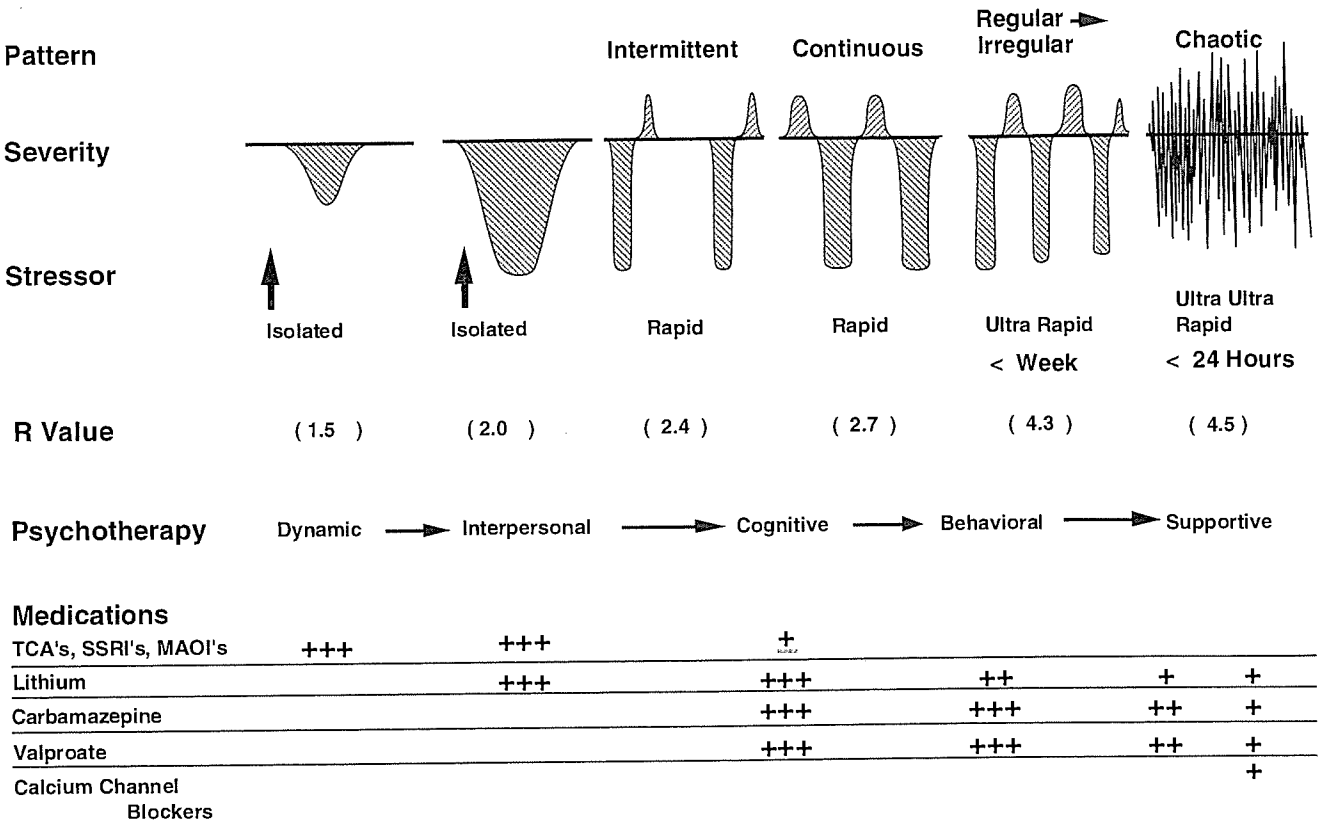

FIGURE 14.8-29 Phases in evolution of mood cycling: potential relation to treatment response.

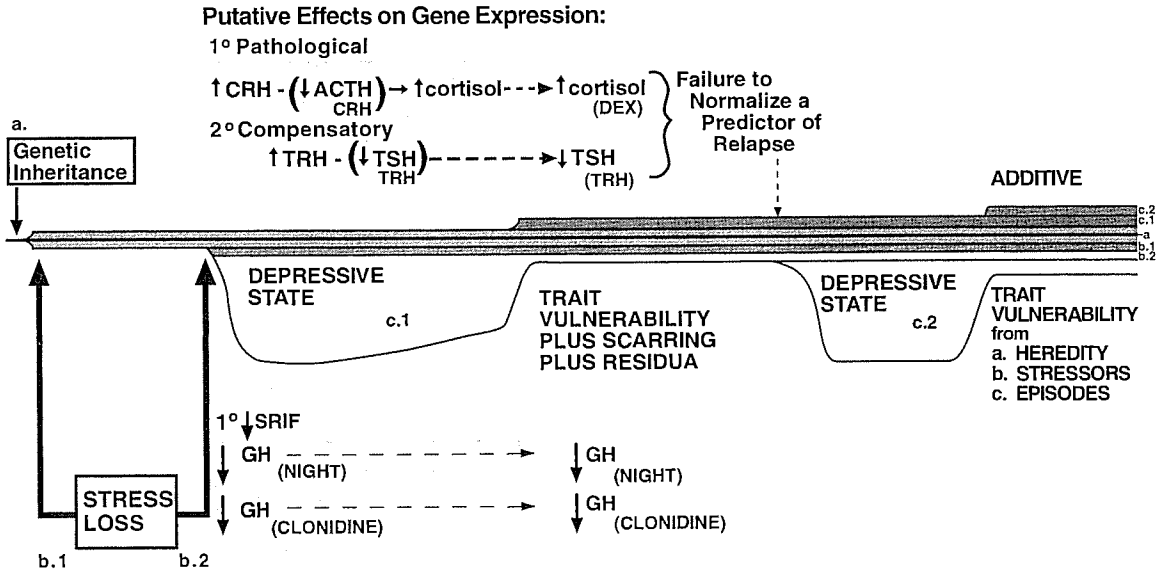

FIGURE 14.8-30 Accumulating experiential genetic vulnerability in recurrent mood disorders. CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; DEX, dexamethasone; SRIF, somatostatin release-inhibiting factor.

of stress-related depressive 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 techniques may become increasingly important in (1) the later, more automatic shifts in mood, (2) helping to maintain active treatment compliance with pharmacotherapies, (3) implementing an early intervention system based on the development of a structured early warning system; and (4) maintaining morale in the face of therapeutic adversity and incomplete response, all of which, in turn, may prevent suicide.

