Cyclothymia

Cyclothymia is marked by manic and depressive states, yet neither are of sufficient intensity nor duration to merit a diagnosis of bipolar disorder or major depressive disorder. The diagnosis of cyclothymia is appropriate if there is a history of hypomania, but no prior episodes of mania or major depression (Table 4-5). Longitudinal followup studies indicate that the risk of bipolar disorder developing in patients with cyclothymia is about 33 percent; although 33 times greater than that for the general population, this rate of risk still is too low to justify viewing cyclothymia as merely an early manifestation of bipolar type I disorder (Howland & Thase, 1993).

Differential Diagnosis

Mood disorders are sometimes caused by general medical conditions or medications. Classic examples include the depressive syndromes associated with dominant hemispheric strokes, hypothyroidism, Cushing's disease, and pancreatic cancer (DSM-IV). Among medications associated with depression, antihypertensives and oral contraceptives are the most frequent examples. Transient depressive syndromes are also common during withdrawal from alcohol and various other drugs of abuse. Mania is not uncommon during high-dose systemic therapy with glucocorticoids and has been associated with intoxication by stimulant and sympathomimetic drugs and with central nervous system (CNS) lupus, CNS human immunodeficiency viral (HIV) infections, and nondominant hemispheric strokes or tumors. Together, mood disorders due to known physiological or medical causes may account for as many as 5 to 15 percent of all treated cases (Quitkin et al., 1993b). They often go unrecognized until after standard therapies have failed.

A challenge to diagnosticians is to balance their search for relatively uncommon disorders with their sensitivity to aspects of the medical history or review of symptoms that might have etiologic significance. For example, the onset of a depressive episode a few weeks or months after the patient has begun taking a new blood-pressure medication should raise the physician's index of suspicion. Ultimately, occult or covert medical illnesses must always be considered when an apparently clear-cut case of a mood disorder is refractory to standard treatments (Depression Guideline Panel, 1993). Cultural influences on the manifestation and diagnosis of depression are also important for the diagnostician to identify (DSM-IV). As discussed in Chapter 2, somatization is especially prevalent in individuals from ethnic minority backgrounds (Lu et al., 1995). Somatization is the expression of mental distress in terms of physical suffering.

Etiology of Mood Disorders

The etiology of depression, the mood disorder most frequently studied, is far from ideally understood. Many cases of depression are triggered by stressful life events, yet not everyone becomes depressed under such circumstances. The intensity and duration of these events, as well as each individual's genetic endowment, coping skills and reaction, and social support network contribute to the likelihood of depression. That is why depression and many other mental disorders are broadly described as the product of a complex interaction between biological and psychosocial factors (see Chapter 2). The relative importance of biological and psychosocial factors may vary across individuals and across different types of depression.

This section of the chapter describes the biological, genetic, and psychosocial factors—such as cognition, personality, and gender—that correlate with, or predispose to, depression. The discussion of genetic factors also incorporates the latest findings about bipolar disorder. Genes are implicated even more strongly in bipolar disorder than they are in major depression, galvanizing a worldwide search to identify chromosomal regions where genes may be located and ultimately to pinpoint the genes themselves (NIMH, 1998).

Biologic Factors in Depression

Much of the scientific effort expended over the past 40 years on the study of depression has been devoted to the search for biologic alterations in brain function. From the beginning, it has been recognized that the clinical heterogeneity of depression disorders may

preclude the possibility of finding a single defect. Researchers have detected abnormal concentrations of many neurotransmitters and their metabolites in urine, plasma, and cerebrospinal fluid in subgroups of patients (Thase & Howland, 1995); dysregulation of the HPA axis (Thase & Howland, 1995); elevated levels of corticotropin-releasing factor (Nemeroff, 1992, 1998; Mitchell, 1998); and, most recently, abnormalities in second messenger systems and neuroimaging (Drevets, 1998; Rush et al., 1998, Steffens & Krishnan, 1998). Much current research focuses on how *the biological abnormalities* interrelate, how they correlate with behavioral and emotional patterns that seem to distinguish one subcategory of major depression from another, and how they respond to diverse forms of therapy.

In the search for biological changes with depression, it must be understood that *a biological abnormality* reliably associated with depression may not actually be a causal factor. For example, a biologic alteration could be a consequence of sleep deprivation or weight loss. *Any biological abnormality* found in conjunction with any mental disorder may be a cause, a correlate, or a consequence, as discussed in Chapter 2. What drives research is the determination to find which of *the biological abnormalities* in depression are true causes, especially ones that might be detectable and treatable *before* the onset of clinical symptoms.

Monoamine Hypothesis

For many years the prevailing hypothesis was that depression was caused by an absolute or relative deficiency of monoamine[8] transmitters in the brain. This line of research was bolstered by the discovery many years ago that reserpine, a medication for hypertension, inadvertently caused depression. It did so by depleting the brain of both serotonin and the three principal catecholamines (dopamine, norepinephrine, and epinephrine). Such findings led to the "catecholamine hypothesis" and the "indoleamine (i.e., serotonin) hypothesis," which in due course led to an integrated "monoamine hypothesis" (Thase & Howland, 1995).

After more than 30 years of research, however, the monoamine hypothesis has been found insufficient to explain the complex etiology of depression. One problem is that many other neurotransmitter systems are altered in depression, including GABA and acetylcholine (Rush et al., 1998). Another problem is that improvement of monoamine neurotransmission with medications and lifting of the clinical signs of depression do not prove that depression actually is caused by defective monoamine neurotransmission. For example, diuretic medications do not specifically correct the physiological defect underlying congestive heart failure, but they do treat its symptoms. Neither impairment of monoamine synthesis, nor excessive degradation of monoamines, is consistently present in association with depression; monoamine precursors do not have consistent antidepressant effects, and a definite temporal lag exists between the quick elevation in monoamine levels and the symptom relief that does not emerge until weeks later (Duman et al., 1997). To account for these discrepancies, one new model of depression proposes that depression results from reductions in neurotrophic factors that are necessary for the survival and function of particular neurons, especially those found in the hippocampus (Duman et al., 1997).

Despite the problems with the hypothesis that monoamine depletion is the *primary* cause of depression, monoamine impairment is certainly one of the manifestations, or correlates, of depression. Therefore, the monoamine hypothesis remains important for treatment purposes. Many currently available pharmacotherapies that relieve depression or cause mania, or both, enhance monoamine activity. One of the foremost classes of drugs for depression, SSRIs, for example, boost the level of serotonin in the brain.

Evolving Views of Depression

An important shortcoming of the monoamine hypothesis was its inattention to the psychosocial risk factors that influence the onset and persistence of

[8] Monoamine neurotransmitters are a chemical class that includes catecholamines (norepinephrine, epinephrine, dopamine) and indoleamines (serotonin).

depressive episodes. The nature and interpretation of, and the response to, stress clearly have important causal roles in depression. The following discussion illustrates ongoing work aimed at understanding the pathophysiology of depression. While incomplete, it offers a coherent integration of the biological, psychological, and social factors that have long been associated clinically with this disorder.

Many decades ago, Hans Selye demonstrated the damaging effects of chronic stress on the HPA axis, the gastrointestinal tract, and the immune system of rats: adrenal hypertrophy, gastric ulceration, and involution of the thymus and lymph nodes (Selye, 1956). Since that time, researchers have provided ample evidence that brain function, and perhaps even anatomic structure, can be influenced by stress, interpretation of stress, and learning (Weiss, 1991; Sapolsky, 1996; McEwen, 1998). Much current research has been directed at stress, the HPA axis, and CRH in the genesis of depression.

Depression can be the outcome of severe and prolonged stress (Brown et al., 1994; Frank et al., 1994; Ingram et al., 1998). The acute stress response is characterized by heightened arousal—the fight-or-flight response—that entails mobilization of the sympathetic nervous system and the HPA axis (see Etiology of Anxiety). Many aspects of the acute stress response are exaggerated, persistent, or dysregulated in depression (Thase & Howland, 1995). Increased activity in the HPA axis in depression is viewed as the "most venerable finding in all of biological psychiatry" (Nemeroff, 1998).

Increased activity of the HPA axis, however, may be secondary to more primary causes, as was the problem with the monoamine hypothesis of depression. For this reason, much attention has been focused on CRH, which is hypersecreted in depression (Nemeroff, 1992, 1998). CRH is the neuropeptide that is released by the hypothalamus to activate the pituitary in the acute stress response. Yet there are many other sources of CRH in the brain.

CRH injections into the brain of laboratory animals produce the signs and symptoms found in depressed patients, including decreased appetite and weight loss, decreased sexual behavior and sleep, and other changes (Sullivan et al., 1998). Furthermore, CRH is found in higher concentrations in the cerebrospinal fluid of depressed patients (Nemeroff, 1998). In autopsy studies of depressed patients, CRH gene expression is elevated, and there are greater numbers of hypothalamic neurons that express CRH (Nemeroff, 1998). These findings have ignited research to uncover how CRH expression in the hypothalamus is regulated, especially by other brain centers such as the hippocampus (Mitchell, 1998). The hippocampus exerts control over the HPA axis through feedback inhibition (Jacobson & Sapolsky, 1991). Shedding light on the regulation of CRH is expected to hold dividends for understanding both anxiety and depression.

Anxiety and Depression

Anxiety and depression frequently coexist, so much so that patients with combinations of anxiety and depression are the rule rather than the exception (Barbee, 1998). And many of the medications used to treat either one are often used to treat the other. Why are anxiety and depression so interrelated?

Clues to answering this question are expected to come from similarities in antecedents, correlates, and consequences of each condition. Certainly, stressful events are frequent, although not universal, antecedents. Overlapping biochemical correlates are found, most notably, an elevation in CRH (Arborelius et al., 1999). Interestingly, one new line of research finds that long-term consequences of anxiety and depression are evident at the same anatomical site—the hippocampus. Human imaging studies of the hippocampus revealed it to have smaller volume in patients with post-traumatic stress disorder (McEwen, 1998) and in patients with recurrent depression (Sheline, 1996). In the latter study, the degree of volume reduction was correlated with the duration of major depression. In both conditions, excess glucocorticoid exposure was thought to be the culprit in inducing the atrophy of hippocampal neurons. But the complete chain of events leading up to and following the hippocampal damage is not yet known.

Psychosocial and Genetic Factors in Depression

If stressful events are the proximate causes of most cases of depression, then why is it that not all people become depressed in the face of stressful events? The answer appears to be that social, psychological, and genetic factors act together to predispose to, or protect against, depression. This section first discusses stressful life events, followed by a discussion of the factors that shape our responses to them.

Stressful Life Events

Adult life can be rife with stressful events, as noted earlier, and although not all people with depression can point to some precipitating event, many episodes of depression are associated with some sort of acute or chronic adversity (Brown et al., 1994; Frank et al., 1994; Ingram et al., 1998).

