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The Psychopathology and Treatment of Bipolar Disorder

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Abstract

In this chapter we review research on the diagnosis, course, etiology, and pharmacological and
psychosocial treatment of bipolar disorder (BD). BD is a highly recurrent and severe illness, with
high rates of suicidality and functional impairment. The disorder is heritable and appears to share
susceptibility genes with schizophrenia. It is characterized by dysregulation in the dopamine and
serotonin systems and by pathology in the brain systems involved in regulating emotion. Psychosocial
stressors, notably life events and familial expressed emotion, significantly influence the course of
the illness in the context of these vulnerabilities. Findings of randomized clinical trials indicate that
psychosocial interventions enhance long-term outcomes when added to pharmacotherapy. Much
remains to be clarified about the interactive contributions of genetic, neurobiological, and
psychosocial factors to the course of the disorder, and the moderators and mediators of treatment
effects.

Keywords

psychosocial stress; expressed emotion; mood disorders; pharmacotherapy; psychotherapy

INTRODUCTION

The purpose of this chapter is to review current research on the diagnosis, epidemiology,
course, etiology, and treatment of bipolar disorder (BD). BD has traditionally been viewed as
a purely biologically based group of disorders, but BD episodes are best understood within a
biopsychosocial framework. That is, recurrences of mania or depression are a result of the
mutually influential interactions between genes, neural pathways, and socioenvironmental
influences. We place special emphasis on new findings regarding the prognostic effects of
psychosocial variables. By extension, effective treatments for BD usually involve psychosocial
treatment in combination with pharmacotherapy.

In the first section, we address recent findings concerning the epidemiology, nosological status,
comorbid features, and course of the disorder. We also discuss recent controversy on BD in
children. In a separate section, we address the interactions of biological and psychosocial risk
factors in the course of the illness. Current pharmacological and psychological treatments are
then reviewed. Finally, we give recommendations for future research on etiology and treatment.

KEY FEATURES OF BIPOLAR DISORDER

Definitions

Bipolar I disorder, formerly termed manic-depressive illness, is defined by at least one lifetime manic or mixed episode (Am. Psychiatr. Assoc. 2000). Diagnostic criteria specify that mania must last at least one week or require hospitalization. Manic symptoms include irritability or euphoria along with symptoms such as decreased need for sleep, grandiose ideas, impulsive behavior, increased talkativeness, racing thoughts, flight of ideas, increased activity, and distractibility. Mixed episodes include manic symptoms and simultaneous depressive symptoms lasting for at least one week. Most, but certainly not all, people with BD I experience periods of depression.

BD II is defined by at least one lifetime hypomanic episode, along with at least one episode of major depression. Hypomania is characterized by the same symptoms as mania but lasts for shorter intervals (four or more days) and, although noticeable to others, is not associated with functional impairment. Episodes of major depression are defined by two or more weeks of intense sadness or loss of interests, accompanied by symptoms such as fatigue, insomnia, psychomotor agitation or retardation, weight gain or loss, cognitive dysfunction, feelings of worthlessness, and suicidal ideation or attempts. "Converting" from BD II to BD I is rare. In one study, only 11% of BD II patients developed full manic or mixed episodes within a 10-year period (Coryell et al. 1995).

Cyclothymia is characterized by two or more years of alterations between hypomanic and depressive symptoms that do not meet the DSM-IV criteria for a major depressive episode or hypomania. BD not otherwise specified is usually reserved for patients whose disorder meets the minimum number of required symptoms but not the duration requirements for a full manic, hypomanic, mixed, or depressive episode. Most of the research has focused on BD I disorder, which is the focus of this review.

Epidemiology

The National Comorbidity Survey replication, based on DSM-IV ($N = 9282$ respondents), estimated a lifetime prevalence rate of 3.9% for BD I and II disorders (Kessler et al. 2005a). A recent epidemiological study in the Netherlands found that cyclothymia affects 4.2% of the population (Regeer et al. 2004). By comparison, major depressive disorder was estimated to have a lifetime prevalence of 16.6% (Kessler et al. 2005b).

Women and men are equally likely to develop BD I, although women report more episodes of depression than do men, and, correspondingly, are more likely to meet the criteria for BD II (e.g., Leibenluft 1997, Schneck et al. 2004). In the National Comorbidity Survey replication, the median age of onset was 25 years. Approximately 25% of patients had onset by age 17. Earlier age at onset is associated with a variety of poor outcomes, including rapid cycling (four or more episodes of illness per year) in adulthood (Coryell et al. 2003, Schneck et al. 2004).

The onset of BD and depression appears to be getting younger with successive birth cohorts (Rice et al. 1987, Ryan et al. 1992, Wickramaratne et al. 1989). In the National Comorbidity Survey replication study (Kessler et al. 2005a), the lifetime risk of BD I or II disorders in the youngest age cohort (18–29 years) was 22 times higher than in the oldest cohort (over 60 years), although the role of age-related reporting biases cannot be ruled out.

The Bipolar Disorder Spectrum

There is much disagreement about where to draw the boundaries of the bipolar spectrum, but some investigators include subsyndromal manic episodes, manic or hypomanic episodes

triggered by antidepressants, or agitated depression (Akiskal et al. 2000, 2005; Smith et al. 2005). When broader definitions of BD are included, lifetime prevalence rates from 6.4% to 10% are reported (Akiskal et al. 2000, McIntyre & Konarski 2004). A reanalysis of the Epidemiological Catchment Area database indicated that 6.4% of the general population met criteria for the BD spectrum (Judd & Akiskal 2003). There are data to support the spectrum concept. Notably, patients with subsyndromal forms of BD are more likely to have family histories of BD than people without subsyndromal symptoms and have high rates of suicide, marital disruption, and psychiatric service utilization (Akiskal 1996, Judd & Akiskal 2003).

Various self-report instruments have been designed to identify persons with or at risk for BD spectrum disorders. The General Behavior Inventory (Depue et al. 1985), a 79-item questionnaire, assesses lifetime experiences of depressive and manic symptoms. High scores during adolescence are associated with psychosocial impairment in adulthood (Klein & Depue 1984), and a youth version discriminated early-onset BD from attention deficit disorders (Danielson et al. 2003). The Hypomanic Personality Scale robustly predicted the onset of bipolar spectrum disorders in a 13-year follow-up of college students (Kwapil et al. 2000).

Comorbidity with Other Disorders

BD patients are highly likely to have comorbid disorders. When 12-month prevalence rates in a community epidemiological sample were considered, the highest tetrachoric correlations were observed between mania/hypomania and attention deficit hyperactivity disorder, followed by oppositional defiant disorder, agoraphobia, panic disorder, generalized anxiety disorder, alcohol dependence, and drug abuse (Kessler et al. 2005b). An epidemiological study using DSM-III estimated that 61% of BD patients had lifetime alcohol (46%) or substance (15%) abuse or dependence disorders (Regier et al. 1990). As is true of all psychiatric disorders, comorbidity robustly predicts poor long-term outcome. Children and adult BD patients with comorbid anxiety, substance use, or psychotic disorders have poorer long-term prognoses than do patients without comorbid features (Feske et al. 2000, Frank et al. 2002, Masi et al. 2004, Otto et al. 2006, Tohen et al. 1990).