The past several decades have seen important advances in the understanding of the neurobiology of the depressive and bipolar dis-

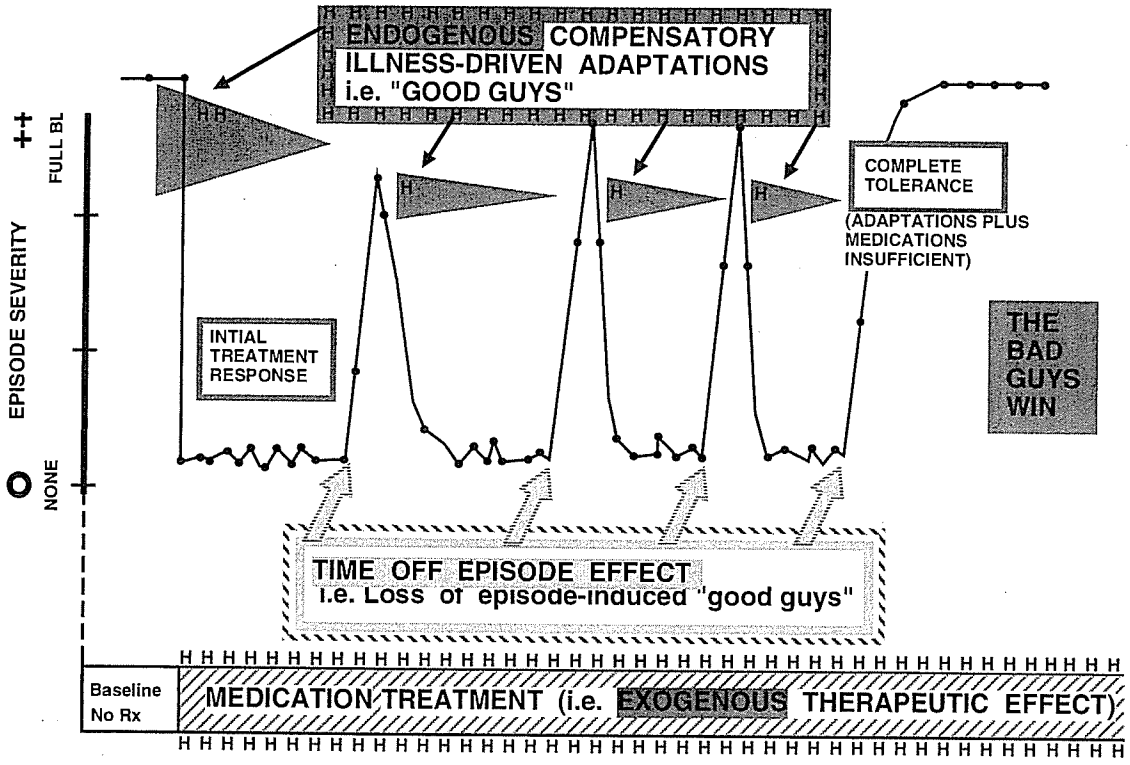

FIGURE 14.8-31 Ratio of "good guys" and "bad guys" drives episode cycling.

orders. Clearly these illnesses involve multiple areas of brain dysfunction and affect a variety of organ systems, altering not only mood, but also motor, cognitive, sleep, appetite, hedonic reward, and other somatic systems. Neurobiological alterations are evident at the level of endocrine dysfunction, reflected not only in altered regulation of glucocorticoids and CRH, TRH, and somatostatin release-inhibiting factor (SRIF) but even the size of the pituitary and the adrenals.

Some of these changes may involve episodic and cyclic alterations in gene transcription related to the primary pathology of the illness (such as increases in CRF), but others may be secondary and adaptive (e.g., increases in TRH) (Fig. 14.8-30). The author has postulated that the ratio of a host of pathological factors ("the bad guys") to the compensatory adaptations ("the good guys") determines the proportions of periods of illness versus well intervals (Fig. 14.8-31). To the extent that exogenous medications can change this ratio by either inhibiting the bad guys or enhancing the good guys, sustained remissions can be achieved, if adequate prophylactic treatment is maintained. This conceptual model based on preclinical data also predicts that clinical loss of prophylactic efficacy via development of tolerance would be delayed or prevented by (1) earlier rather than later treatment; (2) sustained full dosages rather than marginally effective ones; (3) use of the most effective agents with a wide therapeutic margin; and (4) combinations of several marginally effective agents (Table 14.8-16, Fig. 14.8-32). These propositions remain to be directly tested, however.

Functional brain imaging has revealed alterations in blood flow and glucose utilization, often reflecting hypofrontality in depression, at times in direct proportion to the severity of the depressive syndrome. Evidence of hyperactivity in the ventral anterior cingulate gyrus and the medial temporal lobes is also present in some patients, and these differential patterns may be linked to differences in thera-

Table 14.8-16
Other Clinical Predictions From the Preclinical Model of Tolerance Development

Treatment resistance slowed by
Higher dosages
Not escalating dosages
More efficacious drugs: valproate carbamazepine
Treatment initiated early in illness
Combination treatment: carbamazepine plus valproate
Reducing illness drive
Response restored by
Period of drug discontinuation then reexposure
Agents with different mechanisms of action: no cross-tolerance
Future studies → predictive validity:
Maximum tolerated dosages
Stable dosing
Differential rate of treatment resistance?
Studies by Gelenberget et al.
O'Connellet et al, Sarantidis and Waters, Denicoff et al*
Combination > monotherapy?
Treat comorbidities
Randomized study of continuation vs. discontinuation
? Response to gabapentin or lamotrigine

* Denicoff KD, Smith-Jackson EE, Disney ER, Ali SO, Leverich GS, Post RM: Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. J Clin Psychiatry *58*:470, 1997; Gelenberg AJ, Kane JM, Keller MB, Lavori P, Rosenbaum JF, 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; O'Connell RA, Mayo JA, Flatow L, Cuthbertson B, O'Brien BE: Outcome of bipolar disorder on long-term treatment with lithium. Br J Psychiatry *159*:123, 1991; Sarantidis D, Waters B: Predictors of lithium prophylaxis effectiveness. Prog Neuropsychopharmacol *5*:507, 1981.

