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Bipolar Illness

William Coryell, M.D. and Paula J. Clayton, M.D.

Abstract This chapter records the historical significance of the disorder, mania, a symptom complex that has been recognized since antiquity. It shows the development of the concept of bipolarity and the more recent broadening of the concept. This is followed by etiologic considerations, with emphasis on the genetic components, and its epidemiology, risk factors, clinical picture, course, complications, differential diagnosis, and treatment. Updates in this revision apply to all areas subsequent to the history of the concept. They are particularly extensive in the areas of genetic underpinnings, the onset and course of the illness, those features with prognostic value and the various treatment options. Given the considerable accumulation of new findings since the first edition of this volume there is also a new emphasis on meta-analyses to better allow for tentative conclusions.

Keywords Bipolar I · Bipolar II · Mania · Depression · Hypomania · Rapid cycling · SAD · Secondary mania · Mood stabilizer · Course · Suicide

4.1. History

Numerous terms, usually dichotomous, have been used to classify mood disorders. The separation into unipolar disorder and bipolar mood disorders rests on extensively described genetic and clinical differences and has become the most fundamental and widely used of them. Unipolar mood disorder refers to patients who have depression only. Bipolar mood disorder designates patients who have episodes of mania or hypomania. Hypomania without a history of depressive episodes is not considered a diagnosable disorder (1).

Hippocrates is credited with introducing psychiatric diagnoses into medical nomenclature. Two of the six diagnoses that he proposed were mania, derived from a Greek word "to be mad," and melancholia, from "black bile." In his classification, mania referred to acute mental disorders without fever, and melancholia referred to a wide variety of chronic mental illnesses. In the first century AD, Aretaeus noted that depression and excitement often alternated in the same person and therefore might represent different aspects of the same illness. Although it is difficult to tell from the classification systems how pervasive this idea of cycling became in the centuries thereafter, the term mania remained prominent in all. For hundreds of years the diagnosis of mania has been used primarily for an illness with an acute onset and with a mood of merriment, rage or fury (2).

In 1686, Bonet used the term maniaco-melancholicus to characterize such patients. In the 1850s, Falret adopted the term circular insanity, and Baillarger used that of double-form insanity for similar patients (3). In 1874, Kahlbaum (4) referred to patients with cyclothymia. Kraepelin (5) drew on and synthesized the various approaches to nosology bequeathed to him from the preceding centuries. Beginning in 1883, he published nine editions of his textbook on psychiatry, and it was he who separated dementia praecox from manic-depressive illness using clinical descriptions and the natural history of the illnesses.

W. Coryell, M.D. (✉)
George Winokur Professor of Psychiatry, Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, IA, USA
e-mail: william-coryell@uiowa.edu

P.J. Clayton, M.D.
Professor Emerita, University of Minnesota School of Medicine and University of New Mexico School of Medicine, Pasadena, CA, USA
e-mail: pjcpsych@aol.com

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If we could assume that names are given to illnesses in an attempt to organize clinical observations, then it must be said, from the long history of the term mania, that the particular symptom cluster and course of mania has been apparent to clinicians throughout history.

Lange (6) may have first suggested the separation of unipolar from bipolar illness. Pederson et al. (7) noted "periodical depression has no manic phases and differs from manic-depressive psychoses with regard to heredity as well as distribution of somatic types and prognosis." They added that manic-depressive patients were more likely chronic and disabled in contradistinction to periodic depressives, who were more likely to be discharged and recovered. Leonhard (8), Perris (9), and Angst (10) solidified this point of view and the first American researchers to place emphasis on this distinction were Winokur and Clayton (11).

Although bipolar illness was separated from unipolar illness on the basis of differences in age of onset, course, family history, and response to treatment, this separation may not, in the end, prove entirely valid. More recently some data has accumulated that suggest, as Kraepelin (5) did, that the two illnesses may be different forms of the same disorder, with bipolar illness being a more severe, earlier-onset form than recurrent major depressive disorder. This unitary approach has been gaining momentum in the last 10 years and is best exemplified by Cassano et al. (12) and Akiskal and Benazzi (13).