Longitudinal Course

Virtually all patients with BD have illness recurrences. Approximately 20% of patients who enter outpatient treatment have had four or more episodes (rapid cycling) within the prior year (Calabrese et al. 1996, Schneck et al. 2004). Over a one-year period, 37% of BD I patients had recurrences of mania or depression, 60% over two years, and 73% over five years even when treated with pharmacotherapy (Gitlin et al. 1995). Between episodes, most patients experience at least mild-to-moderate symptoms (Judd et al. 2002, Keller et al. 1993, Post et al. 2003). In a prospective study spanning nearly 13 years, subsyndromal symptoms—notably subsyndromal depression—were more common than fully syndromal symptoms and were present during approximately half of the weeks of follow-up (Judd et al. 2002). In general, depressive symptoms of BD illness persist longer than manic symptoms do (Hlastala et al. 1997).

At the other end of the spectrum are the less frequently discussed "unipolar manic" patients. Rates of unipolar mania are high in representative community samples (25%–33% of BD I patients) but are lower in clinically treated samples (approximately 10%) (Depue & Monroe 1978, Karkowski & Kendler 1997, Kessler et al. 1997, Weissman & Myers 1978). The diagnosis of unipolar mania may be unstable, however. In a long-term study of unipolar manic patients, 20 of 27 patients had episodes of depression during a 20-year follow-up (Solomon et al. 2003).

Suicide

BD is associated with higher rates of suicide than any other psychiatric disorder. Rates of completed suicide appear to be as high as 15 times the rates among the general population (Harris & Barraclough 1997) and four times higher than rates among patients with recurrent major depression (Brown et al. 2000). In a 40-year follow-up of 406 BD I and II patients admitted to the University Psychiatric Hospital of Zurich between 1959 and 1963, 11% (n = 45) had committed suicide (Angst et al. 2005). As many as 50% of people with BD attempt suicide during their lifetime (Jamison 2000).

Risk factors for suicide include a predominantly depressed presentation, substance and alcohol abuse or dependence disorders, being young and male, recent illness onset, significant anxiety, impulsiveness, family history of suicidality, and social isolation (Angst et al. 2005, Fawcett et al. 2000, Jamison 2000). Recent life-events stress also appears to be common before suicide (Isometsa et al. 1995). On the hopeful side, uncontrolled studies find that lithium reduces long-term suicide risk, as does treatment with neuroleptics and antidepressants (Angst et al. 2005, Baldessarini et al. 2003).

Psychosocial Impairment and Illness Costs

BD is ranked as the sixth leading cause of disability worldwide (Murray & Lopez 1996). A recent examination of 253 BD I and II patients found that only 33% of patients worked full-time and 9% worked part-time outside of the home (Suppes et al. 2001). Fully 57% reported being unable to work or working only in sheltered settings. Predictors of occupational and social dysfunction include subsyndromal depressive symptoms (Fagiolini et al. 2005), alcohol abuse history (Tohen et al. 1990), anxiety (Kusznir et al. 2000), psychotic symptoms (Tohen et al. 1990), and lower socioeconomic status (Keck et al. 1998).

BD patients experience ongoing functional impairment even between episodes, especially if they have subsyndromal depressive symptoms (Fagiolini et al. 2005). In a 12-month follow-up of BD I patients hospitalized for a manic or mixed episode, 48% recovered from their initial syndrome by 12 months but only 24% achieved functional recovery (Keck et al. 1998). Coryell et al. (1993) found that the effects of manic episodes on work, social, and family disturbance could be observed for as many as five years after an episode.

Conversely, several studies indicate above-average accomplishment among the family members of those with the disorder (Johnson 2005b). BD is believed to be associated with elevated creativity and productivity: Many famous artists, musicians, writers, and politicians appear to have had the disorder (Jamison 1993). There are also temperamental commonalities between BD patients and highly creative persons without psychiatric disorder, including openness to new experiences and novelty seeking (Nowakowska et al. 2005). The family members of BD persons often show high creativity (Richards et al. 1988).

DEVELOPMENTAL PERSPECTIVES ON BIPOLAR DISORDER

In the past 10 years, there has been a notable increase in research focused on how to evaluate and treat BD in childhood and adolescence. That BD can occur in childhood has been known for some time (Strecker 1921) and is not controversial. In contrast, how frequently it occurs and whether its presentation is consistent with adult presentations are matters of considerable debate.

In community samples, between 0% and 2.0% of adolescents meet diagnostic criteria for BD I disorder, and between 0.1% and 0.6% meet criteria for BD II disorder (Kessler et al. 2001, Lewinsohn et al. 1995). As one would expect, prevalence estimates of BD spectrum disorders

are higher in pediatric psychiatric facilities, with estimates from 6.0%–6.9% (Geller et al. 2002, Youngstrom et al. 2005).

There is broad agreement that early-onset BD disorder, when carefully diagnosed, is associated with a wide array of dysfunctions. In a four-year follow-up of prepubertal and early adolescent children with DSM-IV BD I mania or mixed disorder (mean age 10.8), the average duration of manic episodes was 79 weeks, and only 36% recovered fully within one year. At four-year follow-up, 64% had a recurrence of mania (Geller et al. 2004). Other outcomes include high rates of hospitalization, suicidal behavior, psychosis, reckless behavior, aggression, and substance abuse; psychiatric, medical, and educational service utilization; severe family conflicts; significant caregiver burden; and chronic psychosocial impairment (Biederman et al. 2003b, 2004; Brent et al. 1988; Chang et al. 2001; Craney & Geller 2003; Findling et al. 2001; Geller et al. 2000, [2004]; Lewinsohn et al. 2000; McClellan et al. 1999; Perlis et al. 2004; Strober et al. 1995; Wilens et al. 2003).

The DSM-IV criteria for BD are the same for adults and children. Many investigators have argued that DSM-IV criteria should be modified for pediatric BD. Controversy surrounds the diagnostic boundaries of the condition, such as the operational definition of a manic or mixed episode, whether to rely on narrow versus broad phenotypes, whether well-demarcated episodes of mania must occur, the minimum duration of episodes, and even more generally, what constitutes a symptom (Biederman et al. 2003a, Leibenluft et al. 2003, McClellan 2005, McClellan & Werry 2000). This disagreement stems in part from the fact that developmental factors often shape the appearance of mood-disorder symptoms and whether certain symptoms can be expressed at all. For example, credit-card spending sprees and hypersexuality depend upon the availability of the means to carry out one's impulses, which may not be available to children. Moreover, episodes of mania and depression in children appear to onset abruptly and are brief and recurrent (i.e., mood states that occur for only a few hours but switch several times per day). These course patterns raise questions about how to define episodes. The reliability of the diagnosis seems to decrease as youths age (Carlson 2005).

One group (Geller et al. 2002) has recommended that BD not be diagnosed unless euphoric mood and grandiosity are present. Another group (Biederman et al. 1999, Wozniak et al. 2001) points to irritability, aggression, and mixed symptoms as key features, and argues that manic irritability can be a chronic state in some children. Thus, the significance of irritability and aggression to the BD diagnosis is controversial.