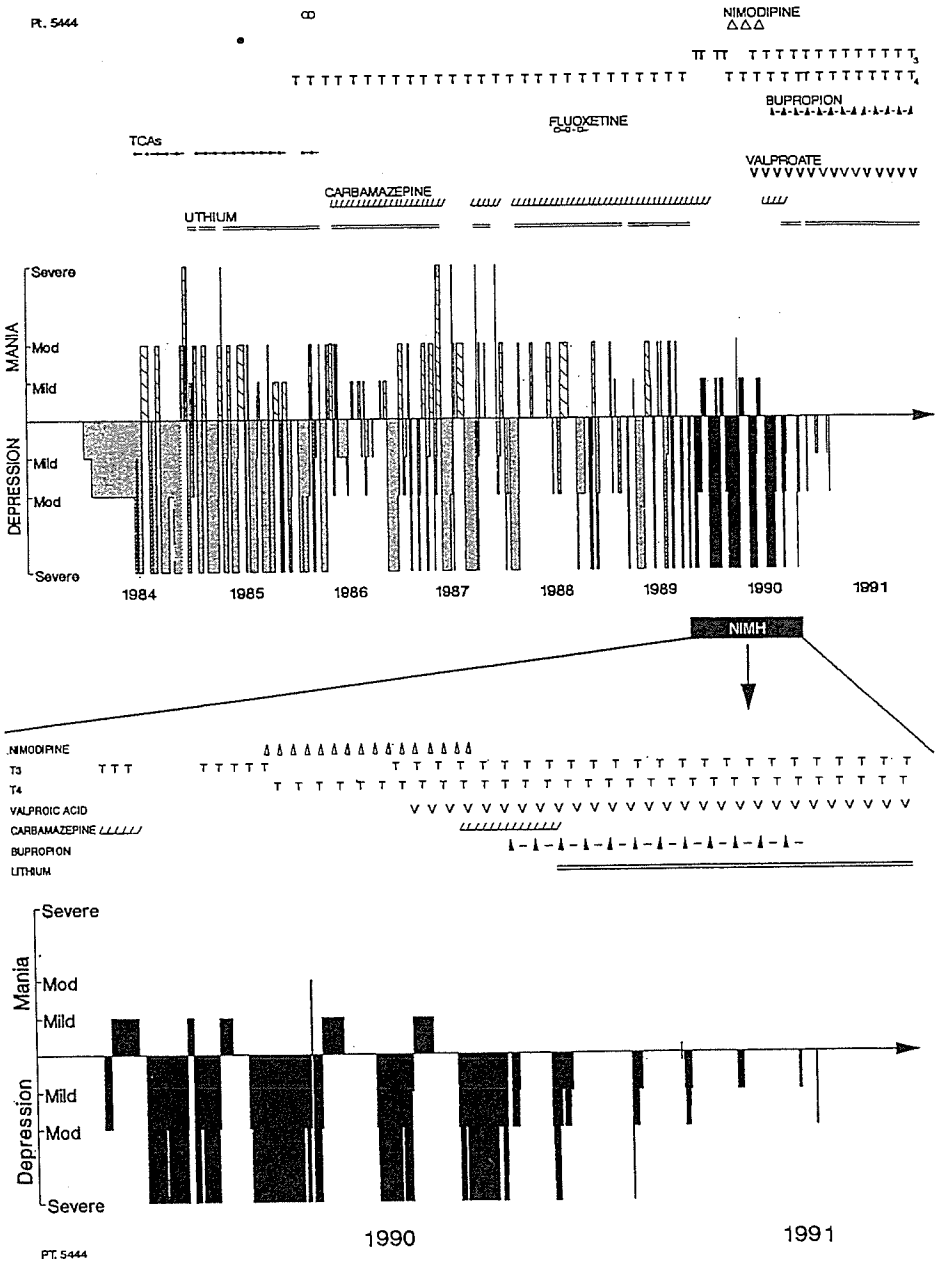

FIGURE 14.8-32 Response to combination therapy in a patient with refractory bipolar I disorder. TCAs, tricyclic antidepressants.

peutic outcome. Both patient and clinician should be aware that a wealth of clinically relevant neurobiological evidence indicates that the mood disorders are potentially life-threatening medical illnesses not different from those that afflict the other major organ systems of the body and, as such, should be treated with equal care and vigor.

FUTURE DIRECTIONS

During this most exciting era for the development of psychobiological theories and therapies for the mood disorders, one hopes for clearer definitions of the different psychotherapies and pharmacotherapies critical for adequate therapeutic intervention in individual patients whose severities, types, patterns, and stages of illness differ. Since the last half of the century, successive generations of pharmacotherapies have led to critical neurobiological hypotheses of the mechanisms underlying the mood disorders, and one hopes that a continued mutually interactive process of more specific treatments, theories, and therapies will be derived from synergistic clinical and basic research in this area.

Not only is there a wealth of information to be learned through controlled research, but each patient has much to teach the practitioner and the theoretician. Precise life charting of the course of recurrent mood disorders and its response to treatment may be invaluable to the patient and clinician in arriving at optimal therapeutics, particularly when evidence from controlled studies currently provides so little direction for most crucial decisions. Although a host of well-tested, promising treatment alternatives are now available and one can anticipate many novel interventions in the near future, a much wider systematic clinical research base is urgently needed to guide the physician to the best therapeutic regimen for each individual bipolar patient. The author hopes that some of the preliminary data, guidelines, and principles outlined in this chapter will assist in this process and that more rapid progress occurs in the study and treatment of this relatively neglected major psychiatric illness.