4.2. Definition

Manic-depressive disease, or manic-depressive illness, is the old term for bipolar disorders as described in the Diagnostic and Statistical Manual of Mental Disorders (DSM 5). Bipolar I disorder requires a history of manic episodes and bipolar II disorder requires both episodes of depression and hypomania in the absence of any episode of mania. Cyclothymic disorder is characterized by at least 2 years of numerous episodes of hypomanic and depressive symptoms. Other Specified Bipolar and Related Disorders encompass presentations which feature symptoms that are characteristic of bipolar disorder but which do not meet the full criteria.

Bipolar I disorder may manifest with manic or depressed phases and either type may include an admixture of the other syndrome. If three symptoms of mania or major depression coexist with the full alternate syndrome for most days of the episode, it is said to have mixed features. The coexistence of full syndromes of both major depression and mania is considered to be a manic episode with depressive features.

For a diagnosis of a manic episode, DSM-5 requires presence of an irritable or elevated mood as well as increased energy and three or more of seven symptoms that last for 1 week. The symptoms cause social impairment and the episode should not be due to an abuse of a drug or a medical condition or treatment.

Specifiers can be used to identify patients with mood-congruent or mood-incongruent psychotic features. This distinction hinges on whether the content of delusions or hallucinations is, or is not, consistent with typical manic themes. If mood-congruent and mood-incongruent features coexist, the episode is specified as mood-incongruent.

Major depressive or manic episodes that begin during pregnancy or within 4 weeks following delivery are specified as having a peripartum onset. If three or more of 12 listed catatonic features dominates a major depressive or manic episode, that episode is considered catatonic.

Bipolar II disorder requires a history of at least one hypomanic episode and of one or more major depressive episodes. The criteria for a hypomanic episode resemble those for a manic episode except that the minimum duration is 4 days and symptoms must not include psychotic features and do not necessitate hospitalization or result in marked impairment.

4.3. Etiology

Genetic factors play a significant role in the etiology of bipolar affective disorder. No other data concerning etiology are as strong as those in the genetic area, and knowledge of family history appears to have practical value. The development of the genome map and of DNA probes for linkage markers led investigators to anticipate the identification of linkages to specific chromosomal markers. To date, however, only a few reproducible risk alleles have been detected. It may be, instead of using categories to divide individuals as affected, unknown and unaffected, it will be more informative to separate individuals by dimensions.

In addition to the genetic factors, studies have also investigated possible etiological roles for biochemical, neuroendocrine, neurophysiologic, and chronobiological abnormalities. Evidence that particular abnormalities are specific to bipolar illness over MDD has been scant, however. Besides the problem of always including some not-yet-identified bipolar patients in unipolar studies (at least 25–33%, up to 50%) one must always consider if the abnormalities described in any particular report occurred during a unipolar or bipolar depression, during a manic phase, pure or mixed, or in a well state, and under what conditions (i.e., on, or recently on, medications).

4.3.1. Genetics

There is no doubt that bipolar disorder is familial; that is, it runs in families, with close relatives being more likely to be affected than unrelated subjects. Three types of studies show the extent to which this is true: (1) family studies, (2) adoption studies, and (3) twin studies.

4.3.1.1. Family Studies

Family studies were originally anecdotal. Falret in 1854 interviewed the parents of patients with circular insanity and obtained compelling evidence as to the hereditary disposition in the illness (3). He concluded that circular insanity was very heritable, but could not decide whether it was more heritable than any other type of mental illness, although he was inclined to think so.

Many decades later Perris (9), Angst (10), and Winokur and Clayton (11) confirmed the heritability of bipolar illness with a series of family studies. Many others have followed and a review of those that included normal control groups estimated that the first-degree relatives of bipolar patients have a sevenfold increase in risk for bipolar illness over that of control subjects (14).

In addition to providing some support for the role of genes in the etiology of bipolar disorder, the results of family studies also speak to the validity of distinctions between bipolar and unipolar disorder and between bipolar I and bipolar II disorders. Their relevance to boundaries between bipolar I disorder and schizoaffective disorder, bipolar type, is covered in the chapter on schizoaffective disorder.