The true test of the validity of narrow versus broad childhood phenotypes would be to determine which develop into true BD I or II disorder and which develop into BD spectrum or non-BD spectrum conditions. Questions have been raised about whether preadolescent mania is the same condition as adult mania (Harrington & Myatt 2003). One long-term study found developmental continuity for a narrow BD phenotype from late adolescence to early adulthood, but not for a broader BD phenotype marked by irritability and euphoria without the associated manic symptoms (Lewinsohn et al. 2000). In a study of 263 children and adolescents with BD spectrum disorders, 25% of participants with subsyndromal symptoms of mania (designated as BD not otherwise specified) developed BD I or II disorders during a 1.5-year follow-up (Birmaher et al. 2006). A six-year follow-up of children with attention deficit hyperactivity disorder found little diagnostic specificity for manic symptoms (Hazell et al. 2003).

ETIOLOGY OF BIPOLAR DISORDER

Genetic Studies

BD is among the most heritable of disorders. The concordance rates for identical twins average 57% percent, compared with 14% percent for fraternal twins (Alda 1997). Heritability

estimates as high as 85% have been obtained (McGuffin et al. 2003). Adoption studies, although few in number, confirm the importance of heritability in BD and unipolar depression (Wender et al. 1986). One twin study found that heritability for depression and mania was correlated, but the correlation was low enough that these vulnerabilities should be considered as distinct (McGuffin et al. 2003).

The risk of BD among children of BD parents is four times greater than the risk among children of healthy parents. However, the risk to children of BD parents of developing a non-BD psychiatric disorder (for example, attention deficit hyperactivity disorder) is 2.7 times greater than the risk to children of healthy parents. Thus, a proportion of the familial risk (through either genetics or family environment) is not specific to BD illness (Hodgins et al. 2002, LaPalme et al. 1997).

Shared Genetic Vulnerabilities to Bipolar Disorder and Schizophrenia

Although once thought genetically distinct, new research indicates a partial overlap in the susceptibility genes for BD and schizophrenia (Berrettini 2003). When examining the first-degree relatives of either BD or schizophrenic probands, there is an increased risk for schizoaffective and major depressive disorders. Further, the monozygotic cotwins of persons with schizophrenic disorder are at increased risk for mania (8.2%) as well as schizophrenia (40.8%). Likewise, the monozygotic cotwins of manic patients are at an increased risk for schizophrenia (13.6%) and mania (36.4%) (Cardno et al. 2002).

The locus of this shared susceptibility has been investigated in numerous studies. Berrettini et al. (1997) and Detera-Wadleigh et al. (1999) found a susceptibility locus for BD on 18p11, whereas Schwab et al. (1998) found evidence for a schizophrenia-linkage disequilibrium in the 18p11.2 region. A meta-analysis (Badner & Gershon 2002) revealed the most promising genome regions for BD were 13q32 and 22q11, whereas for schizophrenia the regions included 8q24, 13q32, and 22q11. Shared linkages to both disorders may also be present in the 8p22 and 10p14 genomic regions (Berrettini 2003). The catechol-O-methyltransferase (COMT) gene, which is responsible for controlling the metabolism of dopamine in the prefrontal cortex, appears to be associated with both schizophrenia and BD (Murray et al. 2004).

Despite these areas of overlap, there are important differences between BD and schizophrenia in brain structure and neuropsychological functioning. In patients with schizophrenia, gray matter, hippocampal, and amygdala volume are reduced relative to BD patients and healthy controls (Altshuler et al. 1998, Strakowski et al. 1999). Neurodevelopmental events such as prenatal and obstetric events have been implicated in the etiological pathways to schizophrenia but not BD (Murray et al. 2004).

Among children who later develop mania, deficits during the premorbid state are primarily in emotional, social, and behavioral development but not intellectual functioning. In contrast, children who later develop schizophrenia show developmental impairments in psychomotor, language, and cognitive functioning (Cannon et al. 1997, 2002). After repeated episodes of illness, however, deteriorations in neuropsychological functioning and ventricular volume can be observed in both disorders (Quraishi & Frangou 2002, Strakowski et al. 2002).

BD and schizophrenia are likely to be a result of many genes contributing to small effects rather than fewer genes of larger effect, with some degree of overlap in the linkage regions. The common susceptibility genes may predispose individuals to dopamine dysregulation and eventual psychosis. However, there are genes whose expression may affect neurodevelopment, illness-specific neurological changes, and environmental factors. These factors distinguish the onset and course of BD from the onset and course of schizophrenia (Murray et al. 2004).

Neurotransmitter Dysregulation

Three neurotransmitters have received the most attention in studies of mood disorders: norepinephrine, dopamine, and serotonin. The original neurotransmitter models suggested depression was tied to low levels of norepinephrine and dopamine, whereas mania was tied to high levels of norepinephrine and dopamine. Mania and depression were both posited to be tied to low levels of serotonin, a neurotransmitter that helps regulate norepinephrine and dopamine. Researchers initially believed that mood disorders would be explained by absolute levels of neurotransmitters in the synaptic cleft that were either too high or too low. Evidence does not entirely support these hypotheses, as the time course of drug responses indicates that changes in receptor sensitivity are more likely to be responsible for symptom stabilization than shifts in absolute neurotransmitter levels (Charney et al. 1981, Thase et al. 2002).

Researchers now focus on the functioning of neurotransmitter systems, such as increased sensitivity of the postsynaptic receptors in pharmacological challenges, neuroimaging, or genetic studies. It is now widely believed that dysregulation in dopamine and serotonin systems interacts with deficits in other neurotransmitter systems, such as GABA and Substance P, to produce symptoms of mood disorders (e.g., Stockmeier 2003). For the sake of brevity, we focus our review on the evidence regarding dysregulation in dopamine and serotonin systems. We focus less on norepinephrine, as it is less clear whether changes in norepinephrine levels are a product or cause of mood symptoms (Thase et al. 2002).

DOPAMINE—Among people without BD, several different dopaminergic drugs have been found to trigger manic symptoms such as increased mood, energy, and talkativeness (Willner 1995). People with BD show pronounced behavioral effects to amphetamine even in the absence of increased binding of dopamine to the receptors (Anand et al. 2000). Furthermore, in approximately 10% of people with a history of mania, one full night of sleep deprivation will trigger manic symptoms by the next morning (Barbini et al. 1998). Sleep deprivation may interfere with normalizing the sensitivity of dopamine receptors (Ebert et al. 1994).

Some theories place emphasis on links between mood disorders and dopamine receptors within specific regions of the brain believed to be involved in reward motivation, including the nucleus accumbens, the ventral tegmentum, and the striatum (Naranjo et al. 2001). Behavioral sensitization paradigms provide one window into studying these pathways. Behavioral sensitization refers to the finding that organisms exposed to repeated intermittent doses of psychomotor stimulants become more responsive to their effects, given certain conditions of intermittency and dosage (Sax & Strakowski 2001). This increased sensitivity may be a result of the enhanced sustained release of dopamine (Robinson & Becker 1986), particularly within pathways involved in modulating reward motivation (Kalivas et al. 1988). First episode patients with BD and schizophrenia demonstrate less behavioral sensitivity than do those not diagnosed with these disorders, perhaps indicating that dopaminergic pathways have already developed increased sensitivity (Strakowski et al. 1996, 1997).