SUGGESTED CROSS-REFERENCES

Biological therapies are discussed in Chapter 31. Section 14.7 provides a thorough discussion of the treatment of depressive (unipolar) disorders. Obsessive-compulsive disorder is covered in Chapter 15. The rest of Chapter 14 can be consulted for other aspects of mood disorders.

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▲ 14.9 Mood Disorders: Psychotherapy

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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 and 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 needing constant reassurance, love, and admiration and being dependent on others for narcissistic gratification and maintenance of self-esteem. Frustration of these dependency needs leads to decreased self-esteem and subsequent depression. This 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.

Little empirical research has been conducted and published on psychoanalytic and psychodynamic approaches to depression. Psychotherapies have been subjected to clinical trials similar in design to those used to test new antidepressant medications. In addition, modern treatment trends have favored more-focused, short-term therapies at the expense of longer-term therapies, such as most of the psychodynamic therapies.

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.

INTERPERSONAL THERAPY (ITP)

Theoretical Concepts Interpersonal therapy 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 interpersonal therapy 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.

Interpersonal therapy 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 patients have brought on and must end by their own efforts.

The interpersonal therapy approach to depression involves three interacting components: symptom formation, social and interpersonal experiences, and enduring personality patterns. Medication may be recommended or 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 essential for recovery.

Goals Interpersonal therapy sets two therapeutic goals: (1) to reduce the patient's depressive symptoms and improve self-esteem and (2) to help the patient develop more-effective strategies for dealing with current social and interpersonal relations. As a short-term psychotherapy, interpersonal therapy does not attempt to restructure the patient's personality. It does, however, recognize the importance of early developmental experiences and assumes the importance of early developmental experiences and that historical conflicts are manifested in current relationships.

General Considerations Interpersonal therapy, 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 defiance mechanisms of 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, interpersonal therapy defines four major problem areas commonly presented by depressed patients: grief, interpersonal role disputes, role transitions, and interpersonal deficits (Table 14.9-1). Associated therapeutic goals and recommended treatment strategies are outlined for each. The choice of specific strategies and techniques depends on the problem area considered most salient for the patient. The four areas are not mutually exclusive, and patients may have multiple problems in more than one area; however, the focus is on only one or two current interpersonal problems, to allow realistic

Table 14.9-1
Focal Problem Areas of Interpersonal Therapy

Problem Areas	Definitions	General Goals and Strategies
Grief	Abnormal grief reactions occur because of failure to go through normal mourning after 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 of 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 of 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

goals and productive treatment strategies. Abnormal grief may involve delayed or distorted mourning or both. The following example is cited in the interpersonal therapy 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, 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 attempts to help the patient make the transition. That goal may include identifying 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 role dispute, the treatment strategies 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.

Table 14.9-2
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

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 longstanding 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. The following example of an interpersonal deficit is cited by the interpersonal therapy manual.

> A 22-year-old unmarried man became severely depressed 1 month after the breakup of a 3-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; subsequently, he had become depressed. Discussion of the patient's current relationship revealed that he felt close to no one but his mother.

The patient's history revealed inadequate social relationships and lack of interpersonal skills. Treatment focused on past significant relationships and 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, which was used to modify maladaptive interpersonal patterns and improve his ability to form relationships with others.

Specific Techniques The specific techniques used in interpersonal therapy 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 14.9-2).

Efficacy In depression interpersonal therapy has been tested in two large controlled studies. The first involved four groups (approxi-

mately 25 outpatients) treated by interpersonal therapy alone, interpersonal therapy plus amitriptyline (Elavil), amitriptyline alone, and a nonscheduled treatment comparison group. All active treatments, including interpersonal therapy alone, were significantly more effective in reducing depressive symptoms than nonscheduled treatment; the combination of interpersonal therapy and amitriptyline was most effective. In addition, the interpersonal therapy groups had much lower dropout rates than those without interpersonal therapy.

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: interpersonal therapy, cognitive-behavioral therapy, imipramine (Tofranil) with clinical management, and placebo with clinical management. In this study all four treatment conditions significantly reduced depressive symptoms. For severely depressed patients interpersonal therapy was significantly more effective than placebo with clinical management in achieving remission of symptoms at 16 weeks. Imipramine with clinical management tended to have the best outcome, particularly for patients with impaired functioning. Imipramine yielded more-rapid effects, with significantly better outcome than all other conditions at 12 weeks. A reanalysis of the NIMH Treatment of Depression Collaborative Research Program supported the superiority of antidepressant medication for depressions that are more severe on the basis of symptoms or psychosocial status.

Among psychotherapies, depressive severity did not appear to predict outcome to treatment. Interpersonal therapy was compared with supportive therapy in depressed human immunodeficiency virus (HIV)-positive patients. Although both treatments reduced depressive symptoms, interpersonal therapy was superior, and gains were sustained.

Interpersonal therapy has been adapted and tested in several different patient types. Interpersonal therapy late-life maintenance, developed for geriatric patients, incorporates approaches to special problems of elderly adults and allows shortened sessions for those who cannot sustain 50-minute sessions. Interpersonal therapy has been modified for use in adolescents, incorporating developmental and interpersonal issues frequently occurring in this age group.

Interpersonal therapy has also been adapted for use in chronic depression, specifically dysthymia. Pilot results from a 16-week open trial of patients with dysthymia were extremely positive in this group of difficult-to-treat patients. A version for patients with bipolar disorder includes material aimed at normalizing sleep-wake cycles, whose alterations often trigger a manic episode. Interpersonal therapy has been adapted specially for depressed patients with marital disputes. A study comparing patients randomly assigned to regular interpersonal therapy or the adapted therapy found similar reductions in depressive symptoms, but better marital outcomes (e.g., greater marital affection) in those receiving the adapted version. In addition to these modifications for different populations with depression, interpersonal therapy has been modified for use in other psychiatric disorders; among these are interpersonal counseling for distress, for hospitalized elderly patients, for substance abuse, and for bulimia nervosa.