The death of a loved one is viewed as one of the most powerful life stressors. The grief that ensues is a universal experience. Common symptoms associated with bereavement include crying spells, appetite and weight loss, and insomnia. Grief, in fact, has such emotional impact that the diagnosis of depressive disorder should not be made unless there are definite complications such as incapacity, psychosis, or suicidal thoughts.

The compelling impact of past parental neglect, physical and sexual abuse, and other forms of maltreatment on both adult emotional well-being and brain function is now firmly established for depression. Early disruption of attachment bonds can lead to enduring problems in developing and maintaining interpersonal relationships and problems with depression and anxiety. Research in animals bears this out as well. In both rodents and primates, maternal deprivation stresses young animals, and a pattern of repeated, severe, early trauma from maternal deprivation may predispose an animal to a lifetime of overreactivity to stress (Plotsky et al., 1995). Conversely, early experience with mild, nontraumatic stressors (such as gentle handling) may help to protect or "immunize" animals against more pathologic responses to subsequent severe stress.

Cognitive Factors

According to cognitive theories of depression, how individuals view and interpret stressful events contributes to whether or not they become depressed. One prominent theory of depression stems from studies of learned helplessness in animals. The theory posits that depression arises from a cognitive state of helplessness and entrapment (Seligman, 1991). The theory was predicated on experiments in which animals were trained in an enclosure in which shocks were unavoidable and inescapable, regardless of avoidance measures that animals attempted. When they later were placed in enclosures in which evasive action could have succeeded, the animals were inactive, immobile, and unable to learn avoidance maneuvers. The earlier experience engendered a behavioral state of helplessness, one in which actions were seen as ineffectual.

In humans there is now ample evidence that the impact of a stressor is moderated by the personal meaning of the event or situation. In other words, the critical factor is the person's interpretation of the stressor's potential impact. Thus, an event interpreted as a threat or danger elicits a nonspecific stress response, and an event interpreted as a loss (of either an attachment bond or a sense of competence) elicits more grieflike depressive responses.

Heightened vulnerability to depression is linked to a constellation of cognitive patterns that predispose to distorted interpretations of a stressful event (Ingram et al., 1998). For example, a romantic breakup will trigger a much stronger emotional response if the affected person believes, "I am incomplete and empty without her love," or "I will never find another who makes me feel the way he does." The cognitive patterns associated with distorted interpretation of stress include relatively harsh or rigid beliefs or attitudes about the importance of romantic love or achievement (again, the centrality of love and work) as well as the tendency to attribute three specific qualities to adverse events: (1) global impact–"This event will have a *big* effect on me"; (2) internality–"*I* should have done something to prevent this," or "This is *my* fault"; and (3) irreversibility–"I'll never be able to recover from this."

According to a recent model of cognitive vulnerability to depression, negative cognitions by themselves are not sufficient to engender depression. This model postulates, on the basis of previously gathered empirical evidence, that interactions between negative cognitions and mildly depressed mood are important in the etiology and recurrences of depression. Patterns or styles of thinking stem from prior negative experiences. When they are activated by adverse life events and a mildly depressed mood, a downward spiral ensues, leading to depression (Ingram et al., 1998).

Temperament and Personality

Responses to life events also can be linked to personality (Hirschfeld & Shea, 1992). Personality may be understood in terms of one's attitudes and beliefs as well as more enduring neurobehavioral predispositions referred to as temperaments. The study of personality and temperament is gaining momentum. Neuroticism (a temperament discussed earlier in this chapter) predisposes to anxiety and depression (Clark et al., 1994). Having an easy-going temperament, on the other hand, protects against depression (IOM, 1994). Further, those with severe personality disorder are particularly likely to have a history of early adversity or maltreatment (Browne & Finkelhor, 1986).

Temperaments are not destiny, however. Parental influences and individual life experiences may determine whether a shy child remains vulnerable or becomes a healthy, albeit somewhat reserved, adult. In adults, several constellations of personality traits are associated with mood disorders: avoidance, dependence, and traits such as reactivity and impulsivity (Hirschfeld & Shea, 1992). People who have such personality traits not only cope less effectively with stressors but also tend to provoke or elicit adversity. A personality disorder or temperamental disturbance may mediate the relationship between stress and depression.

Gender

Major depressive disorder and dysthymia are more prevalent among women than men, as noted earlier. This difference appears in different cultures throughout the world (Weissman et al., 1993). Understanding the gender-related difference is complex and likely related to the interaction of biological and psychosocial factors (Blumenthal, 1994a), including differences in stressful life events as well as to personality (Nolen-Hoeksema et al., in press).

Keys to understanding the sex-related difference in rates in the United States may be found in two types of epidemiologic findings: (1) there are no sex-related differences in rates of bipolar disorder (type I) (NIMH, 1998) and, (2) within the agrarian culture of the Old Order Amish of Lancaster, Pennsylvania, the rate of major depressive disorder is both low (i.e., comparable to that of bipolar disorder)[9] and equivalent for men and women (Egeland et al., 1983). Something about the environment thus appears to interact with a woman's biology to cause a disproportionate incidence of depressive episodes among women (Blumenthal, 1994a).

Research conducted in working-class neighborhoods suggests that the combination of life stress and inadequate social support contributes to women's greater susceptibility to depressive symptoms (Brown et al., 1994). Because women tend to use more ruminative ways of coping (e.g., thinking and talking about a problem, rather than seeking out a distracting activity) and, on average, have less economic power, they may be more likely to perceive their problems as less solvable. That perception increases the likelihood of feeling helpless or entrapped by one's problem. Subtle sex-related differences in hemispheric processing of emotional material may further predispose women to experience emotional stressors more intensely (Baxter et al., 1987). Women are also more likely than men to have experienced past sexual abuse; as noted earlier in this chapter, physical and sexual abuse is strongly associated with the subsequent development of major depressive disorder. Women's greater vulnerability to depression may be amplified by endocrine and reproductive cycling, as well as by a

[9] A small, albeit noteworthy, sex-related difference is seen in the higher incidence of rapid-cycling bipolar disorder in women (cited in Blumenthal, 1994).

greater susceptibility to hypothyroidism (Thase & Howland, 1995). Menopause, on the other hand, has little bearing on gender differences in depression. Contrary to popular beliefs, menopause does not appear to be associated with increased rates of depression in women (Pearlstein et al., 1997). Untreated mental health problems are likely to worsen at menopause, but menopause by itself is not a risk factor for depression (Pearce et al., 1995; Thacker, 1997). The increased risk for depression prenatally or after childbirth suggests a role for hormonal influences, although evidence also exists for the role of stressful life events. In short, psychosocial and environmental factors likely interact with biological factors to account for greater susceptibility to depression among women.

Poor young women (white, black, and Hispanic) appear to be at the greatest risk for depression compared with all other population groups (Miranda & Green, 1999). They have disproportionately higher rates of past exposure to trauma, including rape, sexual abuse, crime victimization, and physical abuse; poorer support systems; and greater barriers to treatment, including financial hardship and lack of insurance (Miranda & Green, 1999). Many of the same problems apply to single mothers, whose risk of depression is double that of married mothers (Brown & Moran, 1997).

The *interaction* between stressful life events, individual experiences, and genetic factors also plays a role in the etiology of depression in women. Some research suggests that genetic factors, which are discussed below, may alter women's sensitivity to the depression-inducing effect of stressful life events (Kendler et al., 1995). A recent report of depression in a sample of 2,662 twins found genetic factors in depression to be stronger for women than men, for whom depression was only weakly familial. For both genders, individual environmental experiences played a large role in depression (Bierut et al., 1999).

Genetic Factors in Depression and Bipolar Disorder

Depression, and especially bipolar disorder, clearly tend to "run in families," and a definite association has been scientifically established (Tsuang & Faraone, 1990). Numerous investigators have documented that susceptibility to a depressive disorder is twofold to fourfold greater among the first-degree relatives of patients with mood disorder than among other people (Tsuang & Faraone, 1990). The risk among first-degree relatives of people with bipolar disorder is about six to eight times greater. Some evidence indicates that first-degree relatives of people with mood disorders are also more susceptible than other people to anxiety and substance abuse disorders (Tsuang & Faraone, 1990).

Remarkable as those statistics may be, they do not by themselves prove a genetic connection. Inasmuch as first-degree relatives typically live in the same environment, share similar values and beliefs, and are subject to similar stressors, the vulnerability to depression could be due to nurture rather than nature. One method to distinguish environmental from genetic factors is to compare concordance rates among same-sex twins. At least in terms of simple genetic theory, a solely hereditary trait that appears in one member of a set of identical (monozygotic) twins also should always appear in the other twin, whereas the trait should appear only 50 percent of the time in same-sex fraternal (dizygotic) twins.

The results of studies comparing the prevalence of depression among twins vary, depending on the specific mood disorder, the age of the study population, and the way the depression is defined. In all instances, however, the reported concordance for mood disorders is greater among monozygotic than among dizygotic twins, and often the proportion is 2 to 1 (Tsuang & Faraone, 1990). In Denmark, Bertelsen and colleagues (1977) found that among 69 monozygotic twins with bipolar illness, 46 co-twins also had bipolar disorder and 14 other co-twins had psychoses, affective personality disorders, or had died by suicide. In studies of monozygotic twins reared separately ("adopted away"), the results also revealed an increased risk of depression and bipolar disorder compared with controls (Mendlewicz & Rainer 1977; Wender et al., 1986). Within the major depressive disorder grouping, greater heritable risk has been associated with more severe, recurrent, or psychotic forms of mood disorders

(Tsuang & Faraone, 1990). Those at greater heritable risk also appear more vulnerable to stressful life events (Kendler et al., 1995).

The availability of modern molecular genetic methods now allows the translation of clinical associations into identification of specific genes (McInnis, 1993; Baron, 1997). Evidence collected to date strongly suggests that vulnerability to mood disorders may be associated with several genes distributed among various chromosomes. For bipolar disorder, numerous distinct chromosomal regions (called loci) show promise, yet the complex nature of inheritance and methodological problems have encumbered investigators (Baron, 1997). Heritability in some cases may be sex linked or vary depending on whether the affected parent is the father or mother of the individual being studied. The genetic process of anticipation (which has been associated with an expansion of trinucleotide repeats) may further alter the expression of illness across generations (McInnis, 1993). Thus, the genetic complexities of the common depressive disorders ultimately may rival their clinical heterogeneity (Tsuang & Faraone, 1990).