In animal models, a set of candidate genes for BD have been identified that relate to DARPP-32 activity, which is involved in modulating dopamine signaling within the niagrostriatal pathway (Ogden et al. 2004). An extensive number of human studies have tested for polymorphisms in the genes modulating the sensitivity of different dopamine receptors. At present, no consistent findings have emerged for polymorphisms in the D1, D2, D3, and D4 receptor genes or the dopamine transporter genes. Positive associations have been found only for small subgroups or have failed to replicate (Chiaroni et al. 2000, Georgieva et al. 2002, Gorwood et al. 2000, Lopez et al. 2005, Manki et al. 1996, Muglia et al. 2002). The enormous complexity of the genes modulating dopamine production and receptor sensitivity mandates more research.

SEROTONIN—Neuroimaging studies indicate mood disorders are generally associated with decreased sensitivity of the serotonin receptors (Stockmeier 2003). Furthermore, serotonin systems can be challenged by manipulating levels of tryptophan, the precursor to serotonin (Staley et al. 1998). Consistent with the idea that decreased sensitivity of serotonin receptors is involved in BD, persons with a positive family history of BD develop more cognitive deficits after a serotonin-depletion procedure than persons without a family history (Sobczak et al. 2002). In one study, however, a procedure used to increase serotonin levels, tryptophan loading, produced similar cognitive deficits in family history–positive participants compared with family history–negative participants (Sobcazk et al. 2003). Such effects are consistent with dysregulation in serotonergic systems, but the nature of that dysregulation remains undefined.

Much research has focused on genes modulating the serotonin transporter, which is found on the presynaptic membrane and regulates levels of serotonin in the cleft. A meta-analysis of 150 studies found that BD was not consistently related to genes regulating serotonin receptors, although it was related to polymorphisms in two loci related to the serotonin transporter: the promoter locus and the VNTR (various number of tandem repeats, usually 9, 10, or 12 repeats) locus (Anguelova et al. 2003). A separate meta-analysis, however, did not replicate this conclusion (Lotrich & Pollock 2004).

Brain Regions Involved in Bipolar Disorder

Many of the brain regions involved when healthy people experience strong emotions have been implicated in the pathology of BD (Phillips et al. 2003). In functional studies, BD I disorder is associated with elevated activity in the amygdala (Kruger et al. 2003), a key brain structure involved in identifying the significance of emotionally relevant stimuli of both negative and positive valence. PET studies and functional MRI studies of activity during cognitive or emotional tasks have each shown a pattern of amygdala hyperactivity among people with BD I disorder (Chang et al. 2004, Lawrence et al. 2004). People with BD also demonstrate diminished activity of the hippocampus and prefrontal cortex (Kruger et al. 2003). During depression, diminished activity in the anterior cingulate is observed (Mayberg et al. 2004).

In parallel with the findings of functional studies, structural studies have found that BD is associated with a smaller-than-average volume in the prefrontal cortex, basal ganglia, hippocampus, and anterior cingulate; some studies also report an above-average volume of the amygdala (Phillips et al. 2003). Taken together, these structural and functional deficits are consistent with the models of limbic-cortical dysfunction proposed for unipolar depression (Davidson et al. 2002, Mayberg et al. 2004). That is, elevated activity in the amygdala might contribute to emotional sensitivity, whereas diminished activity of the cortical regions might interfere with effective planning and goal pursuit in the context of emotion, leading to a low capacity to regulate emotion.

Neural activity in these regions appears to change with episode status. During mania, persons with BD may show diminished reactivity to negative stimuli compared with healthy or euthymic persons. For example, after viewing faces with different negative emotional expressions, Lennox et al. (2004) found decreased amygdala and subgenul anterior cingulate cortex activation in manic BD patients compared with controls. Hence, brain regions involved in identifying the importance of negative stimuli, as well as regulating responses to those stimuli, appear to become less active during manic episodes. This is consistent with evidence for cognitive and behavioral insensitivity to negative stimuli during manic episodes, described further below. Other studies have found that both at rest and during motor tasks, the level of activity in the basal ganglia is positively correlated with the concurrent level of manic symptoms (Blumberg et al. 1999, Caligiuri et al. 2003).

Hence, one theory is that BD is related to dysregulation in brain regions relevant to emotion, including the amygdala, basal ganglia, and dorsal anterior cingulate. During mania, people may become less sensitive to negative stimuli, which may be reflected in a diminished neural responsivity to cues of threat. Hyperactivity in the basal ganglia may contribute to increased reward motivation (Knutson et al. 2001).

PSYCHOSOCIAL PREDICTORS OF THE COURSE OF BIPOLAR DISORDER

By the end of the 1980s, researchers began to acknowledge that biological and genetic models of BD did not explain the enormous heterogeneity in the course of the illness over time (Prien & Potter 1990). This recognition contributed to a renewed emphasis on psychosocial predictors in the course of the disorder. For example, Ellicott et al. (1990) found that BD patients with high life events–stress scores were at 4.5 greater risk for relapse in a two-year follow-up than patients with medium or low life events–stress scores. Miklowitz et al. (1988) found that BD I manic patients who returned after a hospitalization to families rated high on expressed emotion (EE) attitudes (criticism, hostility, or emotional overinvolvement) or who showed high levels of caregiver-to-patient affective negativity (criticism, hostility, or guilt-induction) during face-to-face interactions were at high risk for relapse. Those whose families had high EE or high affective negativity were highly likely to relapse within nine months (94%), whereas those whose families rated low on both attributes were unlikely to relapse (17%).

Although these first-generation studies established the prognostic role of psychosocial factors, they did not address how psychosocial variables influence depression versus mania. A second generation of research has examined which psychosocial variables influence the course of BD depression and which influence the course of mania.

Psychosocial Predictors of Depression within Bipolar Disorder

The symptomatology and neurobiology of unipolar and BD depression have many strong parallels (Cuellar et al. 2005). Given this, it is not surprising that many of the psychosocial predictors of unipolar depression also predict the course of BD depression. Here, we focus on many of the variables known to predict unipolar depression, including negative life events (Monroe et al. 2001), low social support (Brown & Andrews 1986), EE (Butzlaff & Hooley 1998), neuroticism (Gunderson et al. 1999), and negative cognitive styles (Alloy et al. 2000).

As reviewed by Johnson (2005a), three cross-sectional studies with careful methodological procedures have found that negative life events are equally common before episodes of BD depression and unipolar depression (Malkoff-Schwartz et al. 2000, Pardoen et al. 1996, Perris 1984). Prospective research has also found that stressful life events lengthen the time to recovery from a depressive episode (Johnson & Miller 1997) and predict increases in BD depression over several months (Johnson 2005a).

Several studies have examined moderators of life events effects. Two studies of undergraduates with a history of hypomanic or depressive symptoms found that negative life events predicted increases in depressive symptoms only among students with negative cognitive styles (Alloy et al. 1999, Reilly-Harrington et al. 1999). Despite early theories of "kindling" (Post & Weiss 1998), studies have not consistently found that life events are more potent in provoking initial episodes than later episodes (Hammen & Gitlin 1997, Hlastala et al. 2000).

Given the strong parallels between these environmental predictors of unipolar and BD depression, one might expect that other psychosocial predictors of unipolar depression would be operative in BD depression. Consistent with this idea, two prospective studies of BD found that neuroticism was associated with increasing depressive symptoms but was unrelated to manic symptoms (Heerlein et al. 1998, Lozano & Johnson 2001). Similarly, low social support

is a predictor of BD depression but not mania (Johnson et al. 1999). Familial EE predicted a poorer course of depressive symptoms in two studies (Kim & Miklowitz 2004, Yan et al. 2004).