COGNITIVE-BEHAVIORAL THERAPY

Theoretical Concepts Cognitive-behavioral therapy stems from four major previous theories: psychoanalytic theory, phenomenological philosophy, cognitive psychology, and behavioral psychology. Salient common features include recognition of the importance of the subjectiveness of conscious experience (one's perceptual experience of reality rather than the objective reality) and recognition of the emotional consequences of irrational beliefs and thoughts.

Table 14.9-3
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 external events without basis
Absolutist, dichotomous thinking	Tendency to place experience into all-or-none categories

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 14.9-3). Such cognitive dysfunctions form the core of depression, while affective and physical changes and other associated features of depression are its consequences.

Cognitive theory conceptualized depression as involving negative cognitions regarding the cognitive triad (ideas of oneself, the world, and one's future). The self is perceived as defective, inadequate, deprived, worthless, and undesirable. The world appears as a negative, demanding, and defeating place, and one expects failure and punishment, continued hardship, 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 (e.g., 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 are either all bad or all good. Symptoms of depression follow from the cognitive error. For example, apathy and low energy result from the individual's expectation of failure in all areas. Similarly, a paralysis of will stems from the individual's pessimism and feeling 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 the test negative conditions; (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 therapist in 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 empathetic, 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 14.9-4).

Didactic Aspects The didactic aspects include explaining the cognitive triad, schemas, and faulty logic to the patient. The therapist tells the patient that they will formulate hypotheses together and test them over the course of treatment. The therapist presents a full explanation of the relation 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, which involve little explanation.

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 man 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 woman thinks "that person doesn't like me" if someone passes her in the hall without saying hello.

Table 14.9-4 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
Mastering activities
Graded task assignment
Cognitive rehearsal
Self-reliance training
Role playing
Diversion techniques

TESTING AUTOMATIC THOUGHTS The therapist, acting as 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 cannot live up to these expectations.

A 32-year-old depressed computer programmer had self-denigrating thoughts about his ability to complete homework assignments.

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 problem 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 1 week of practice was unreasonable. After considering 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 2-year history of depression reported that she frequently felt sad and hurt at work because of the curt and gruff way her boss interacted with her. She reported an automatic thought following an interaction in which her boss stated "I wish things around here ran smoother." "He doesn't like me. He doesn't think I'm doing a good job." The therapist helped her 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 this unhappiness to influence how he interacted with the patient, and that he was preoccupied with personal problems that made him unhappy at work and inattentive to the way he interacted with his employees.

IDENTIFYING MALADAPTIVE ASSUMPTIONS As the patient and therapist continue to identify automatic thoughts, patterns usually become apparent that represent 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, failure, and subsequent depression.

ANALYZING MALADAPTIVE ASSUMPTIONS Testing the accuracy of maladaptive assumptions is similar to testing the validity of automatic thoughts. In one particularly effective technique the therapist asks 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, to help patients understand the inaccuracy of their cognitive assumptions and learn new strategies and ways of dealing with issues. A repertoire of behavioral techniques is used in cognitive-behavioral therapy.

1. Among the first things done is scheduling 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 their mastery of these activities and the pleasure derived from them. They are often surprised how much more mastery and pleasure they gain than they had believed.
3. To simplify the situation and allow miniaccomplishments, tasks are often subdivided into subtasks, as in graded task assignments, to show patients they can succeed.
4. In cognitive rehearsal the patient first imagines the various steps involved in meeting and mastering a challenge and then rehearses various aspects of them.
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, a particularly powerful and useful technique, is used to elicit automatic thoughts and learn new behaviors.
7. Diversion techniques help 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 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, 9 included a pill placebo, waiting list, or nonspecific treatment as a control. In most studies, cognitive-behavioral therapy was superior to the control condition in reducing depressive symptoms. The one notable exception is the NIMH Treatment of Depression Collaborative Research Program, in which cognitive-behavioral therapy did not differ significantly from the placebo clinical management condition. Cognitive-behavioral therapy was found to be superior to pharmacotherapy alone in two studies conducted in the 1970s. In three more-recent studies, including the Treatment of Depression Collaborative Research Program, there were no differences in efficacy between antidepressant medication and cognitive behavioral therapy. However, in the NIMH study, imipramine (Tofranil) was significantly more effective than cognitive-behavioral therapy for more severely depressed and impaired patients. In six studies that compared cognitive-behavior therapy alone with that therapy plus pharmacotherapy, five found no differences between the two outcomes and one found the combined treatment superior to cognitive-behavioral therapy alone.

BEHAVIORAL APPROACHES

Theoretical Concepts Although a number of behavioral approaches to depression exist, 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 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 followed by 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 below. Despite some differences in focus, behavioral 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 in determining behavioral change.

The behavioral approach was first applied to depression in 1965 by Charles B. Ferster, who proposed that depression is caused by a person's loss of positive reinforcement (e.g., 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 generating and maintaining depression (through lack of available reinforcers or when the available reinforcers are not contingent on the person's behavior) and also reversing it. Ferster also proposed that a social skills deficit—characterized by difficulty in obtaining social reinforcement—might increase a person's difficulty 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 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.

At this time behavioral approaches have been incorporated into cognitive approaches to the treatment of depression. An exception to this is the Coping with Depression Course developed by Peter Lewinsohn and colleagues at the University of Oregon, which encourages increasing the number of pleasurable events and improving social skills in a group format.

SELECTION OF TREATMENT APPROACH

The availability of several effective treatment approaches for the treatment of patients with depression means that the clinician must choose a treatment strategy for an individual patient with depression, which raises several questions. When is it appropriate to use these short-term psychotherapies as a sole treatment? Are there patients for whom the use of antidepressants, a less expensive treatment strategy, is equally or more beneficial? When is it warranted or advisable to use a combined-treatment approach including the use of psychotherapy and antidepressants simultaneously or sequentially? In addition, there is the question of whether the different types of psychotherapy might be more or less effective for different kinds of patients

A wealth of studies have examined the association between patient characteristics (including features characterizing the depression) and outcome within and across different psychotherapeutic and antidepressant treatments. Findings have often been inconsistent, but some themes have arisen that have important implications for treatment choice.