For the first of these distinctions, nearly all comparisons between the relatives of bipolar patients and those of unipolar patients have found the former to have substantially higher rates of bipolar illness. Some have also found more unipolar illness among the relatives of bipolar probands than among controls but this may be accounted for, in large part, by the substantial proportion of seemingly unipolar patients that eventually develop manic episodes. In fact, a family history of mania is among the most reproducible of the features that predict the development of mania among seemingly unipolar patients (15).

Regarding the distinction between bipolar I and bipolar II conditions, relevant studies appeared later and are fewer in number. The largest of these used data from the NIMH Collaborative Depression Study (CDS) (16). In a comparison of non-bipolar, bipolar II, and bipolar I probands grouped according to Research Diagnostic Criteria (RDC) (17), bipolar II disorder was most often diagnosed in the relatives of bipolar II probands and bipolar I disorder in the relatives of bipolar I probands (18). Other studies have observed a similar pattern (19).

More recent support for the separation of bipolar I and bipolar II conditions derives from an analysis of risk factors for diagnostic stability over a lengthy observation period (15). Probands who began follow-up with a diagnosis of non-bipolar disorder were more likely to switch to bipolar II disorder if their interviewed relatives had bipolar II disorder. Those who switched to bipolar I disorder were more likely to have had relatives with bipolar I disorder.

The diagnostic reliability of bipolar II disorder is problematic for several reasons. First, because patients rarely seek help for a hypomanic episode, clinicians usually diagnose on the basis of episodes that occurred in the sometimes distant past. Second, because hypomania, by definition, does not result in serious impairment and, in contrast to most mental disorders, need not involve impairment at all, such features as increased mood and energy may shade imperceptibly into correlates of normal mood fluctuations.

The CDS findings of Rice et al. (20) are pertinent to this problem. First-degree relatives of probands with MDD or bipolar disorder were reinterviewed blindly after a 6-year interval. A history of hypomania obtained at the first interview was recalled in the second interview in only 1 of 10 cases. Of the seven given a diagnosis of bipolar II disorder in one but not the other interview, all were related to probands who had a bipolar disorder. This suggests that if at least one of repeated screenings for past hypomania is positive, then the true diagnosis is most likely to be bipolar II disorder, even if some of those screenings were negative.

4.3.1.2. Adoption Studies

In contrast to family studies, adoption studies offer a means to separate familial transmission attributable to being raised by a parent with bipolar disorder from that due to being genetically related. Adoption studies are understandably difficult to accomplish and only two exist for bipolar disorder. One of these found that the adopted-away offspring of bipolar biological parents were four times more likely to have bipolar disorder than were adopted-away offspring of parents without bipolar disorder (21). Another found a twofold difference (22).

4.3.1.3. Twin Studies

Comparisons of monozygotic and dizygotic twins with and without bipolar disorder are another way to separate nature and nurture. The systematic review of six of these yielded median concordance rates of 39 and 5% for monozygotic and dizygotic

twin pairs, respectively (23). The heritability of bipolar I disorder is approximately 80% (24, 25), more than twice the 35% for unipolar major depression as derived from a weighted mean across seven studies (26). The heritabilities of bipolar II disorder and cyclothymia have been estimated at 58% and 68%, respectively.

4.3.1.4. Genetic Studies

Many linkage studies of bipolar disorder have sought to identify rare gene variants that carry high disease risk. The lack of clearly replicable findings has led to the conclusion that very few cases of bipolar disorder result from such genes. Rapid advances in the efficacy of genome mapping have made possible studies of unrelated subjects in order to detect population-level associations between disease and genes of smaller effect. Further progress in the relevant technology then allowed genome-wide association studies (27), an approach that has had some success. Currently, a small number of polymorphisms have shown associations that are strong and replicable (28).

Perhaps the most notable of these is CACNA1C (29). This gene encodes major L-type alpha subunits in the brain and is thus of particular interest given the apparent efficacy of L-type calcium channel blockers in mood disorders (30). However, this and other polymorphisms within the calcium channel subunit have also been associated with MDD and schizophrenia (31). Such findings have revived controversies over the Kraepelinian distinction between schizophrenia and mood disorders and have supported a greater emphasis on the study of spectrum variables rather than diagnostic categories (32).