Previous reviews (Cuellar et al. 2005, Johnson & Kizer 2002) have summarized research on negatively biased cognition in BD disorder. Although negative cognitive styles are often documented in BD disorder, they are most likely to be found during depression compared with well periods (Johnson & Kizer 2002), they more consistently predict depression than mania (Johnson & Fingerhut 2004), and they can be explained by the presence of depressive history rather than manic history (Alloy et al. 1999). Furthermore, negative cognitive styles and low self-esteem predict increases in depression over time (Johnson & Fingerhut 2004, Johnson et al. 2000).

In sum, variables that influence the course of unipolar depression also influence BD depression, including negative life events, poor social support, family EE, negative cognitive styles, and low self-esteem. The strong parallels between unipolar and BD depression suggest psychosocial treatment approaches developed for unipolar depression might apply to BD depression.

Psychosocial Predictors of Mania

Compared with BD depression, less is known about the psychosocial variables influencing mania. Available models highlight three types of predictors of mania: negative threats (the manic-defense model), goal engagement, and life events involving sleep deprivation.

THE MANIC-DEFENSE MODEL—Psychodynamic models have long conceptualized mania as a defense against loss experiences and painful awareness of negative feelings about the self (Adler 1964). As reviewed by Johnson (2005a), six out of the eight available cross-sectional studies show negative life events are no more common before than after manic episodes. Similarly, in prospective studies, no direct effects have been obtained for negative life events as a predictor of mania (Alloy et al. 1999, Johnson et al. 2000, McPherson et al. 1993, Reilly-Harrington et al. 1999), nor is there evidence that negative cognitive styles predict increases in mania (Johnson & Fingerhut 2004). Despite the absence of direct effects, two studies found that students with BD spectrum disorders who had negative cognitive styles were at increased risk for hypomanic symptoms after negative life events (Alloy et al. 1999, Reilly-Harrington et al. 1999). In sum, literature on life events provides only weak support for the manic-defense model.

Beyond the role of threats, the manic-defense theory suggests that mania unfolds as part of a defensive process. In support of this idea, two studies found that people with remitted BD tend to endorse positive views of the self when asked directly but display more negative cognitive styles on subtler cognitive measures than healthy controls, including measures of attributions for negative life events or attention to negative words (Lyon et al. 1999, Winters & Neale 1985). Other research suggests that in the context of a threat (writing an essay about their own mortality), people with high vulnerability to hypomania demonstrate more defensive responses than people with low vulnerability to mania (Johnson et al. 2005a). They are also more likely to pursue highly stimulating, sensation-seeking activities (Thomas & Bentall 2002). Hence, people with BD may show certain types of defensiveness, but there is a lack of evidence to show that this defensiveness spirals into mania in the context of negative life events.

GOAL DYSREGULATION—The goal dysregulation model suggests that mania may result from excess goal engagement secondary to increased sensitivity of the dopaminergic reward pathways (Johnson 2005b). People with a history of mania and students vulnerable to mania

describe themselves as more sensitive to rewards (Meyer et al. 1999, 2001). People with BD place a stably high emphasis on goal pursuit, even when not in an episode (Johnson 2005b).

Johnson et al. (2000) hypothesize that excess reward sensitivity may heighten reactivity to success, such that manic symptoms would be more likely to occur after life events involving goal attainment. Results of a longitudinal study supported this hypothesis: goal-attainment life events predicted increases in manic symptoms but not depressive symptoms. Such effects were apparent even after controlling for baseline levels of manic symptoms and excluding life events that could have been caused by the patients' symptoms.

Laboratory studies provide a glimpse into possible explanations of the processes that contribute to manic symptoms after an initial success. In studies of responses to standardized (false) success feedback, people vulnerable to BD demonstrate more robust increases in confidence than nonvulnerable people (Johnson et al. 2005b, Stern & Berrenberg 1979). With increases in manic symptoms, people with BD remember more positive than negative memories (Eich et al. 1997), pay less attention to negative stimuli (Murphy et al. 1999), and become unable to accurately detect negative facial expressions (Lembke & Ketter 2002). Impulsivity, or the tendency to pursue rewards without awareness of potential negative consequences, also becomes elevated as people become manic (Swann et al. 2004).

Mood-state dependent shifts in cognition and particularly in confidence may contribute to increased goal-setting (Johnson et al. 2005b). In turn, increases in goal setting and time spent pursuing goals predict increases in manic symptoms over several months (Lozano & Johnson 2001). In sum, goal attainments and success feedback may trigger increased goal engagement, and this excess goal engagement may contribute to a positive feedback loop that accelerates the development of manic symptoms (Johnson 2005b).

SCHEDULE DISRUPTION—Wehr et al. (1987) hypothesized that sleep disruption might be one way in which life events trigger episodes of BD, noting episodes are often preceded by life events interfering with the ability to sleep (e.g., transmeridian flights, childbearing). This theory was developed more precisely by Ehlers et al. (1988, 1993). In the elaborated model, significant others serve the role of timekeepers ("social zeitgebers") whereas other social influences ("social zeitstorers") disrupt the ability of the BD person to maintain daily rhythms (e.g., a job with shifting work hours).

Malkoff-Schwartz et al. (1998) conducted interviews with BD patients to assess the life events preceding their most recent illness episode. They found that patients reported more life events involving social-rhythm disruption (events that affect sleep or wake times, patterns of social stimulation, or daily routines) in the eight weeks preceding the onset of mania than in the eight weeks preceding depression. They replicated these results in a second study (Malkoff-Schwartz et al. 2000). Such findings provide one more potential mechanism for understanding how life events affect the onset of mania.

In sum, the variables hypothesized to influence the onset of mania include life events involving goal attainment, life events involving sleep/wake cycle disruption, and defensiveness in response to threats. As discussed below, some of these risk factors are amenable to modification through psychosocial intervention.

TREATMENT OF BIPOLAR DISORDER, I: PHARMACOTHERAPY

Drug treatment for BD has three symptom targets—manic symptoms, mixed episodes, or depression—and is usually given in stages. In acute treatment, the objective is to resolve an episode that has already developed. In maintenance treatment, the objective is to delay the occurrence of future episodes, minimize the severity of episodes that do occur, and reduce the

severity of symptoms between episodes. Far more research has been conducted on acute treatment than on maintenance treatment. Because space precludes an exhaustive review of pharmacotherapy, we refer the reader to Goldberg (2004) or Kowatch & DelBello (2003).

Mood Stabilizer and Atypical Antipsychotic Treatment

The strictest definition of a mood stabilizer is a medication effective in treating or preventing manic, mixed, or depressive episodes without triggering episodes of the opposite polarity (Keck et al. 2002). Currently, the Food and Drug Administration has approved only five medications for BD: lithium, the traditional antipsychotic chlorpromazine (Thorazine), the anticonvulsant divalproex sodium (also known as valproate, and usually marketed as Depakote, Depakene, or Depakon), the atypical antipsychotic olanzapine (Zyprexa), and the anticonvulsant lamotrigine (Lamictal). Other medications used "off-label" for BD include other anticonvulsants [e.g., carbamazepine (Tegretol), oxcarbazepine (Trileptal), and topiramate (Topamax)] and other atypical antipsychotics [risperidone (risperdal), ziprasidone (Geodon), quetiapine (Seroquel), aripiprazole (Abilify), and clozapine (clozaril)]. These medications are often combined with antidepressants or anxiolytic agents.