Based on a comprehensive review of the genetics literature, the National Institute of Mental Health Genetics Workgroup recently evaluated several mood disorders according to their readiness for large-scale genetics research initiatives. Bipolar disorder was rated in the highest category, meaning that the evidence was strong enough to justify large-scale molecular genetic studies. Depression, eating disorders, obsessive-compulsive disorder, and panic disorder were rated in the second highest category, which called for nonmolecular genetic and/or epidemiological studies to document further their estimated heritability (NIMH, 1998).

Treatment of Mood Disorders

So much is known about the assortment of pharmacological and psychosocial treatments for mood disorders that the most salient problem is not with treatment, but rather with getting people *into* treatment.

Surveys consistently document that a majority of individuals with depression receive no specific form of treatment (Katon et al., 1992; Narrow et al., 1993; Wells et al., 1994; Thase, 1996). Nearly 40 percent of people with bipolar disorder are untreated in 1 year, according to the Epidemiologic Catchment Area survey (Regier et al., 1993). Undertreatment of mood disorders stems from many factors, including societal stigma, financial barriers to treatment, underrecognition by health care providers, and underappreciation by consumers of the potential benefits of treatment (e.g., Regier et al., 1988; Wells et al., 1994; Hirschfeld et al., 1997). The symptoms of depression, such as feelings of worthlessness, excessive guilt, and lack of motivation, also deter consumers from seeking treatment; and members of racial and ethnic minority groups often encounter special barriers, as discussed in Chapter 2.

Mood disorders have profoundly deleterious consequences on well-being: their toll on quality of life and economic productivity matches that of heart disease and is greater than that of peptic ulcer, arthritis, hypertension, or diabetes (Wells et al., 1989).

Stages of Therapy

The treatment of mood disorders is complex because it involves several stages: acute, continuation, and maintenance stages. The stages apply to pharmacotherapy and psychosocial therapy alike. Most patients pass through these stages to restore full functioning.

Acute Phase Therapy

Acute phase treatment with either psychotherapy or pharmacotherapy covers the time period leading up to an initial treatment response. A treatment response is defined by a significant reduction (i.e., ≥ 50 percent) in symptom severity, such that the patient no longer meets syndromal criteria for the disorder (Frank et al., 1991b). The acute phase for medication typically requires 6 to 8 weeks (Depression Guideline Panel, 1993), during which patients are seen weekly or biweekly for monitoring of symptoms, side effects, dosage adjustments, and support (Fawcett et al., 1987). Psychotherapies during the acute phase for depression typically consist of 6 to 20 weekly visits.

Outpatient Treatment. In outpatient clinical trials, about 50 to 70 percent of depressed patients who complete treatment respond to either antidepressants or psychotherapies (Depression Guideline Panel, 1993). An acute treatment response includes the effects of placebo expectancy, spontaneous remission, and active treatment. The magnitude of the active treatment effect may be estimated from randomized clinical trials by subtracting the placebo response rate from that of active medication. Overall, the active treatment effect for major depression typically ranges from 20 to 40 percent, after accounting for a placebo response rate of about 30 percent (Depression Guideline Panel, 1993). Although psychotherapy trials do not employ placebos in the form of an inert pill, they do rely on comparisons of active treatment with psychological placebos (e.g., a form of therapy inappropriate for a given disorder), a comparison form of treatment, or wait list (i.e., no therapy). The figures cited above must be understood as rough averages. The efficacy of specific pharmacotherapies and psychotherapies is covered later in this section.

Acute phase therapy is often compromised by patients leaving treatment. Attrition rates from clinical trials often are as high as 30 to 40 percent, and rates of nonadherence[10] are even higher (Depression Guideline Panel, 1993). Medication side effects are a factor, as are other factors such as inadequate psychoeducation (resulting in unrealistic expectations about treatment), ambivalence about seeing a therapist or taking medication, and practical roadblocks (e.g., the cost or accessibility of services).

Another problem is clinician failure to monitor symptomatic response and to change treatments in a timely manner. Antidepressants should be changed if there is no clear effect within 4 to 6 weeks (Nierenberg et al., 1995; Quitkin et al., 1996). Similar data are not available for psychotherapies, but revisions to the treatment plan should be considered, including the addition of antidepressant medication, if there is no symptomatic improvement within 3 or 4 months (Depression Guideline Panel, 1993).

Acute Inpatient Treatment. Hospitalization for acute treatment of depression is necessary for about 5 to 10 percent of major depressive episodes and for up to 50 percent of manic episodes. The principal reasons for hospitalization are overwhelming severity of symptoms and functional incapacity and suicidal or other life-threatening behavior. Hospital median lengths of stay now are about 5 to 7 days for depression and 9 to 14 days for mania. Such abbreviated stays have reduced costs but necessitate greater transitional or aftercare services. Few severely depressed or manic people are in remission after only 1 to 2 weeks of treatment.

Electroconvulsive Therapy. As described above, first-line treatment for most people with depression today consists of antidepressant medication, psychotherapy, or the combination (Potter et al., 1991; Depression Guideline Panel, 1993). In situations where these options are not effective or too slow (for example, in a person with delusional depression and intense, unremitting suicidality) electroconvulsive therapy (ECT) may be considered. ECT, sometimes referred to as *electroshock* or *shock treatment,* was developed in the 1930s based on the mistaken belief that epilepsy (seizure disorder) and schizophrenia could not exist at the same time in an individual. Accumulated clinical experience—later confirmed in controlled clinical trials, which included the use of simulated or "sham" ECT as a control (Janicak et al., 1985)—determined ECT to be highly effective against severe depression, some acute psychotic states, and mania (Small et al., 1988). No controlled study has shown any other treatment to have superior efficacy to ECT in the treatment of depression (Janicak et al., 1985; Rudorfer et al., 1997). ECT has not been demonstrated to be effective in dysthymia, substance abuse, or anxiety or personality disorders. The foregoing conclusions, and many of those discussed below, are the products of review of extensive research conducted over several decades (Depression Guideline Panel, 1993; Rudorfer et al., 1997) as well as by an independent panel of

[10] Nonadherence is defined as lack of adherence to prescribed activities such as keeping appointments, taking medication, and completing assignments.

scientists, practitioners, and consumers (NIH & NIMH Consensus Conference, 1985).

ECT consists of a series of brief generalized seizures induced by passing an electric current through the brain by means of two electrodes placed on the scalp. A typical course of ECT entails 6 to 12 treatments, administered at a rate of three times per week, on either an inpatient or outpatient basis. The exact mechanisms by which ECT exerts its therapeutic effect are not yet known. The production of an adequate, generalized seizure using the proper amount of electrical stimulation at each treatment session is required for therapeutic efficacy (Sackheim et al., 1993).

With the development of effective medications for the treatment of major mental disorders a half-century ago, the need for ECT lessened but did not disappear. Prior to that time, ECT often had been administered for a variety of conditions for which it is not effective, and administered without anesthesia or neuromuscular blockade. The result was grand mal seizures that could produce injuries and even fractures. Despite the availability of a range of effective antidepressant medications and psychotherapies, as discussed above, ECT continues to be used (Rosenbach et al., 1997), occupying a narrower but important niche. It is generally reserved for the special circumstances where the usual first-line treatments are ineffective or cannot be taken, or where ECT is known to be particularly beneficial, such as depression or mania accompanied by psychosis or catatonia (NIH & NIMH Consensus Conference, 1985; Depression Guideline Panel, 1993; Potter & Rudorfer, 1993). Examples of specific indications include depression unresponsive to multiple medication trials, or accompanied by a physical illness or pregnancy, which renders the use of a usually preferred antidepressant dangerous to the patient or to a developing fetus. Under such circumstances, carefully weighing risks and benefits, ECT may be the safest treatment option for severe depression. It should be administered under controlled conditions, with appropriate personnel (Rudorfer et al., 1997).

Although the average 60 to 70 percent response rate seen with ECT is comparable to that obtained with pharmacotherapy, there is evidence that the antidepressant effect of ECT occurs faster than that seen with medication, encouraging the use of ECT where depression is accompanied by potentially uncontrollable suicidal ideas and actions (Rudorfer et al., 1997). However, ECT does not exert a long-term protection against suicide. Indeed, it is now recognized that a single course of ECT should be regarded as a short-term treatment for an acute episode of illness. To sustain the response to ECT, continuation treatment, often in the form of antidepressant and/or mood stabilizer medication, must be instituted (Sackeim, 1994). Individuals who repeatedly relapse following ECT despite continuation medication may be candidates for maintenance ECT, delivered on an outpatient basis at a rate of one treatment weekly to as infrequently as monthly (Sackeim, 1994; Rudorfer et al., 1997).

The major risks of ECT are those of brief general anesthesia, which was introduced along with muscle relaxation and oxygenation to protect against injury and to reduce patient anxiety. There are virtually no absolute health contraindications precluding its use where warranted (Potter & Rudorfer, 1993; Rudorfer et al., 1997).

The most common adverse effects of this treatment are confusion and memory loss for events surrounding the period of ECT treatment. The confusion and disorientation seen upon awakening after ECT typically clear within an hour. More persistent memory problems are variable. Most typical with standard, bilateral electrode placement (one electrode on each side of the head) has been a pattern of loss of memories for the time of the ECT series and extending back an average of 6 months, combined with impairment with learning new information, which continues for perhaps 2 months following ECT (NIH & NIMH Consensus Conference, 1985). Well-designed neuropsychological studies have consistently shown that by several months after completion of ECT, the ability to learn and remember are normal (Calev, 1994). Although most patients return to full functioning following successful ECT, the degree of post-treatment memory impairment and resulting impact on functioning are highly variable

across individuals (NIH & NIMH Consensus Conference, 1985; CMHS, 1998). While clearly the exception rather than the rule, no reliable data on the incidence of severe post-ECT memory impairment are available. Fears that ECT causes gross structural brain pathology have not been supported by decades of methodologically sound research in both humans and animals (NIH & NIMH Consensus Conference, 1985; Devanand et al., 1994; Weiner & Krystal, 1994; Greenberg, 1997; CMHS, 1998). The decision to use ECT must be evaluated for each individual, weighing the potential benefits and known risks of all available and appropriate treatments in the context of informed consent (NIH & NIMH Consensus Conference, 1985).