Who Should Receive Psychotherapy and Who Should Get Antidepressants? The psychotherapeutic treatment approaches described above were developed for use with outpatients with nonbipolar, nonpsychotic depressions. They were neither developed for nor intended for sole use of severely depressed inpatients or for patients with bipolar disorder depression, although evaluation of their use in combination with pharmacotherapy for such patients has begun.

Nonetheless, within the population of nonbipolar, nonpsychotic outpatients with major depressive disorder, the question of whether or not the use of psychotherapy alone can provide an outcome equal to that with antidepressants and if so, for which outpatients is a controversial subject. There is a long-standing clinical belief that antidepressants should be used for more severely depressed patients or for endogenous depressions. Findings regarding endogenous depression have been mixed, but most show that outpatients with endogenous depression (as defined by the Research Diagnostic Criteria) do not respond better to pharmacotherapy than to psychotherapy. Antidepressants are preferred for patients with melancholia marked by vegetative symptoms and psychomotor disturbances. Outpatients with major depressive disorder are characterized by a range of symptom severity and a range of impaired functioning associated with the depression. The NIMH Treatment of Depression Collaborative Research Program examined the efficacy of cognitive-behavioral therapy, interpersonal therapy, pharmacotherapy (imipramine plus clinical management), and pill placebo plus clinical management for more- and less-severely depressed outpatients with major depressive disorder. Severity was defined in two ways: one based on symptom severity and one based on symptoms and impaired functioning. For the patients with more-severe symptoms, interpersonal therapy was comparable to imipramine treatment, suggesting that interpersonal therapy may be an effective alternative treatment for patients who cannot or do not want to use medications. Imipramine treatment was superior to both psychotherapies for patients with more severely impaired functioning. Patients with less severe depression by both definitions showed no differences in response to the treatments, including placebo plus clinical management. Other studies examining the comparative efficacy of cognitive-behavioral therapy and antidepressants with more severely depressed patients (defined by symptom severity) have not found an advantage for pharmacotherapy. Such studies have not examined whether treatment differences exist for patients with more severely impaired functioning.

Choice of Psychotherapy Providing efficacious psychotherapy the treatment of depression requires trained clinicians in the various modalities. Whether different patients respond preferentially to specific forms of psychotherapy is important for several reasons, including the ability to provide more-efficient, targeted treatments as well as increasing the understanding of the mechanisms by which these treatments effect change. To date, studies examining predictors of treatment response to psychotherapy have been disappointingly inconsistent and inconclusive. Few studies have included more than one form of psychotherapy to allow examination of predictors of differential treatment response within the same study.

The NIMH study found significant interactions between treatment and pretreatment levels of social functioning and dysfunctional attitudes. Patients with relatively less impairment in social functioning responded better to interpersonal therapy than those with more impairment. Patients with lower levels of dysfunctional attitudes did better in cognitive-behavioral therapy than those with higher levels. Other studies have also shown that high scores on measures of dysfunctional attitudes predict a poorer outcome in cognitive-behavioral therapy although one study reported no association. Together these findings suggest that patients may require a minimal level of proficiency in the area of functioning that the treatment targets to benefit from the treatment, at least in the short term.

In general, the more severe the dysfunctional attitudes, the poorer the response to cognitive-behavioral therapy. Since this therapy theoretically and practically focuses on identification and reversal of negative cognitions about oneself, the world, and the future, one would expect that patients with dysfunctional attitudes would profit most from this specific therapy. Most of the studies support just the opposite conclusion. One study did find that a negative life event (e.g., divorce, or death of a loved one) mitigated this association and rendered severity of dysfunctional beliefs nonpredictive.

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 to be corrected, 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.

Role of Biological Measures Evidence is mounting that depressions associated with biological abnormalities respond

less well to psychotherapy. In a study of patients with recurrent major depression, 50 patients had normal sleep profiles and 41 had abnormal profiles (in terms of sleep efficiency, rapid eye movement [REM] latency, and REM density). All patients received short-term interpersonal therapy. Those with abnormal sleep profiles responded significantly more poorly than those with normal sleep profiles, and most nonresponders responded to subsequent pharmacotherapy. In a study of unmedicated inpatients with major depressive disorder, those with abnormally high hypothalamic-pituitary-adrenocortical activity were less responsive to cognitive-behavioral therapy than those with normal hypothalamic-pituitary-adrenocortical activity. Other investigations focused on sleep abnormalities. Reduced REM sleep latency was associated with a poor response to placebo and a favorable response to antidepressants; studies examining reduced REM latency and psychotherapy response have not shown it to predict a poorer response. Michael Thase and colleagues studied a composite measure of sleep abnormality, including REM latency, REM density, and sleep efficiency, and its association with response to cognitive-behavioral therapy or interpersonal therapy. Patients with an abnormal sleep profile have a poorer response to both forms of psychotherapy. These patients were also more likely to have recurrent episodes of depression. The abnormal sleep profiles were not simply markers of depression severity.

Some other patient characteristics have been found to predict response across treatments in general. Longer duration of the current episode and the diagnosis of dysthymic disorder prior to the onset of the major depressive disorder (double depression) predict a poorer response; higher expectations of improvement are associated with better outcomes with different forms of treatment.

Combined Pharmacotherapy and Psychotherapy

When should patients be treated with a combination of psychotherapy and pharmacotherapy? Clinical practice commonly provides both forms of treatment; the rationale is that the antidepressant medication is most effective for such vegetative symptoms as sleep disturbance, appetite disturbance, and anhedonia, while psychotherapy improves marital and family relationships, social functioning, and occupational performance. The empirical evidence supporting this belief is minimal.