Evidence for Drug Efficacy in Randomized Clinical Trials

TREATMENT OF MANIA—Lithium has the most extensive empirical record of controlling episodes of mania and preventing recurrences. Approximately 60%–70% of persons with BD show a remission of manic symptoms on lithium (for review, see Goldberg 2000). The benefits of lithium do not come without costs: weight gain, sedation, stomach irritation, thirst, motor tremors, and kidney clearance problems.

Recent pharmacological research has focused on the comparative efficacy of anticonvulsants. Originally, much hope was placed on carbamazepine, which has been shown to be as good as lithium in controlling mania and effective as an adjunct to lithium for rapid-cycling patients (Denicoff et al. 1997). However, its ease of use is limited by its side-effect profile, which can include neurotoxicity, elevation of liver enzymes, a drop in sodium levels, and a depression of the white blood cells. Divalproex sodium appears to be as effective as lithium in controlling manic episodes but with a milder side-effect profile (Bowden et al. 1994). Certain illness features predict a favorable response to divalproex, including mixed states, rapid cycling, and substance abuse (Goldberg 2004). Its efficacy in long-term relapse prevention is not clear (Bowden et al. 2000). Side effects of divalproex include nausea, stomach pain, fatigue, weight gain, and, similar to carbamazepine, elevated liver enzymes and depressions of platelet counts.

The atypical antipsychotic olanzapine has been found to be effective in the treatment of mania (both adult and pediatric onset), with particularly strong effects on mixed states and rapid cycling (Frazier et al. 2001, Gonzalez-Pinto et al. 2002, Tohen et al. 2000). Its efficacy in preventing manic or mixed-episode recurrences is at least as good as, and in some studies better than lithium or divalproex (Tohen et al. 2003, 2005). It also strengthens the long-term prophylactic effects of lithium and divalproex when used adjunctively (Tohen et al. 2002b, 2002c). Other atypical antipsychotics also show promise in treating manic episodes in adults (e.g., Hirschfeld et al. 2004; Keck et al. 2003; Sachs et al. 2002, 2004). Quetiapine is effective in controlling manic symptoms in adolescents (DelBello et al. 2002, 2006). Unfortunately, most atypical antipsychotics are associated with significant weight gain and sedation (Kowatch & DelBello 2003, McIntyre & Konarski 2005).

TREATMENT OF DEPRESSION—Most mood stabilizers are more effective in reducing manic than depressive symptoms (Thase & Sachs 2000). Although standard antidepressants appear relatively effective in treating episodes of BD depression when used in combination with mood stabilizers (e.g., Sachs et al. 1994), they can induce mania and accelerate mood

cycling in 20%–40% of patients when administered without a mood stabilizer (Altshuler et al. 1995, Goldberg & Whiteside 2002). Fortunately, one study found that the alternative of lithium and divalproex was as effective in treating BD depression as the combination of a mood stabilizer and a selective serotonin reuptake inhibitor (Young et al. 2000). As a result of these and other findings, some investigators advise against the use of antidepressants for BD depression (e.g., Ghaemi et al. 2001). However, a recent naturalistic study found that BD patients successfully treated for depression with mood stabilizers and selective serotonin reuptake inhibitors were less likely to develop depression and no more likely to develop mania if they continued antidepressants for six months after remission (Altshuler et al. 2003). Current treatment guidelines only recommend treatment with antidepressants if other agents have failed in BD depression, and then only in combination with a mood stabilizing or an atypical antipsychotic agent.

Lamotrigine appears to be an efficacious acute and maintenance treatment for BD depression (Bowden et al. 2003, Calabrese et al. 1999). It was also found to be effective in preventing relapse in a six-month study of rapid-cycling BD II patients, most of whom suffered from recurrent depressions (Calabrese et al. 2000). Adverse reactions to lamotrigine can include a serious skin rash in a small percentage of patients, which if unchecked can progress into Stevens-Johnson syndrome (Goldberg 2004).

Mechanisms of Drug Action

Goodwin & Jamison (1990) observed that most of the effective pharmacological treatments for BD affect levels of dopamine and serotonin. Current research on the action mechanisms of mood stabilizers centers upon signal-transduction pathways responsible for communicating chemical signals from the postsynaptic receptors to the cell nucleus and nearby cells. Lithium and valproate both inhibit protein kinase C (Manji 2001). Lithium also inhibits calcium, glutamate, and G-proteins, all components of the intracellular signaling cascade (Jope 1999, Manji 2001). There is increasing evidence that lithium and the selective serotonin reuptake inhibitors have neuroprotective effects in preventing apoptosis (cell death) (Rowe & Chuang 2004, Young et al. 2002).

Anticonvulsants are believed to have "antikindling" effects via diminishing excitation and enhancing inhibition in the mesolimbic system and other brain circuits responsible for affect regulation (Goldberg 2004). Lamotrigine and carbamazepine reduce the outflow, the presynaptic release, or the postsynaptic uptake of excitatory amino acids such as glutamate.

The traditional antipsychotic agents such as chlorpromazine or haloperidol are dopamine-blocking agents vary in their affinity for the D2 receptor. These medications have severe extrapyramidal side effects (e.g., restlessness, sedation) and the longer-term risk of tardive dyskinesia. Newer atypical antipsychotics such as olanzapine block not only dopamine but certain serotonin receptors as well. These agents appear to have mood stabilizing as well as antipsychotic effects and appear to have a more modest side-effect profile (e.g., Tohen et al. 2002a). There is debate, however, about whether traditional and atypical antipsychotics really differ in tolerability when considering dropout rates due to side effects (Lieberman et al. 2005).

Antidepressants alleviate depression primarily through serotonergic, dopaminergic, and noradrenergic mechanisms. They may also reduce the output of glucocorticoids, which, if overproduced, can lead to the destruction of cells in the hippocampus (Sapolsky 2000).

The Problem of Medication Nonadherence

Despite the availability of effective treatment options, many BD patients stop their medications against medical advice. Up to 60% are fully or partially nonadherent in the year after a manic

or mixed episode. One study found that patients in a community clinic took lithium for an average of only 76 days (Johnson & McFarland 1996). Only approximately 21% of patients who take lithium are continuously adherent with it (Weiss et al. 1998). Patients who discontinue medications, particularly if they do so rapidly, are at a greatly increased risk of relapse and suicide (Keck et al. 1998, Strober et al. 1990, Suppes et al. 1993, Tondo & Baldessarini 2000).

Nonadherence is a serious problem for all long-lasting medical conditions with intermittent symptoms. Beyond this, medication issues specific to BD include unpleasant side effects (e.g., weight gain, fatigue, cognitive dysfunction), missing high periods or periods of exuberance or creativity, lack of family or social supports, and lack of information about the disorder (Aagaard & Vestergaard 1990, Goodwin & Jamison 1990, Jamison & Akiskal 1983). The patients at highest risk for nonadherence are younger, have more severe illnesses or recent hospitalizations, and are more likely to have comorbid personality disorders or alcohol/substance disorders (Colom et al. 2000).