Advances in treatment technique over the past generation have enabled a reduction of adverse cognitive effects of ECT (NIH & NIMH Consensus Conference, 1985; Rudorfer et al., 1997). Nearly all ECT devices deliver a lower current, *brief-pulse* electrical stimulation, rather than the original sine wave output; with a brief pulse electrical wave, a therapeutic seizure may be induced with as little as one-third the electrical power as with the older method, thereby reducing the potential for confusion and memory disturbance (Andrade et al., 1998). Placement of both stimulus electrodes on one side of the head ("unilateral" ECT), over the nondominant (generally right) cerebral hemisphere, results in delivery of the initial electrical stimulation away from the primary learning and memory centers. According to several controlled trials, unilateral ECT is associated with virtually no detectable, persistent memory loss (Horne et al., 1985; NIH Consensus Conference, 1985; Rudorfer et al., 1997). However, most clinicians find unilateral ECT less potent and more slowly acting an intervention than conventional bilateral ECT, particularly in the most severe cases of depression or in mania. One approach that is sometimes used is to begin a trial of ECT with unilateral electrode placement and switch to bilateral treatment after about six treatments if there has been no response. Research has demonstrated that the relationship of electrical dose to clinical response differs depending on electrode placement; for bilateral ECT, as long as an adequate seizure is obtained, any additional dosage will merely add to the cognitive toxicity, whereas for unilateral electrode placement, a therapeutic effect will not be achieved unless the electrical stimulus is more than minimally above the seizure threshold (Sackeim et al., 1993). Even a moderately high electrical dosage in unilateral ECT still has fewer cognitive adverse effects than bilateral ECT. On the other hand, high-dose bilateral ECT may be unnecessarily risky and may be a preventable cause of severe memory impairment. Some types of medication, such as lithium, also add to confusion and cognitive impairment when given during a course of ECT and are best avoided. Medications that raise the seizure threshold and make it harder to obtain a therapeutic effect from ECT, including anticonvulsants and some minor tranquilizers, may also need to be tapered or discontinued.

Informed consent is an integral part of the ECT process (NIH & NIMH Consensus Conference, 1985). The potential benefits and risks of this treatment, and of available alternative interventions, should be carefully reviewed and discussed with patients and, where appropriate, family or friends. Prospective candidates for ECT should be informed, for example, that its benefits are short-lived without active continuation treatment, and that there may be some risk of permanent severe memory loss after ECT. In most cases of depression, the benefit-to-risk ratio will favor the use of medication and/or psychotherapy as the preferred course of action (Depression Guideline Panel, 1993). Where medication has not succeeded, or is fraught with unusual risk, or where the potential benefits of ECT are great, such as in delusional depression, the balance of potential benefits to risks may tilt in favor of ECT. Active discussion with the treatment team, supplemented by the growing amount of printed and videotaped information packages for consumers, is necessary in the decisionmaking process, both prior to and throughout a course of ECT. Consent may be revoked at any time during a series of ECT sessions.

Although many people have fears related to stories of forced ECT in the past, the use of this modality on an involuntary basis today is uncommon. Involuntary

ECT may not be initiated by a physician or family member without a judicial proceeding. In every state, the administration of ECT on an involuntary basis requires such a judicial proceeding at which patients may be represented by legal counsel. As a rule, such petitions are granted only where the prompt institution of ECT is regarded as potentially lifesaving, as in the case of a person who is in grave danger because of lack of food or fluid intake caused by catatonia. Recent epidemiological surveys show that the modern use of ECT is generally limited to evidence-based indications (Hermann et al., 1999). Indeed, concern has been raised that in some settings, particularly in the public sector and outside major metropolitan areas, ECT may be underutilized due to the wide variability in the availability of this treatment across the country (Hermann et al., 1995). Consequently, minority patients tend to be underrepresented among those receiving ECT (Rudorfer et al., 1997).

On balance, the evidence supports the conclusion that modern ECT is among those treatments effective for the treatment of select severe mental disorders, when used in accord with current standards of care, including appropriate informed consent.

Continuation Phase Therapy

Successful acute phase antidepressant pharmacotherapy or ECT should almost always be followed by at least 6 months of continued treatment (Prien & Kupfer, 1986; Depression Guideline Panel, 1993; Rudorfer et al., 1997). During this phase, known as the continuation phase, most patients are seen biweekly or monthly. The primary goal of continuation pharmacotherapy is to prevent relapse (i.e., an exacerbation of symptoms sufficient to meet syndromal criteria). Continuation pharmacotherapy reduces the risk of relapse from 40-60 percent to 10-20 percent (Prien & Kupfer, 1986; Thase, 1993). Relapse despite continuation pharmacotherapy might suggest either nonadherence (Myers & Branthwaithe, 1992) or loss of a placebo response (Quitkin et al., 1993a).

A second goal of continuation pharmacotherapy is consolidation of a response into a complete remission and subsequent recovery (i.e., 6 months of sustained remission). A remission is defined as a complete resolution of affective symptoms to a level similar to healthy people (Frank et al., 1991a). As residual symptoms are associated with increased relapse risk (Keller et al., 1992; Thase et al., 1992), recovery should be achieved before withdrawing antidepressant pharmacotherapy.

Many psychotherapists similarly taper a successful course of treatment by scheduling several sessions (every other week or monthly) prior to termination. There is some evidence, albeit weak, that relapse is less common following successful treatment with one type of psychotherapy—cognitive-behavioral therapy—than with antidepressants (Kovacs et al., 1981; Blackburn et al., 1986; Simons et al., 1986; Evans et al., 1992). If confirmed, this advantage may offset the greater short-term costs of psychotherapy.

Maintenance Phase Therapies

Maintenance pharmacotherapy is intended to prevent future recurrences of mood disorders (Kupfer, 1991; Thase, 1993; Prien & Kocsis, 1995). A recurrence is viewed as a new episode of illness, in contrast to relapse, which represents reactivation of the index episode (Frank et al., 1991a). Maintenance pharmacotherapy is typically recommended for individuals with a history of three or more depressive episodes, chronic depression, or bipolar disorder (Kupfer, 1991; Thase, 1993; Prien & Kocsis, 1995). Maintenance pharmacotherapy, which may extend for years, typically requires monthly or quarterly visits.

Longer term, preventive psychotherapy to prevent recurrences has not been studied extensively. However, in one study of patients with highly recurrent depression, monthly sessions of interpersonal psychotherapy were significantly more effective than placebo but less effective than pharmacotherapy (Frank et al., 1991a).

Specific Treatments for Episodes of Depression and Mania

This section describes specific types of pharmacotherapies and psychosocial therapies for *episodes* of depression and mania. Treatment generally targets

symptom patterns rather than specific disorders. Differences in the treatment strategy for unipolar and bipolar depression are described where relevant.

Treatment of Major Depressive Episodes

Pharmacotherapies

Antidepressant medications are effective across the full range of severity of major depressive episodes in major depressive disorder and bipolar disorder (American Psychiatric Association, 1993; Depression Guideline Panel, 1993; Frank et al., 1993). The degree of effectiveness, however, varies according to the intensity of the depressive episode. With mild depressive episodes, the overall response rate is about 70 percent, including a placebo rate of about 60 percent (Thase & Howland, 1995). With severe depressive episodes, the overall response rate is much lower, as is the placebo rate. For example, with psychotic depression, the overall response rate to any one drug is only about 20 to 40 percent (Spiker, 1985), including a placebo response rate of less than 10 percent (Spiker & Kupfer, 1988; Schatzberg & Rothschild, 1992). Psychotic depression is treated with either an antidepressant/antipsychotic combination *or* ECT (Spiker, 1985; Schatzberg & Rothschild, 1992).

There are four major classes of antidepressant medications. The tricyclic and heterocyclic antidepressants (TCAs and HCAs) are named for their chemical structure. The MAOIs and SSRIs are classified by their initial neurochemical effects. In general, MAOIs and SSRIs increase the level of a target neurotransmitter by two distinct mechanisms. But, as discussed below, these classes of medications have many other effects. They also have some differential effects depending on the race or ethnicity of the patient.

The mode of action of antidepressants is complex and only partly understood. Put simply, most antidepressants are designed to heighten the level of a target neurotransmitter at the neuronal synapse. This can be accomplished by one or more of the following therapeutic actions: boosting the neurotransmitter's synthesis, blocking its degradation, preventing its reuptake from the synapse into the presynaptic neuron, or mimicking its binding to postsynaptic receptors. To make matters more complicated, many antidepressant drugs affect more than one neurotransmitter. Explaining how any one drug alleviates depression probably entails multiple therapeutic actions, direct and indirect, on more than one neurotransmitter system (Feighner, 1999).

Selection of a particular antidepressant for a particular patient depends upon the patient's past treatment history, the likelihood of side effects, safety in overdose, and expense (Depression Guideline Panel, 1993). A vast majority of U.S. psychiatrists favor the SSRIs as "first-line" medications (Olfson & Klerman, 1993). These agents are viewed more favorably than the TCAs because of their ease of use, more manageable side effects, and safety in overdose (Kapur et al., 1992; Preskorn & Burke, 1992). Perhaps the major drawback of the SSRIs is their expense: they are only available as name brands (until 2002 when they begin to come off patent). At minimum, SSRI therapy costs about $80 per month (Burke et al., 1994), and patients taking higher doses face proportionally greater costs.

Four SSRIs have been approved by the FDA for treatment of depression: fluoxetine, sertraline, paroxetine, and citalopram. A fifth SSRI, fluvoxamine, is approved for treatment of obsessive-compulsive disorder, yet is used off-label for depression.[11] There are few compelling reasons to pick one SSRI over another for treatment of uncomplicated major depression, because they are more similar than different (Aguglia et al., 1993; Schone & Ludwig, 1993; Tignol, 1993; Preskorn, 1995). There are, however, several distinguishing pharmacokinetic differences between SSRIs, including elimination half-life (the time it takes for the plasma level of the drug to decrease 50 percent from steady-state), propensity for drug-drug interactions (e.g., via inhibition of hepatic enzymes), and antidepressant activity of metabolite(s) (DeVane, 1992). In general, SSRIs are more likely to be

[11] Technically, FDA approves drugs for a selected indication (a disorder in a certain population). However, once the drug is marketed, doctors are at liberty to prescribe it for unapproved (off-label) indications.

metabolized more slowly by African Americans and Asians, resulting in higher blood levels (Lin et al., 1997).

The SSRIs as a class of drugs have their own class-specific side effects, including nausea, diarrhea, headache, tremor, daytime sedation, failure to achieve orgasm, nervousness, and insomnia. Attrition from acute phase therapy because of side effects is typically 10 to 20 percent (Preskorn & Burke, 1992). The incidence of treatment-related suicidal thoughts for the SSRIs is low and comparable to the rate observed for other antidepressants (Beasley et al., 1991; Fava & Rosenbaum, 1991), despite reports to the contrary (Breggin & Breggin, 1994).

Some concern persists that the SSRIs are less effective than the TCAs for treatment of severe depressions, including melancholic and psychotic subtypes (Potter et al., 1991; Nelson, 1994). Yet there is no definitive answer (Danish University Antidepressant Group, 1986, 1990; Pande & Sayler, 1993; Roose et al., 1994; Stuppaeck et al., 1994).