Nonetheless, is combined treatment more efficacious than either treatment modality alone? Is there a subgroup of patients for whom combined treatment may be more efficacious? Is combined therapy of more benefit when a broader range of outcome measures (e.g., different aspects of functioning, time to remission, prophylactic effects) is considered? Numerous studies have compared combined treatment with single-modality treatment; sometimes pharmacotherapy alone, sometimes psychotherapy alone, and sometimes both single modalities in the same study. The results of such studies have been inconsistent but, more often than not, have shown no clear advantage to the use of combined treatment over a single modality. Results from a meta-analysis showed a modest advantage of combined treatment. More recently, data from several treatment studies of nonbipolar, nonpsychotic, major depressive disorder, using similar assessment and standardized treatment protocols, were combined in a meta-analysis of original data from the same institution, which yielded a much larger sample than previously studied. The single-modality psychotherapy protocols included either cognitive-behavioral therapy or interpersonal therapy; the combined modality was interpersonal therapy plus antidepressant pharmacotherapy. Combined treatment was not significantly more effective in the milder (less severe symptoms) depressions; however, among patients with more-severe and recurrent depressions, combined treatment was of highly significant advantage.

Thus, while no clear, definitive answers exist, evidence is accumulating that patients with milder depressions may be offered psychotherapy first. Patients with more-severe symptoms and more seriously impaired functioning should receive treatment that includes an antidepressant. Biological measures, including indicators of hypothalamic-pituitary-adrenocortical axis abnormality and sleep abnormalities, hold promise as indicators of differential treatment assignment but unfortunately are not feasible for use in most clinical settings currently. The research on combined treatment to date has focused primarily on acute-phase treatment and on simultaneous administration of both forms of treatment. The strategy of combining psychotherapy and pharmacotherapy in sequenced treatments remains to be examined. For more severe depression characterized by impaired ability to think and concentrate, for example, it may make sense to begin treatment with antidepressant treatment, adding psychotherapy when cognitive functioning and energy levels improve.

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 interpersonal therapy, cognitive-behavioral therapy, and behavioral therapy in certain groups of patients during this period. However, an episode of depression does not necessarily end when the acute symptoms have abated. In fact, symptoms may relapse if treatment is discontinued too soon after their initial control; presumably because the short-term treatment (especially pharmacotherapy) has not cured the illness but ameliorated or reduced the symptoms temporarily. This situation is analogous to the effect of insulin on diabetes mellitus. Depression is now recognized as recurrent and often chronic; therefore, withdrawal of the treatment may result in return of the illness.

An important consequence of our recognition of the long-term nature of the illness is the need for treatment beyond the acute phase, 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 in untreated patients (i.e., to the putative true end of an untreated episode). For depression, the continuation phase in pharmacological treatments generally lasts approximately 6 to 9 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 reduce the risk for future episodes or symptoms of depression. Do short-term psychotherapies confer a prophylactic effect in the future? Following a positive response, is it helpful to continue the treatments into the continuation and maintenance phases?

Prophylactic Effect of Short-Term Therapies

Follow-up studies of patients responding positively to short-term treatment for depression have attempted to determine whether treatment offers long-term prophylactic effects.

For interpersonal therapy, one study reported no difference in relapse or recurrence at 1-year follow-up among patients in a 16-week clinical trial who were treated with interpersonal therapy, ami-

triptyline, amitriptyline plus interpersonal therapy, or nonscheduled treatment. However, patients treated with interpersonal therapy had better social functioning at a 1-year reevaluation point. Most follow-up studies have examined relapse rates in patients successfully treated with cognitive therapy or antidepressant medication. These 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 difference (i.e., did the results represent enduring effects of the cognitive therapy or differences in risk for relapse between patients who respond to drugs and those who respond to psychotherapy). The question of what aspects of cognitive-behavioral therapy (specifically, behavioral activation, automatic thought modification and change of core beliefs) might be responsible for the lower relapse rates that have been observed was examined in a study providing one, two, or all three components and assessing outcome over 2 years.

Despite finding that cognitive behavioral therapy decreases symptoms and possibly lowers relapse rates, the perceived success of both psychotherapy and pharmacological treatments depends on how outcome is defined. When outcome is defined as complete remission of symptoms and maintenance of symptom-free remission for an extended period following treatment, 12 to 16 weeks of treatment (with psychotherapy or pharmacotherapy) is insufficient for most patients with major depression. The NIMH Treatment of Depression Collaborative Research Program reported the proportion of all patients starting treatment who achieved complete remission (at least 8 weeks without symptoms) at the end of treatment and maintained remission for 18 months: 30 percent of patients receiving cognitive-behavioral therapy, 26 percent of those receiving interpersonal therapy and 19 percent of those receiving placebo with clinical management. Another study of cognitive-behavioral therapy with a 2-year follow-up similarly reported that 25 percent of patients recovered and remained in remission. Considering optimal outcome highlights the need for longer treatment for full recovery as well as the need for continuation and maintenance treatments.

Treatment During the Continuation Phase Does continued treatment after successive resolution of symptoms help prevent relapses and recurrences? This clinically important question has received some attention in recent years for cognitive-behavioral therapy. In one study 42 subjects who received short-term therapy were followed for 1 year. At 3 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 received no additional treatment. The authors found no difference in relapse rates or depressive symptoms between the two groups at 1 year, suggesting that continued treatment with cognitive therapy after successful resolution of symptoms does not improve outcome. However, this is a single study, and further research is needed. There are no studies on the use of interpersonal or behavior therapy in the continuation phase. Another effectiveness study examined whether providing cognitive-behavioral therapy following successful antidepressant treatment of recurrent major depressive disorder reduced relapse rates. Cognitive-behavioral therapy reduced residual symptoms following drug discontinuation and reduced relapse rates over 2 years compared with clinical management.

Treatment During the Maintenance Phase Does therapy continued a year or more after successive treatment help prevent the occurrence of new episodes? In a landmark study by Ellen Frank and colleagues, 128 patients with recurrent major depressive disorder who had responded to a combined short-term and continuation treatment of imipramine and interpersonal therapy were randomly assigned to different maintenance treatment groups. The results strongly support long-term, continued treatment (especially pharmacotherapy) in patients with a history of recurrent episodes of depression. Some evidence indicates that long-term treatment is useful in delaying or preventing recurrences in patients with recurrent depression. However, the value of continuation and maintenance treatment with psychotherapy awaits further research.