TREATMENT OF BIPOLAR DISORDER, II: PSYCHOSOCIAL INTERVENTION

Psychosocial interventions are intended to be used in conjunction with pharmacotherapy. Currently available psychosocial treatments differ in their presumed mechanisms of action, whether they are initiated during the period after an episode or after a period of remission and whether they are delivered in individual versus group modalities. For more extensive reviews of the psychosocial intervention literature, see Miklowitz & Otto (2006) or Johnson & Leahy (2004).

Psychoeducation

Psychoeducation, which is a component of all psychosocial interventions for BD, includes acquainting patients with strategies to identify symptoms and implement relapse-prevention procedures (e.g., emergency medication), promote drug adherence, minimize risk factors (e.g., substance abuse, interpersonal stress), and maximize protective factors (e.g., regular sleep/wake cycles). Psychoeducation has been delivered in group, family, and individual formats.

GROUP PSYCHOEDUCATION—Group psychoeducation enables patients to learn self-care skills and decrease stigma by meeting with others with the illness. Colom et al. (2003) assessed the efficacy of psychoeducation and support groups among 120 adult patients with BD I and II who had been in remission for at least six months. All patients received mood-stabilizing medications. One group received 21 weekly sessions of structured group psychoeducation and another received 21 unstructured, nondidactic group sessions. At the end of two years, fewer of the group psychoeducation patients (67%) than the control patients (92%) had relapsed, and fewer had been hospitalized. Patients, however, were more likely to drop out of the structured psychoeducation groups (27%) than the unstructured groups (12%).

Simon et al. (2005) evaluated a multicomponent care-management intervention in a large (*N* = 441) managed care–based BD sample. BD patients who had received treatment within the care network within the prior year were randomly assigned to pharmacotherapy or a care-management program consisting of pharmacotherapy, telephone-based monitoring, care planning within an interdisciplinary team, and group psychoeducation following the model of Bauer & McBride (1996; Bauer et al. 1998). In the first year of the study, patients in the program had lower mania scores and spent less time hypomanic or manic than those in the control group. Results of a two-year follow-up are pending.

INDIVIDUAL PSYCHOEDUCATIONAL APPROACHES—Although individual psychoeducation is often cited in treatment guidelines as the most essential element of

psychotherapy for BD patients (e.g., Yatham et al. 2005), few randomized controlled studies have actually examined its efficacy. Perry et al. (1999) examined the benefits of adding 7–12 sessions of individual psychoeducation to medication in comparison with routine care and medication. Psychoeducation sessions instructed patients how to identify their early warning signs of recurrence and obtain emergency medical intervention. The investigators observed a 30% reduction in manic relapses, a longer time before manic relapse, and enhanced social functioning in the treatment condition. The intervention did not affect time to depressive relapse. A second study found that a nine-month, 21-session individual psychoeducation was not as effective as a family psychoeducational intervention of equal duration in preventing recurrences or rehospitalizations over two years (Rea et al. 2003). Nonetheless, individual psychoeducation in conjunction with pharmacotherapy may be a cost-effective way of reducing manic symptoms.

Family-Based Approaches

Family interventions have a long history in BD (e.g., Davenport et al. 1977, Fitzgerald 1972). The first randomized trial (Clarkin et al. 1990) assigned 186 psychotic and affectively ill inpatients to a brief psychoeducational family intervention (average nine sessions) or to usual hospital care. The family intervention focused on improving adjustment to community life after hospital discharge. Patients who received the intervention had fewer symptoms and better functioning than control patients 6–18 months later. However, only 21 of the patients had BD.

Based in part on findings that family psychoeducational interventions are effective in delaying relapses of schizophrenia (Falloon et al. 1985, Hogarty et al. 1991, Leff et al. 1985), Miklowitz & Goldstein (1990) designed a family-focused treatment (FFT) for recently episodic BD patients. This approach is based on the idea that improving knowledge about BD, reducing high EE attitudes, and enhancing communication will reduce relapse rates. The treatment involves three stages: psychoeducation for the patient and family members about BD, communication-enhancement training, and problem-solving skills training. The psychoeducational segment includes a relapse prevention drill.

In the first randomized trial, FFT was combined with standard pharmacotherapy and compared with a brief psychoeducational control (two sessions of family psychoeducation plus crisis intervention sessions as needed over nine months). BD I patients ($N = 101$) were recruited during or shortly after a manic, mixed, or depressive episode. Over a two-year follow-up, patients in FFT were three times more likely to complete the study without relapsing (52% versus 17%) and had longer periods of remission without relapse (73.5 weeks versus 53.2 weeks). They also had greater improvements over time in depression and mania symptoms and better adherence to medications than did patients in the comparison group (Miklowitz et al. 2003a). A process analysis revealed that patients in FFT demonstrated more improved communication with their relatives than patients in the psychoeducational control (Simoneau et al. 1999).

In the second trial, Rea et al. (2003) compared FFT plus pharmacotherapy with a comparably intensive (21 session) individual psychoeducational treatment plus pharmacotherapy for BD patients hospitalized for a manic episode ($N = 53$). In the first study year, no differences emerged in relapse or rehospitalization rates. Over a 1- to 2-year post-treatment follow-up, however, patients in FFT had much lower rates of rehospitalization (12%) and relapse (28%) than did patients in the individual psychoeducational therapy (60% and 60%, respectively). The results suggest that FFT, although costly in the short term, may save money in the long term by reducing hospitalization costs.

Two open trials have extended the use of FFT into pediatric BD samples. Pavuluri et al. (2004) examined a combination of pharmacotherapy, FFT, and cognitive-behavioral therapy

(CBT) (12 sessions) for 34 school-aged (mean 11 years) children. Reductions from pre- to post-treatment were observed in mania, aggression, psychosis, depression, and global-functioning scores. A one-year open trial of FFT and medications for 20 adolescent patients (mean 14.8 years) who began in an acute period of illness showed substantial reductions in depression, mania, and parent-rated problem-behavior scores (Miklowitz et al. 2004).

Finally, testing a different family psychoeducational model, Fristad et al. (2002, 2003) found that children with unipolar disorder and BD randomly assigned to multifamily groups showed greater mood stability over six months than children assigned to a wait list, even though children in the two conditions received equivalent pharmacotherapy. Parents in the multifamily groups reported a greater understanding of mood disorder, more positive family interactions, and increased use of appropriate psychosocial and medical services than wait-list parents.

In sum, family interventions have been shown to be effective adjuncts to drug treatment for BD adults and possibly adolescents and children. When patients are not able to include family members in treatment, individual or group treatments are the sole options.

Individual Cognitive-Behavioral Therapy

Interest in the applicability of CBT to BD began in the early 1980s (Cochran 1984). The most recent CBT models (e.g., Basco & Rush 1996; Lam et al. 2003, 2005b; Newman et al. 2001; Patelis-Siotis et al. 2001; Scott et al. 2001; Zaretsky et al. 1999) focus on psychoeducation as well as cognitive restructuring to challenge overly negative and hyperpositive (e.g., "I will lose out in a big way if I do not invest in this stock now") cognitions.