Side effects and potential lethality in overdose are the major drawbacks of the TCAs. An overdose of as little as 7-day supply of a TCA can result in potentially fatal cardiac arrhythmias (Kapur et al., 1992). TCA treatment is typically initiated at lower dosages and titrated upward with careful attention to response and side effects. Doses for African Americans and Asians should be monitored more closely, because their slower metabolism of TCAs can lead to higher blood concentrations (Lin et al., 1997). Similarly, studies also suggest that there may be gender differences in drug metabolism and that plasma levels may change over the course of the menstrual cycle (Blumenthal, 1994b).

In addition to the four major classes of antidepressants are bupropion, which is discussed below, and three newer FDA-approved antidepressants that have mixed or compound synaptic effects. Venlafaxine, the first of these newer antidepressants, inhibits reuptake of both serotonin and, at higher doses, norepinephrine. In contrast to the TCAs, venlafaxine has somewhat milder side effects (Bolden-Watson & Richelson, 1993), which are like those of the SSRIs. Venlafaxine also has a low risk of cardiotoxicity and, although experience is limited, it appears to be less toxic than the others in overdose. Venlafaxine has shown promise in treatment of severe (Guelfi et al., 1995) or refractory (Nierenberg et al., 1994) depressive states and is superior to fluoxetine in one inpatient study (Clerc et al., 1994). Venlafaxine also occasionally causes increased blood pressure, and this can be a particular concern at higher doses (Thase, 1998).

Nefazodone, the second newer antidepressant, is unique in terms of both structure and neurochemical effects (Taylor et al., 1995). In contrast to the SSRIs, nefazodone improves sleep efficiency (Armitage et al., 1994). Its side effect profile is comparable to the other newer antidepressants, but it has the advantage of a lower rate of sexual side effects (Preskorn, 1995). The more recently FDA-approved antidepressant, mirtazapine, blocks two types of serotonin receptors, the 5-HT_2 and 5-HT_3 receptors (Feighner, 1999). Mirtazapine is also a potent antihistamine and tends to be more sedating than most other newer antidepressants. Weight gain can be another troublesome side effect.

Figure 4-2 presents summary findings on newer pharmacotherapies from a recent review of the treatment of depression by the Agency for Health Care Policy and Research (AHCPR, 1999). There have been few studies of gender differences in clinical response to treatments for depression. A recent report (Kornstein et al., in press) found women with chronic depression to respond better to a SSRI than a tricyclic, yet the opposite for men. This effect was primarily in premenopausal women. The AHCPR report (1999) also noted that there were almost no data to address the efficacy of pharmacotherapies in post partum or pregnant women.

Alternate Pharmacotherapies

Regardless of the initial choice of pharmacotherapy, about 30 to 50 percent of patients do not respond to the initial medication. It has not been established firmly whether patients who respond poorly to one class of antidepressants should be switched automatically to an alternate class (Thase & Rush, 1997). Several studies

have examined the efficacy of the TCAs and SSRIs when used in sequence (Peselow et al., 1989; Beasley et al., 1990). Approximately 30 to 50 percent of those not responsive to one class will respond to the other (Thase & Rush, 1997).

Among other types of antidepressants, the MAOIs and bupropion are important alternatives for SSRI and TCA nonresponders (Thase & Rush, 1995). These agents also may be relatively more effective than TCAs or SSRIs for treatment of depressions characterized by atypical or reversed vegetative symptoms (Goodnick & Extein, 1989; Quitkin et al., 1993b; Thase et al., 1995). Bupropion and the MAOIs also are good choices to treat bipolar depression (Himmelhoch et al., 1991; Thase et al., 1992; Sachs et al., 1994). Bupropion also has the advantage of a low rate of sexual side effects (Gardner & Johnston, 1985; Walker et al., 1993).

Bupropion's efficacy and overall side effect profile might justify its first-line use for all types of depression (e.g., Kiev et al., 1994). Furthermore, bupropion has a novel neurochemical profile in terms of effects on dopamine and norepinephrine (Ascher et al., 1995). However, worries about an increased risk of seizures delayed bupropion's introduction to the U.S. market by more than 5 years (Davidson, 1989). Although clearly effective for a broad range of depressions, use of the MAOIs has been limited for decades by concerns that when taken with certain foods containing the chemical tyramine (for example, some aged cheeses and red wines); these medications may cause a potentially lethal hypertensive reaction (Thase et al., 1995). There has been continued interest in development of safer, selective and reversible MAOIs.

Hypericum (St. John's Wort). The widespread publicity and use of the botanical product from the yellow-flowering *Hypericum perforatum* plant with or without medical supervision is well ahead of the science database supporting the effectiveness of this putative antidepressant. Controlled trials, mainly in Germany, have been positive in mild-to-moderate depression, with only mild gastrointestinal side effects reported (Linde et al., 1996). However, most of those studies were methodologically flawed, in areas including diagnosis (more similar to adjustment disorder with depressed mood than major depression), length of trial (often an inadequate 4 weeks), and either lack of placebo control or unusually low or high placebo response rates (Salzman, 1998).

Figure 4-2. Treatment of depression—newer pharmacotherapies: Summary findings

- Newer antidepressant drugs* are effective treatments for major depression and dysthymia.
  - They are efficacious in primary care and specialty mental health care settings:
    - Major depression:
      50 percent response to active agent
      32 percent response to placebo
    - Dysthymia (fluoxetine, sertraline, and amisulpride):
      59 percent response to active agent
      37 percent response to placebo
- Both older and newer antidepressants demonstrate similar efficacy.
- Drop-out rates due to all causes combined are similar for newer and older agents:
  - Drop-out rates due to adverse effects are slightly higher for older agents.
  - Newer agents are often easier to use because of single daily dosing and less titration.

*SSRIs and all other antidepressants marketed subsequently.
Source: AHCPR, 1999.

Post-marketing surveillance in Germany, which found few adverse effects of *Hypericum,* depended upon spontaneous reporting of side effects by patients, an approach that would not be considered acceptable in this country (Deltito & Beyer, 1998). In clinical use, the most commonly encountered adverse effect noted appears to be sensitivity to sunlight.

Basic questions about mechanism of action and even the optimal formulation of a pharmaceutical product from the plant remain; dosage in the randomized German trials varied by sixfold (Linde et al., 1996). Several pharmacologically active components of St. John's wort, including hypericin,

have been identified (Nathan, 1999); although their long half-lives in theory should permit once daily dosing, in practice a schedule of 300 mg three times a time is most commonly used. While initial speculation about significant MAO-inhibiting properties of hypericum have been largely discounted, possible serotonergic mechanisms suggest that combining this agent with an SSRI or other serotonergic antidepressant should be approached with caution. However, data regarding safety of hypericum in preclinical models or clinical samples are few (Nathan, 1999). At least two placebo-controlled trials in the United States are under way to compare the efficacy of *Hypericum* with that of an SSRI.

Augmentation Strategies

The transition from one antidepressant to another is time consuming, and patients sometimes feel worse in the process (Thase & Rush, 1997). Many clinicians bypass these problems by using a second medication to augment an ineffective antidepressant. The best studied strategies of this type are lithium augmentation, thyroid augmentation, and TCA-SSRI combinations (Nierenberg & White, 1990; Thase & Rush, 1997; Crismon et al., 1999).

Increasingly, clinicians are adding a noradrenergic TCA to an ineffective SSRI or vice versa. In an earlier era, such polypharmacy (the prescription of multiple drugs at the same time) was frowned upon. Thus far, the evidence supporting TCA-SSRI combinations is not conclusive (Thase & Rush, 1995). Caution is needed when using these agents in combination because SSRIs inhibit metabolism of several TCAs, resulting in a substantial increase in blood levels and toxicity or other adverse side effects from TCAs (Preskorn & Burke, 1992).

Psychotherapy and Counseling

Many people prefer psychotherapy or counseling over medication for treatment of depression (Roper, 1986; Seligman,1995). Research conducted in the past two decades has helped to establish at least several newer forms of time-limited psychotherapy as being as effective as antidepressant pharmacotherapy in mild-to-moderate depressions (DiMascio et al., 1979; Elkin et al., 1989; Hollon et al., 1992; Depression Guideline Panel, 1993; Thase, 1995; Persons et al., 1996). The newer depression-specific therapies include cognitive-behavioral therapy (Beck et al., 1979) and interpersonal psychotherapy (Klerman et al., 1984). These approaches use a time-limited approach, a present tense ("here-and-now") focus, and emphasize patient education and active collaboration. Interpersonal psychotherapy centers around four common problem areas: role disputes, role transitions, unresolved grief, and social deficits. Cognitive-behavioral therapy takes a more structured approach by emphasizing the interactive nature of thoughts, emotions, and behavior. It also helps the depressed patient to learn how to improve coping and lessen symptom distress.

There is no evidence that cognitive-behavioral therapy and interpersonal psychotherapy are differentially effective (Elkin et al., 1989; Thase, 1995). As reported earlier, both therapies appear to have some relapse prevention effects, although they are much less studied than the pharmacotherapies. Other more traditional forms of counseling and psychotherapy have not been extensively studied using a randomized clinical trial design (Depression Guideline Panel, 1993). It is important to determine if these more traditional treatments, as commonly practiced, are as effective as interpersonal psychotherapy or cognitive-behavioral therapy.

The brevity of this section reflects the succinctness of the findings on the effectiveness of these interventions as well as the lack of differential responses and "side effects." It does not reflect a preference or superiority of medication except in conditions such as psychotic depression where psychotherapies are not effective.

Bipolar Depression

Treatment of bipolar depression[12] has received surprisingly little study (Zornberg & Pope, 1993). Most psychiatrists prescribe the same antidepressants for

[12] Bipolar depression refers to episodes with symptoms of depression in patients diagnosed with bipolar disorder.

treatment of bipolar depression as for major depressive disorder, although evidence is lacking to support this practice. It also is not certain that the same strategies should be used for treatment of depression in bipolar II (i.e., major depression plus a history of hypomania) and bipolar I (i.e., major depression with a history of at least one prior manic episode) (DSM-IV).

Pharmacotherapy of bipolar depression typically begins with lithium or an alternate mood stabilizer (DSM-IV; Frances et al., 1996). Mood stabilizers reduce the risk of cycling and have modest antidepressant effects; response rates of 30 to 50 percent are typical (DSM-IV; Zornberg & Pope, 1993). For bipolar depressions refractory to mood stabilizers, an antidepressant is typically added. Bipolar depression may be more responsive to nonsedating antidepressants, including the MAOIs, SSRIs, and bupropion (Cohn et al., 1989; Haykal & Akiskal, 1990; Himmelhoch et al., 1991; Peet, 1994; Sachs et al., 1994).The optimal length of continuation phase pharmacotherapy of bipolar depression has not been established empirically (DSM-IV). During the continuation phase, the risk of depressive relapse must be counterbalanced against the risk of inducing mania or rapid cycling (Kukopulos et al., 1980; Wehr & Goodwin, 1987; Solomon et al., 1995). Although not all studies are in agreement, antidepressants may increase mood cycling in a vulnerable subgroup, such as women with bipolar II disorder (Coryell et al., 1992; Bauer et al., 1994). Lithium is associated with increased risk of congenital anomalies when taken during the first trimester of pregnancy, and the anticonvulsants are contraindicated (see Cohen et al., 1994, for a review). This is problematic in view of the high risk of recurrence in pregnant bipolar women (Viguera & Cohen 1998).