DYSTHYMIC DISORDER AND CHRONICITY

Most of our knowledge on the treatment of depression comes from the study of patients with acute major depression, and far less is known 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 6-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 impaired quality of life associated with dysthymic disorder, which exceeds 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 adverse effects; and (3) with or without medication, the long-standing patterns of social withdrawal, lack of assertiveness, impaired 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 patient's ability 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 benefits.

More-recent developments in the treatment of dysthymic disorder include modification of psychotherapeutic approaches specifically for the treatment of dysthymic disorder as well as preliminary open-trial studies investigating their effectiveness. The chronic interpersonal and social deficits associated with dysthymic disorder provide a strong rationale for the use of interpersonal therapy with dysthymic patients, and a manual was recently developed. Aspects of dysthymic disorder that distinguish it from acute depression and require modification of interpersonal therapy include the lack of an acute precipitant, the characterological features often associated with the presence of a chronic mood disorder (e.g., 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, choosing a focus of treatment becomes more difficult. While all four interpersonal therapy problem areas occur in dysthymic patients, their frequency as a primary focus differs from that in acute depression. Grief is rarely the primary focus, interpersonal deficits more frequently are. The frequent absence of interpersonal relationships in the patient's life requires increased focus on the therapeutic relationship, which is used as a model for other interpersonal interactions.

Participation in activities is used to examine social behaviors,

expectations, and desires. Relationships that do exist are often unsatisfactory because of the difficulty these individuals have in asserting themselves, expressing anger, or setting limits. Interpersonal therapy for these patients emphasizes exploring what the patient desires from the relationships and what options are available to alter the relationships. The patient is helped to begin to identify personal needs, assert them, and set limits. The expression of anger is encouraged and supported. Preliminary support for the use of interpersonal therapy for dysthymic disorder was provided by a nonrandomized pilot study of 19 patients treated with interpersonal therapy, desipramine (Norpramin), or both.

Cognitive-behavioral therapy was adapted for patients with dysthymic disorder by James McCullough. This modification was piloted in an open study of 10 patients, 9 of whom improved substantially and sustained their remissions for 2 years. The goal of the therapy is to teach the patient to accept total responsibility for the depression and to achieve and maintain mood control by enacting adaptive daily-living strategies. The approach, cognitive-behavior therapy for the chronic depression is being tested in a multicenter random-assignment study of it and nefazodone (Serzone) alone or in combination in a sample of patients with chronic and double depression.

PSYCHOSOCIAL TREATMENT OF BIPOLAR DISORDER

The clinical and research literature on major depressive disorder is replete with both psychotherapeutic and psychopharmacological approaches. In sharp contrast, the literature on treatment of bipolar disorders focuses almost exclusively on psychopharmacology, specifically on the use of lithium (Eskalith) as the treatment of choice. The introduction of lithium has influenced the diagnostic system, clinical practice, and the therapeutic outcome of patients with bipolar disorders for 20 years. It is as close to a wonder drug as has been experienced in psychiatry.

However, lithium is far from a cure for bipolar disorders; about one-third of patients either do not respond or respond only partially. 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 disorders, 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 disorders who are on a prescribed medication regimen either do not comply fully with their doctor's instructions or discontinue treatment altogether. Physical adverse effects and the psychological unwillingness to take pills add to the noncompliance problem. Lithium noncompliance or discontinuation increases relapse. Psychotherapy combined with lithium may increase medication compliance and yield a better clinical outcome.

Adjunctive psychotherapy can also provide important educational benefits. It can help the patient and family members learn to identify early warnings of impending mania so that more-rapid interventions can occur and to identify problems that exacerbate or precipitate episodes.

Little has been written about psychotherapeutic approaches to 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 disorders. Unfortunately no empirical research has been published on the efficacy of these approaches, but they are sufficiently important that a description of each is included here. These short-term, outpatient interventions, were inspired by the well-documented success of similar programs used with schizophrenia patients.

Miklowitz and Goldstein The treatment package developed by David J. Miklowitz and Michael J. Goldstein is based on behavioral family-management techniques. Based on the premise that the family attributes considered important in predicting the course of schizophrenia are also associated with the course of bipolar disorders, the program focuses 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 substitute for a traditional medication regimen but to be adjunctive therapy. The program for patients recently discharged after an episode of hypermania includes 21 1-hour sessions conducted in the patient's home over a 9-month period. They include 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 9 months 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 treatment package developed by Monica R. Basco and A. John Rush is designed around four goals: (1) educating the patient about bipolar disorder; (2) teaching cognitive-behavioral skills for coping with the psychosocial stressors and cognitive and behavioral problems associated with manic and depressive symptoms; (3) facilitating compliance with a prescribed medication regimen; and (4) monitoring the occurrence, severity, and course of manic and depressive symptoms. The protocol is divided into three phases. The first phase, consisting of 1-hour sessions, once a week for 5 weeks, teaches the patient about the causes, systems, 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 1-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 prepare for the next session.

Investigators have developed and are currently studying the effectiveness of an adaptation of interpersonal therapy disorder for bipolar patients, called social rhythm interpersonal psychotherapy. Interpersonal interventions are integrated with a structured focus on stabilizing daily activities, including sleep, eating, work, and interpersonal interactions. This treatment is being examined in the acute and maintenance treatment of bipolar disorder patients.

SUGGESTED CROSS-REFERENCES

Information regarding related aspects of mood disorders are discussed further in the other sections of Chapter 14, Chapter 30 on psychotherapies also outlines behavioral and cognitive therapies and

other psychosocial treatments. Psychiatric treatments of adolescents are reviewed in Chapter 48, and treatments in the elderly population are included in Section 51.4. Application of psychosocial treatment to schizophrenia may be found in Section 12.9.

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