Lam et al. (2003, 2005b) tested six months of CBT (12–18 sessions, plus two booster sessions after six months) with pharmacotherapy versus usual care and pharmacotherapy for 103 BD patients. Importantly, the patients had had at least three episodes in the past five years but had been in remission for at least six months. At one year, relapse rates were 44% in the CBT condition and 75% in the usual care condition. Patients in CBT also spent fewer days in illness episodes. Twelve to 30 months after treatment, CBT did not prevent relapse relative to usual care but did continue to show a positive influence on mood and days spent in episodes.

As with other treatments based heavily on approaches for unipolar depression, the effects of CBT were stronger on depression than mania (Lam et al. 2005b). Moreover, patients who reported high scores on a scale measuring "Sense of Hyper-Positive Self" had high rates of relapse even if they received CBT (Lam et al. 2005a). Lam et al. recommend the development of focused CBT techniques to address dysfunctional cognitions that go along with hypomania or grandiosity (dynamism, persuasiveness, and productiveness).

A multicenter trial across five sites ($N = 253$) in the United Kingdom (Scott et al. 2006) sheds further light on the effectiveness of CBT. The study compared 22 sessions of CBT plus medication with treatment-as-usual and medication. The patients had been in various clinical states before entry into the trial. A total of 60% of the patients had a recurrence during the 18-month follow-up, but no differential effects were found for CBT on time to recurrence. A posthoc analysis revealed patients with less than 13 prior episodes had fewer recurrences if treated with CBT than treatment-as-usual. However, the opposite pattern was apparent among patients with 13 or more episodes, who were more likely to have recurrences in CBT than treatment-as-usual. These results suggest that CBT may be most suited to patients in the early stages of their disorder or those with a less-recurrent course. Because sites varied in their experience in treating people with BD, analyses of cross-site effects will likely provide helpful information to clarify these results.

Interpersonal and Social-Rhythm Therapy

As discussed above, one model suggests BD symptoms are triggered by disruptions in daily routines and sleep/wake cycles. Frank et al. (2000) developed the interpersonal and social-rhythm therapy (IPSRT), derived from the interpersonal therapy for depression. Interpersonal therapy has been found in several randomized trials to be effective in stabilizing major depressive episodes and preventing recurrences (Elkin et al. 1995, Frank et al. 1990, Weissman et al. 2000).

IPSRT is usually begun after an episode and includes techniques to stabilize social rhythms and resolve interpersonal problems that preceded that episode. Therapists teach patients to track their daily routines and sleep/wake cycles and identify events (e.g., upcoming travel, visits from relatives) that may provoke changes in these routines.

IPSRT has been examined in two studies. In the Pittsburgh Maintenance Therapies study (Frank et al. 2005), acutely ill patients were randomly assigned to one of two weekly psychosocial treatments as an adjunct to medication management: IPSRT or clinical management. Clinical management was an active treatment focused on symptom control and medication adherence. Once patients were stabilized, they were randomly reassigned to IPSRT or active clinical management for a two-year maintenance phase. IPSRT in the acute phase was associated with more time before recurrences in the maintenance phase than clinical management. IPSRT was most effective in delaying recurrences in the maintenance phase when patients succeeded in stabilizing their daily routines and sleep/wake cycles during the acute phase. One caveat, however, is that continued treatment with IPSRT during the maintenance phase did not affect recurrence rates during maintenance.

In a nonrandomized trial, Miklowitz et al. (2003b) examined the effects of individual IPSRT sessions in combination with FFT (mean 29 sessions over one year) for BD I and II patients ($N = 30$) who had had a recent episode of illness. All patients received standard medication management. Part of the rationale for involving family members was that patients would have an easier time stabilizing social rhythms if spouses or parents assisted them in the process. The outcomes of patients in the combined treatment were compared with those of 70 historical comparison patients who received medication, two sessions of family education, and crisis management. Over the study year, patients in integrated family and individual therapy took longer to relapse and experienced less depressive symptoms than patients in the comparison condition, even after medication regimens were statistically controlled. Combination treatment did not affect manic symptoms. Little is known about the mechanisms involved in treatment response with IPSRT. Interestingly, two case studies show that sleep regulation alone can improve bipolar mood symptoms (Wehr et al. 1998).

SUMMARY AND FUTURE DIRECTIONS

BD is a highly recurrent, debilitating illness. Major strides have been made in clarifying its diagnostic boundaries, its etiology from the vantage point of basic neurobiology and psychosocial stressors, and effective treatments. Nonetheless, much remains to be clarified about the basic psychopathology and treatment of this disorder.

Similar to unipolar depression, BD is characterized by pathology in the brain systems involved in regulating emotion. Given the disorder's neural correlates, it is not surprising that psychosocial variables expected to trigger negative emotions, such as negative life events and EE in caregivers, exert a major influence on the course of disorder and are particularly tied to BD depression. Evidence regarding the unique predictors of mania is less well established. A growing body of research suggests remitted BD is associated with high sensitivity to reward and ambitious goal setting and that during mania, people develop cognitions that may contain

overly optimistic biases (Johnson 2005b). Given that mania is specifically associated with the brain regions involved in reward motivation, excess goal engagement may be one pathway into mania. Sleep dysregulation also appears predictive of manic symptoms, and congruently, life events involving schedule disruption are common before manic episodes begin. There is some evidence that people with BD are more defensive than are non-BD persons regarding negative thoughts and feelings.

Randomized controlled treatment trials indicate that mood-stabilizing medications and psychoeducational approaches help stabilize mania, whereas lamotrigine, FFT, and CBT appear more effective with depression (Lam et al. 2005b; Miklowitz et al. 2003a, 2003b; Scott et al. 2001). Future studies should examine the optimal combinations of pharmacotherapy and psychotherapy, perhaps using strategies to maximize the effects of different therapeutic agents on opposite poles of the disorder. Studies should also evaluate treatment staging strategies, such as stabilizing BD depressed patients on mood stabilizers and antidepressants and then determine whether adding a psychosocial intervention enables quicker discontinuation of the antidepressant.

The role of psychosocial interventions in the prevention of BD—or in delaying the onset of a first manic episode—is a particularly promising area. In 56 children with BD, all of whom had a parent with BD, age at onset of mania was 2–3 years later in children with prior exposure to either divalproex, carbamazepine, or lithium compared with those without such exposure (M.E. Howe, K. Saxena, and K. Chang, under review). Possibly, psychosocial interventions will achieve similar results with at-risk children. Prevention of first manic episodes may translate into less severe mood symptoms over time, fewer hospitalizations, lower illness costs, and less risk of suicide.

Identifying mechanisms of therapeutic action may enable investigators to design psychosocial interventions that are more efficient and have greater longevity of effects (Hollon et al. 2002). Do psychosocial interventions reduce the impact of variables shown to be prognostic in BD (e.g., stressful life events)? To what degree do they help patients modulate or regulate emotional states? Teaching skills to communicate effectively within a high EE family (Simoneau et al. 1999) or to modify depressotypic cognitive distortions (Scott et al. 2001) may decrease patients' sensitivity to stress or threat, which may translate into more stable emotional states.

Finally, pharmacological and psychosocial interventions have largely neglected the impact of BD on suicidal thoughts or actions and functional outcomes. Although interventions reduce rates of relapse, we cannot conclude that these effects translate into higher quality of life. Psychosocial interventions may make their strongest contribution in this arena.

Acknowledgments

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