Pharmacotherapy, Psychosocial Therapy, and Multimodal Therapy

The relative efficacy of pharmacotherapy and the newer forms of psychosocial treatment, such as interpersonal psychotherapy and the cognitive-behavioral therapies, is a controversial topic (Meterissian & Bradwejn, 1989; Klein & Ross, 1993; Munoz et al., 1994; Persons et al., 1996). For major depressive episodes of mild to moderate severity, meta-analyses of randomized clinical trials document the relative equivalence of these treatments (Dobson, 1989; Depression Guideline Panel, 1993). Yet for patients with bipolar and psychotic depression, who were excluded from these studies, pharmacotherapy is required: there is no evidence that these types of depressive episodes can be effectively treated with psychotherapy alone (Depression Guideline Panel, 1993; Thase, 1995). Current standards of practice suggest that therapists who withhold somatic treatments (i.e., pharmacotherapy or ECT) from such patients risk malpractice (DSM-IV; Klerman, 1990; American Psychiatric Association, 1993; Depression Guideline Panel, 1993).

For patients hospitalized with depression, somatic therapies also are considered the standard of care (American Psychiatric Association, 1993). Again, there is little evidence for the efficacy of psychosocial treatments alone when used instead of pharmacotherapy, although several studies suggest that carefully selected inpatients may respond to intensive cognitive-behavioral therapy (DeJong et al., 1986; Thase et al., 1991). However, in an era in which inpatient stays are measured in days, rather than in weeks, this option is seldom feasible. Combined therapies emphasizing both pharmacologic and intensive psychosocial treatments hold greater promise to improve the outcome of hospitalized patients, particularly if inpatient care is followed by ambulatory treatment (Miller et al., 1990; Scott, 1992).

Combined therapies—also called multimodal treatments—are especially valuable for outpatients with severe forms of depression. According to a recent meta-analysis of six studies, combined therapy (cognitive or interpersonal psychotherapy *plus* pharmacotherapy) was significantly more effective than psychotherapy alone for more severe recurrent depression. In milder depressions, psychotherapy alone was nearly as effective as combined therapy (Thase et al., 1997b). This meta-analysis was unable to compare combined

therapy with pharmacotherapy alone or placebo due to an insufficient number of patients.

In summary, the DSM-IV definition of major depressive disorder spans a heterogenous group of conditions that benefit from psychosocial and/or pharmacological therapies. People with mild to moderate depression respond to psychotherapy or pharmacotherapy alone. People with severe depression require pharmacotherapy or ECT and they may also benefit from the addition of psychosocial therapy.

Preventing Relapse of Major Depressive Episodes

Recurrent Depression. Maintenance pharmacotherapy is the best-studied means to reduce the risk of recurrent depression (Prien & Kocsis, 1995; Thase & Sullivan, 1995). The magnitude of effectiveness in prevention of recurrent depressive episodes depends on the dose of the active agent used, the inherent risk of the population (i.e., chronicity, age, and number of prior episodes), the length of time being considered, and the patient's adherence to the treatment regimen (Thase, 1993). Early studies, which tended to use lower dosages of medications, generally documented a twofold advantage relative to placebo (e.g., 60 vs. 30 percent) (Prien & Kocsis, 1995). In a more recent study of recurrent unipolar depression, the drug-placebo difference was nearly fivefold (Frank et al., 1990; Kupfer et al., 1992). This trial, in contrast to earlier randomized clinical trials, used a much higher dosage of imipramine, suggesting that full-dose maintenance pharmacotherapy may improve prophylaxis. Indeed, this was subsequently confirmed in a randomized clinical trial comparing full- and half-dose maintenance strategies (Frank et al., 1993).

There are few published studies on the prophylactic benefits of long-term pharmacotherapy with SSRIs, bupropion, nefazodone, or venlafaxine. However, available studies uniformly document 1 year efficacy rates of 80 to 90 percent in preventing recurrence of depression (Montgomery et al., 1988; Doogan & Caillard, 1992; Claghorn & Feighner, 1993; Duboff, 1993; Shrivastava et al., 1994; Franchini et al., 1997; Stewart et al., 1998). Thus, maintenance therapy with the newer agents is likely to yield outcomes comparable to the TCAs (Thase & Sullivan, 1995).

How does maintenance pharmacotherapy compare with psychotherapy? In one study of recurrent depression, monthly sessions of maintenance interpersonal psychotherapy had a 3-year success rate of about 35 percent (i.e., a rate falling between those for active and placebo pharmacotherapy) (Frank et al., 1990). Subsequent studies found maintenance interpersonal psychotherapy to be either a powerful or ineffective prophylactic therapy, depending on the patient/treatment match (Kupfer et al., 1990; Frank et al., 1991a; Spanier et al., 1996).

Bipolar Depression. No recent randomized clinical trials have examined prophylaxis against recurrent depression in bipolar disorder. In one older, well-controlled study, recurrence rates of more than 60 percent were observed despite maintenance treatment with lithium, either alone or in combination with imipramine (Shapiro et al., 1989).

Treatment of Mania

Acute Phase Efficacy

Success rates of 80 to 90 percent were once expected with lithium for the acute phase treatment of mania (e.g., Schou, 1989); however, lithium response rates of only 40 to 50 percent are now commonplace (Frances et al., 1996). Most recent studies thus underscore the limitations of lithium in mania (e.g., Gelenberg et al., 1989; Small et al., 1991; Freeman et al., 1992; Bowden et al., 1994). The apparent decline in lithium responsiveness may be partly due to sampling bias (i.e., university hospitals treat more refractory patients), but could also be attributable to factors such as younger age of onset, increased drug abuse comorbidity, or shorter therapeutic trials necessitated by briefer hospital stay (Solomon et al., 1995). The effectiveness of acute phase lithium treatment also is partially dependent on the clinical characteristics of the manic episode: dysphoric/mixed, psychotic, and rapid cycling episodes are less responsive to lithium alone (DSM-IV; Solomon et al., 1995).

A number of other medications initially developed for other indications are increasingly used for lithium-refractory or lithium-intolerant mania. The efficacy of two medications, the anticonvulsants carbamazepine and divalproex sodium, has been documented in randomized clinical trials (e.g., Small et al., 1991; Freeman et al., 1992; Bowden et al., 1994; Keller et al., 1992). Divalproex sodium has received FDA approval for the treatment of mania. The specific mechanisms of action for these agents have not been established, although they may stabilize neuronal membrane systems, including the cyclic adenosine monophosphate second messenger system (Post, 1990). The anticonvulsant medications under investigation for their effectiveness in mania include lamotrigine and gabapentin.

Another newer treatment, verapamil, is a calcium channel blocker initially approved by the FDA for treatment of cardiac arrhythmias and hypertension. Since the mid-1980s, clinical reports and evidence from small randomized clinical trials suggest that the calcium channel blockers may have antimanic effects (Dubovsky et al., 1986; Garza-Trevino et al., 1992; Janicak et al., 1992, 1998). Like lithium and the anticonvulsants, the mechanism of action of verapamil has not been established. There is evidence of abnormalities of intracellular calcium levels in bipolar disorder (Dubovsky et al., 1992), and calcium's role in modulating second messenger systems (Wachtel, 1990) has spurred continued interest in this class of medication. If effective, verapamil does have the additional advantage of having a lower potential for causing birth defects than does lithium, divalproex, or carbamazepine.

Adjunctive neuroleptics and high-potency benzodiazepines are used often in combination with mood stabilizers to treat mania. The very real risk of tardive dyskinesia has led to a shift in favor of adjunctive use of benzodiazepines instead of neuroleptics for acute stabilization of mania (Chouinard, 1988; Lenox et al., 1992). The novel antipsychotic clozapine has shown promise in otherwise refractory manic states (Suppes et al., 1992), although such treatment requires careful monitoring to help protect against development of agranulocytosis, a potentially lethal bone marrow toxicity. Other newer antipsychotic medications, including risperidone and olanzapine, have safer side effect profiles than clozapine and are now being studied in mania. For manic patients who are not responsive to or tolerant of pharmacotherapy, ECT is a viable alternative (Black et al., 1987; Mukherjee et al., 1994). Further discussion of antipsychotic drugs and their side effects is found in the section on schizophrenia.

Maintenance Treatment to Prevent Recurrences of Mania

The efficacy of lithium for prevention of mania also appears to be significantly lower now than in previous decades; recurrence rates of 40 to 60 percent are now typical despite ongoing lithium therapy (Prien et al., 1984; Gelenberg et al., 1989; Winokur et al., 1993). Still, more than 20 studies document the effectiveness of lithium in preventing suicide (Goodwin & Jamison, 1990). Medication noncompliance almost certainly plays a role in the failure of longer term lithium maintenance therapy (Aagaard et al., 1988). Indeed, abrupt discontinuation of lithium has been shown to accelerate the risk of relapse (Suppes et al., 1993). Medication "holidays" may similarly induce a lithium-refractory state (Post, 1992), although data are conflicting (Coryell et al., 1998). As noted earlier, antidepressant cotherapy also may accelerate cycle frequency or induce lithium-resistant rapid cycling (Kukopulos et al., 1980; Wehr & Goodwin, 1987).

With increasing recognition of the limitations of lithium prophylaxis, the anticonvulsants are used increasingly for maintenance therapy of bipolar disorder. Several randomized clinical trials have demonstrated the prophylactic efficacy of carbamazepine (Placidi et al., 1986; Lerer et al., 1987; Coxhead et al., 1992), whereas the value of divalproex preventive therapy is only supported by uncontrolled studies (Calabrese & Delucchi, 1990; McElroy et al., 1992; Post, 1990). Because of increased teratogenic risk associated with these agents, there is a need to obtain and evaluate information on alternative interventions for women with bipolar disorder of childbearing age.

Service Delivery for Mood Disorders

The mood disorders are associated with significant suffering and high social costs, as explained above (Broadhead et al., 1990; Greenberg et al., 1993; Wells et al., 1989; Wells et al., 1996). Many treatments are efficacious, yet in the case of depression, significant numbers of individuals either receive no care or inappropriate care (Katon et al., 1992; Narrow et al., 1993; Wells et al., 1994; Thase, 1996). Limitations in insurance benefits or in the management strategies employed in managed care arrangements may make it impossible to deliver recommended treatments. In addition, treatment outcome in real-world practice is not as effective as that demonstrated in clinical trials, a problem known as the gap between efficacy and effectiveness (see Chapter 2). The gap is greatest in the primary care setting, although it also is observed in specialty mental health practice. There is a need to develop case identification approaches for women in obstetrics/gynecology settings due to the high risk of recurrence in childbearing women with bipolar disorder. Little attention also has been paid to screening and mental health services for women in obstetrics/gynecology settings despite their high risk of depression (Miranda et al., 1998).

Primary care practice has been studied extensively, revealing low rates of both recognition and appropriate treatment of depression. Approximately one-third to one-half of patients with major depression go unrecognized in primary care settings (Gerber et al., 1989; Simon & Von Korff, 1995). Poor recognition leads to unnecessary and expensive diagnostic procedures, particularly in response to patients' vague somatic complaints (Callahan et al., 1996). Fewer than one-half receive antidepressant medication according to Agency for Health Care Policy Research recommendations for dosage and duration (Simon et al., 1993; Rost et al., 1994; Katon 1995, 1996; Schulberg et al., 1995; Simon & Von Korff, 1995). About 40 percent discontinue their medication on their own during the first 4 to 6 weeks of treatment, and fewer still continue their medication for the recommended period of 6 months (Simon et al., 1993). Although drug treatment is the most common strategy for treating depression in primary care practice (Olfson & Klerman, 1992; Williams et al., 1999), about one-half of primary care physicians express a preference to include counseling or therapy as a component of treatment (Meredith et al., 1994, 1996). Few primary care practitioners, however, have formal training in psychotherapy, nor do they have the time (Meredith et al., 1994, 1996). A variety of strategies have been developed to improve the management of depression in primary care settings (cited in Katon et al., 1997). These are discussed in more detail in Chapter 5 because of the special problem of recognizing and treating depression among older adults.

Another major service delivery issue focuses on the substantial number of individuals with mood disorders who go on to develop a chronic and disabling course. Their needs for a wide array of services are similar to those of individuals with schizophrenia. Many of the service delivery issues relevant to individuals with severe and persistent mood disorders are presented in the final sections of this chapter.

Schizophrenia

Overview

Our understanding of schizophrenia has evolved since its symptoms were first catalogued by German psychiatrist Emil Kraepelin in the late 19th century (Andreasen, 1997a). Even though the cause of this disorder remains elusive, its frightening symptoms and biological correlates have come to be quite well defined. Yet misconceptions abound about symptoms: schizophrenia is *neither* "split personality" *nor* "multiple personality." Furthermore, people with schizophrenia are not perpetually incoherent or psychotic (DSM-IV; Mason et al., 1997) (Table 4-6).

Schizophrenia *is* characterized by profound disruption in cognition and emotion, affecting the most fundamental human attributes: language, thought, perception, affect, and sense of self. The array of symptoms, while wide ranging, frequently includes psychotic manifestations, such as hearing internal voices or experiencing other sensations not connected to an obvious source (hallucinations) and assigning

Table 4-6. DSM-IV diagnostic criteria for schizophrenia

A. *Characteristic symptoms:* Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

(1) delusions

(2) hallucinations

(3) disorganized speech (e.g., frequent derailment or incoherence)

(4) grossly disorganized or catatonic behavior

(5) negative symptoms, i.e., affective flattening, alogia, or avolition

Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.

B. *Social/occupational dysfunction:* For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. *Duration:* Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. *Schizoaffective and mood disorder exclusion:* Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either (1) no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. *Substance/general medical condition exclusion:* 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.

F. *Relationship to a pervasive developmental disorder:* If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

unusual significance or meaning to normal events or holding fixed false personal beliefs (delusions). No single symptom is definitive for diagnosis; rather, the diagnosis encompasses a pattern of signs and symptoms, in conjunction with impaired occupational or social functioning (DSM-IV).

Symptoms are typically divided into positive and negative symptoms (see Table 4-7) because of their impact on diagnosis and treatment (Crow, 1985; Andreasen, 1995; Eaton et al., 1995; Klosterkotter et al., 1995; Maziade et al., 1996). Positive symptoms are those that appear to reflect an excess or distortion of normal functions (Peralta & Cuesta, 1998). The diagnosis of schizophrenia, according to DSM-IV, requires at least 1-month duration of two or more positive symptoms, unless hallucinations or delusions are especially bizarre, in which case one alone suffices for diagnosis. Negative symptoms are those that appear to reflect a diminution or loss of normal functions (Roy & DeVriendt, 1994; Crow, 1995; Blanchard et al., 1998). These often persist in the lives of people with schizophrenia during periods of low (or absent)

Table 4-7. Positive and negative symptoms of schizophrenia

Positive Symptoms of Schizophrenia

Delusions are firmly held erroneous beliefs due to distortions or exaggerations of reasoning and/or misinterpretations of perceptions or experiences. Delusions of being followed or watched are common, as are beliefs that comments, radio or TV programs, etc., are directing special messages directly to him/her.

Hallucinations are distortions or exaggerations of perception in any of the senses, although auditory hallucinations ("hearing voices" within, distinct from one's own thoughts) are the most common, followed by visual hallucinations.

Disorganized speech/thinking, also described as "thought disorder" or "loosening of associations," is a key aspect of schizophrenia. Disorganized thinking is usually assessed primarily based on the person's speech. Therefore, tangential, loosely associated, or incoherent speech severe enough to substantially impair effective communication is used as an indicator of thought disorder by the DSM-IV.

Grossly disorganized behavior includes difficulty in goal-directed behavior (leading to difficulties in activities in daily living), unpredictable agitation or silliness, social disinhibition, or behaviors that are bizarre to onlookers. Their purposelessness distinguishes them from unusual behavior prompted by delusional beliefs.

Catatonic behaviors are characterized by a marked decrease in reaction to the immediate surrounding environment, sometimes taking the form of motionless and apparent unawareness, rigid or bizarre postures, or aimless excess motor activity.

Other symptoms sometimes present in schizophrenia but not often enough to be definitional alone include affect inappropriate to the situation or stimuli, unusual motor behavior (pacing, rocking), depersonalization, derealization, and somatic preoccupations.

Negative Symptoms of Schizophrenia

Affective flattening is the reduction in the range and intensity of emotional expression, including facial expression, voice tone, eye contact, and body language.

Alogia, or poverty of speech, is the lessening of speech fluency and productivity, thought to reflect slowing or blocked thoughts, and often manifested as laconic, empty replies to questions.

Avolition is the reduction, difficulty, or inability to initiate and persist in goal-directed behavior; it is often mistaken for apparent disinterest.

positive symptoms. Negative symptoms are difficult to evaluate because they are not as grossly abnormal as positives ones and may be caused by a variety of other factors as well (e.g., as an adaptation to a persecutory delusion). However, advancements in diagnostic assessment tools are being made.

Diagnosis is complicated by early treatment of schizophrenia's positive symptoms. Antipsychotic medications, particularly the traditional ones, often produce side effects that closely resemble the negative symptoms of affective flattening and avolition. In addition, other negative symptoms are sometimes present in schizophrenia but not often enough to satisfy diagnostic criteria (DSM-IV): loss of usual interests or pleasures (anhedonia); disturbances of sleep and eating; dysphoric mood (depressed, anxious, irritable, or angry mood); and difficulty concentrating or focusing attention.

Currently, discussion is ongoing within the field regarding the need for a third category of symptoms for diagnosis: disorganized symptoms (Brekke et al., 1995; Cuesta & Peralta, 1995). Disorganized symptoms include thought disorder, confusion, disorientation, and memory problems. While they are listed by DSM-IV as common in schizophrenia—especially during exacerbations of positive or negative symptoms (DSM-IV)—they do not yet constitute a formal new category of symptoms. Some researchers think that a new category is not warranted because disorganized symptoms may instead reflect an underlying

dysfunction common to several psychotic disorders, rather than being unique to schizophrenia (Toomey et al., 1998).

Cognitive Dysfunction

Recently there has also been more clinical and research attention on cognitive difficulties that many people with schizophrenia experience (Levin et al., 1989; Harvey et al., 1996). Cognitive problems include information processing (Cadenhead et al., 1997), abstract categorization (Keri et al., 1998), planning and regulating goal-directed behavior ("executive functions"), cognitive flexibility, attention, memory, and visual processing (Cornblatt & Keilp, 1994; Mahurin et al., 1998). These cognitive problems are especially associated with negative and disorganized symptoms but seem to be distinct (Basso et al., 1998; Brekke et al., 1995; Cuesta & Peralta, 1995; Voruganti et al., 1997), although others disagree (Roy & DeVriendt, 1994).

These cognitive problems vary from person to person and can change over time. In some situations it is unclear whether such deficits are due to the illness or to the side effects of certain neuroleptic medications (Zalewski et al., 1998). As research on brain functioning grows more sophisticated, some models posit dysfunction of fundamental cognitive processes at the *center* of schizophrenia, rather than as one of numerous symptoms (Andreasen, 1997a, 1997b; Andreasen et al., 1996). On the basis of neuropsychological and neuroanatomical data, for example, some researchers posit that schizophrenia is a disorder of the prefrontal cortex and its ability to perform the essential cognitive function of working memory (Goldman-Rakic & Selemon, 1997). Problems in such fundamental areas as paying selective attention, problem-solving, and remembering can cause serious difficulties in learning new skills (social interaction, treatment and rehabilitation) and performing daily tasks (Medalia et al., 1998); treatment of such deficits is discussed in later sections of the chapter.

Functional Impairment

The criteria for a diagnosis of schizophrenia include functional impairment in addition to the constellation of symptoms outlined above. For formal diagnosis, a person must be experiencing significant dysfunction in one or more major areas of life activities such as interpersonal relations, work or education, family life, communication, or self-care (Docherty et al., 1996; Patterson et al., 1997, 1998). These problems result from the complex of symptoms and their sequelae, but have been linked more to negative than to positive symptoms (Ho et al., 1998). They have serious economic, social, and psychological effects: unemployment, disrupted education, limited social relationships, isolation, legal involvement, family stress, and substance abuse. Such sequelae form the most distressing aspects of the illness for many people and contribute to the increased risk of suicide among people diagnosed with schizophrenia.

Cultural Variation

On first consideration, symptoms like hallucinations, delusions, and bizarre behavior seem easily defined and clearly pathological. However, increased attention to cultural variation has made it very clear that what is considered delusional in one culture may be accepted as normal in another (Lu et al., 1995). For example, among members of some cultural groups, "visions" or "voices" of religious figures are part of normal religious experience. In many communities, "seeing" or being "visited" by a recently deceased person are not unusual among family members. Therefore, labeling an experience as pathological or a psychiatric symptom can be a subtle process for the clinician with a different cultural or ethnic background from the patient; indeed, cultural variations and nuances may occur within the diverse subpopulations of a single racial, ethnic, or cultural group. Often, however, clinicians' training, skills, and views tend to reflect their own social and cultural influences.

Clinicians can misinterpret and misdiagnose patients whose cognitive style, norms of emotional expression, and social behavior are from a different culture, unless clinicians become culturally competent

(see Chapter 2 and Center for Mental Health Services [CMHS], 1997). For example, clinicians may misinterpret a client's deferential avoidance of direct eye contact as a sign of withdrawal or paranoia, or a normal emotional reserve as flattened affect if they are unaware of the norms of cultural groups other than their own. There is some empirical evidence that such misinterpretations happen widely. One finding is that African-American patients are more likely than white patients to be diagnosed with severe psychotic disorders in clinical settings (Snowden & Cheung, 1990; Hu et al., 1991; Lawson et al., 1994, Strakowski et al., 1995). The overdiagnosis of psychotic disorders among African Americans is interpreted by some as evidence of clinician bias.

People with differing cultural backgrounds also may experience and exhibit true schizophrenia symptoms differently (Brekke & Barrio, 1997; Thakker & Ward, 1998). Culture shapes the content and form of positive and negative symptoms (Maslowski et al., 1998). For example, people in non-Western countries report catatonic behavior among psychiatric patients much more commonly than in the United States. How culture, societal conditions, and diagnosing tendencies among clinicians in various countries interact to create these differences is being studied but is not yet well understood.

No description of symptoms can adequately convey a person's experience of schizophrenia or other serious mental illness. Two individuals with very different internal experiences and outward presentations may be diagnosed with schizophrenia, if both meet the diagnostic criteria (Brazo & Dollfus, 1997; Kirkpatrick et al., 1998). Additionally, their symptoms and presentation may vary considerably over time (Ribeyre & Dollfus, 1996). This considerable variation (Basso et al., 1997; Sperling et al., 1997) has led to the naming of several subtypes of schizophrenia, depending on what symptoms are most prominent. Currently these are seen as variations within a single disorder. Similarly, the diagnosis is often difficult because other mental disorders share some common features. Diagnosis depends on the details of how people behave and what they report during an evaluation, the diagnostician, and variations in the illness over time. Therefore, many people receive more than one diagnostic label over the course of their involvement with mental health services. Refining the definition of schizophrenia and other serious mental illnesses to account for these individual and cultural variations remains a challenge to researchers and clinicians.

Prevalence

Studies of schizophrenia's prevalence in the general population vary depending on the way diagnostic criteria are applied and the population, setting, and method of study (Hafner & an der Heiden, 1997). In general, 1-year prevalence in adults ages 18 to 54 is estimated to be 1.3 percent (Table 4-1). Onset generally occurs during young adulthood (mid-20s for men, late-20s for women), although earlier and later onset do occur. It may be abrupt or gradual, but most people experience some early signs, such as increasing social withdrawal, loss of interests, unusual behavior, or decreases in functioning prior to the beginning of active positive symptoms. These are often the first behaviors to worry family members and friends.

Prevalence of Comorbid Medical Illness

The mortality rate in persons with schizophrenia is significantly higher than that of the general population. While elevated suicide accounts for some of the excess mortality—and is a serious problem in its own right—comorbid somatic illnesses also contribute to excess mortality. Until recently, there was little information on the prevalence of comorbid medical illnesses in people with schizophrenia (Jeste et al., 1996). A recent study was among the first to document systematically that people with schizophrenia are beset by vision and dental problems, as well as by high blood pressure, diabetes, and sexually transmitted diseases. Their self-reported lifetime rates of high blood pressure (34.1 percent), diabetes (14.9 percent), and sexually transmitted diseases (10.0 percent) are higher than those for people of similar age in the general population (Dixon et al., 1999; Dixon et al., in press-a). The reasons for excess medical comorbidity are unclear, yet medical comorbidity is independently

associated with lower perceived physical health status, more severe psychosis and depression, and greater likelihood of a history of a suicide attempt (Dixon et al., 1999). These findings have important implications for improving patient management (Dixon et al., in press-b).

Course and Recovery

It is difficult to study the course of schizophrenia and other serious mental illnesses because of the changing nature of diagnosis, treatment, and social norms (Schultz et al., 1997). Overall, research indicates that schizophrenia's course over time varies considerably from person to person (DSM-IV; Wiersma et al., 1998) and varies for any one person (Moller & von Zerssen, 1995). The variability may emanate from the underlying heterogeneity of the disease process itself, as well as from biological and genetic vulnerability, neurocognitive impairments, socio-cultural stressors, and personal and social factors that confer protection against stress and vulnerability (Liberman et al., 1980; Nuechterlein et al., 1994). Most individuals experience periods of symptom exacerbation and remission, while others maintain a steady level of symptoms and disability which can range from moderate to severe (Wiersma et al., 1998).

Most people experience at least one, often more, relapse after their first actively psychotic episode (Herz & Melville, 1980; Falloon, 1984; Gaebel et al., 1993; Wiersma et al., 1998). Often these are periods of more intense positive symptoms, yet the person continues to struggle with negative symptoms in between episodes (Gupta et al., 1997; Schultz et al., 1997). However, whether such exacerbations have the same degree of disabling and distressing effects each time depends greatly on the person's coping skills and support system. Over time, many people learn successful ways of managing even severe symptoms to moderate their disruptiveness to daily life (e.g., Hamera et al., 1992). Therefore, earlier years with the illness are often more difficult than later ones. Additionally, gradual onset and delays in obtaining treatment seem to raise the risk of longer episodes of acute illness over time (Wiersma et al., 1998). Early treatment with antipsychotic medications has been found to predict better long-term outcomes for people experiencing their first psychotic episode, as compared with a variety of control groups, including those in more advanced stages (Lieberman et al., 1996; Wyatt et al., 1997, 1998; Wyatt & Henter, 1998).

The course of schizophrenia is also influenced by personal orientation and motivation, and by supports in the form of skill-building assistance and rehabilitation (Lieberman et al., 1996; Awad et al., 1997; Hafner & an der Heiden, 1997). These, in turn, are heavily influenced by regional, cultural, and socioeconomic factors in addition to individual factors (Dassori et al., 1995).

Family factors also are related to the course of illness. Following hospitalization, patients who return home are more likely to relapse if their family is identified as critical, hostile, or emotionally overinvolved than if their family is not so identified (Jenkins & Karno, 1992; Bebbington & Kuipers, 1994). This is a controversial finding because it appears to blame family members (Hatfield et al., 1987). However, recent studies suggest an interaction between families and the patient (Goldstein, 1995b), suggesting that the negative emotions of some family members may be a reaction to, more than a cause of relapse in, the family member. Blaming either the family or the patient overlooks important ways both parties interact and how such interactions are associated with the course of schizophrenia. In addition, there is a need to examine what part the role of families' prosocial functioning (family warmth and family support) plays in the course of schizophrenia to identify how family factors can serve as protective factors (Lopez et al., in press).

Despite the variability, some generalizations about the long-term course of schizophrenia are possible largely on the basis of longitudinal research. A small percentage (10 percent or so) of patients seem to remain severely ill over long periods of time (Jablensky et al., 1992; Gerbaldo et al., 1995). Most do not return to their prior state of mental function. Yet several long-term studies reveal that about one-half to two-thirds of people with schizophrenia significantly improve or

recover, some completely (for a review see Harding et al., 1992). These studies were important because they began to dispel the traditional view, dating back to the 19th century, that schizophrenia had a uniformly downhill course (Harding et al., 1992). Several other longitudinal studies, however, found less favorable patient outcomes with other cohorts of patients (Harrow et al., 1997). The differences in outcomes between the studies are thought to be explained on the basis of differences in patient age, length of followup, expectations about prognosis, and types of services received (Harrow et al., 1997).

The importance of a rehabilitation focus in shaping patient outcome was supported by one of the only direct comparisons between patient cohorts. The Vermont cohort consisted of the most severely affected patients from the "back wards" of the state hospital (Harding et al., 1987). As part of a statewide program of deinstitutionalization, the cohort was released in the 1950s to a hospital-based rehabilitation program and then to what was at the time an innovative, broad-based community rehabilitation program, which incorporated social, residential, and vocational components.[13] Patients' degree of recovery at followup after three decades was measured by global functional improvement and other functional measures. One-half to two-thirds of the Vermont cohort significantly improved or recovered (Harding et al., 1987). The receipt of community-based rehabilitation was considered key to their recovery on the basis of a study comparing their progress with that of a matched cohort of deinstitutionalized patients from Maine. The Maine cohort did not function as well after receiving more traditional aftercare services without a rehabilitation emphasis (DeSisto et al., 1995a, 1995b). Although the findings from the Vermont cohort, as well as those from a cohort in Switzerland (Ciompi, 1980), are widely cited by consumers as evidence of recovery from mental illness, a topic discussed in detail in Chapter 2, it bears noting that patients in the Vermont cohort represented a less rigorously defined conceptualization of schizophrenia than is common today, which may account, in part, for the more favorable outcomes.

In summary, schizophrenia does not follow a single pathway. Rather, like other mental and somatic disorders, course and recovery are determined by a constellation of biological, psychological, and sociocultural factors. That different degrees of recovery are attainable has offered hope to consumers and families.

Gender and Age at Onset

There appear to be gender differences in the course and prognosis of schizophrenia. Women are more likely than men to experience later onset, more pronounced mood symptoms, and better prognosis (DSM-IV), although the prognosis difference recently has come under question.

Current research (e.g., Hafner & an der Heiden, 1997; Hafner et al., 1998) suggests that some of the apparent gender differences in course and outcome occur because for some women schizophrenia does not develop until after menopause. This delay is thought to be related to the protective effects of estrogen, the levels of which diminish at menopause. According to this line of reasoning, men have no such delay because they lack the protective estrogen levels. Therefore, a higher proportion of men develop schizophrenia earlier.

Generally, early onset (younger than age 25 in most studies) is associated with more gradual development of symptoms, more prominent negative symptoms across the course (DSM-IV), and more neuropsychological problems (Basso et al., 1997; Symonds et al., 1997), regardless of gender. Early onset also usually involves more disruption of adult milestones, such as education, employment achievements, and long-term social relationships (Nowotny et al., 1996). People with later onset often have reached these milestones, cushioning them from disruptive sequelae and enabling better coping with symptoms (Hafner et al., 1998). Therefore, early onset (more men than women) often yields a more difficult first several years, although not necessarily a worse long-term outcome.

[13] These are the vital components of most contemporary rehabilitation programs (see section on service delivery).