4.3.2. Biochemical and Neuroendocrine Parameters

The depressant effect of reserpine when given for hypertension, and the antidepressant effects of a monoamine oxidase inhibitor when given for tuberculosis, led to the development of the biogenic amine hypothesis for the etiology of depression. The classic amine hypothesis held that depressive illness arises from a functional deficit of either norepinephrine or serotonin at critical synapses in the central nervous system. Conversely, an excess of such amines is associated with mania. It is evident that the third biogenic amine, dopamine, is also important and that other neurotransmitters or neuromodulators, such as those of the cholinergic, GABAergic, and endorphin systems, play roles in bipolar disorder. Janowsky et al. (33) suggested that an affective state may represent a balance between central cholinergic and adrenergic neurotransmitters and that depression may be a disorder of cholinergic predominance and mania, the opposite. In keeping with this, pilocarpine has been shown to rapidly decrease manic symptoms (34). More recently glutamatergic modulators have attracted particular interest in the search for additional new stabilizers (35).

Early observations of the affective state of patients with excesses or deficiencies of corticosteroids (Cushing's syndrome and Addison's disease) led to the measurement of corticosteroids in the plasma and urine of patients with depression. Some depressed patients had elevated levels of corticosteroids that returned to normal with recovery (36). Capitalizing on an endocrine challenge test for the diagnosis of Cushing's disease, Carroll et al. (37) began to systematically evaluate the dexamethasone suppression test (DST) in depressed patients. They reported that 67% of depressed melancholic inpatients and outpatients given 1 mg of dexamethasone at 11:00 p.m. failed to suppress cortisol at 8:00 a.m., 4:00 p.m., or 11:00 p.m. the next day (37).

The prospect of a long awaited diagnostic laboratory test in psychiatry together with the pathophysiologic implications of the findings and the ease with which the DST could be conducted, resulted in a profusion of studies. A recent review of published comparisons between samples with depressive disorders and comparison samples included those from 361 studies (38). The preponderance of findings indicated substantially higher rates of HPA axis hyperactivity in the depressed groups with an effect size of $d = 0.70$ for results of the DST. Effect sizes were higher in groups with older mean ages or with greater overall severity and were therefore larger in groups comprised of inpatients or of patients with melancholic or psychotic depression. Despite some findings to the contrary, most studies of bipolar disorder found HPA hyperactivity to be more likely in depressed and mixed manic phases than in purely manic phases.

4.3.3. Chronobiology

Numerous lines of evidence link bipolar disorder to disturbances in biological circadian rhythms. These include observations of phase advances in patients with bipolar disorder (39), the therapeutic benefits of induced phase advances (40), of sleep deprivation (41), and of morning light exposure, whether administered intentionally (42) or not (43). Also relevant is the seasonality that many with bipolar disorder experience (44) and the tendency for travel across time zones to provoke mania or depression, depending on the direction of travel (45, 46). Accordingly, refinements of therapeutic interventions that affect these rhythms have evolved to include serial sleep deprivation (47) and sleep deprivation combined with light therapy (48), lithium (49, 50), or antidepressants (51–53).

4.3.4. Brain Imaging

Numerous structural imaging studies exist and have generated highly variable results, perhaps because typical sample sizes have not been large enough for the number of regions tested (54). Among the more consistent observations are that, in comparisons to well controls, bipolar patients have larger lateral ventricles and smaller cross-sectional areas of the corpus callosum. Hyperintensities, particularly those that are manifest in deep white matter, are substantially more prevalent in patients with bipolar disorder than in well controls or in subjects with unipolar disorder (54). Relative to those with MDD, individuals with bipolar disorder have smaller corpus callosum cross-sectional areas and larger hippocampal volumes (55). Because bipolar patients taking lithium have larger hippocampal grey matter volumes than do those taking other mood stabilizers (56), the much greater use of lithium in bipolar disorder than in unipolar disorders may account for the observed differences between them in hippocampal volumes.

Functional neuroimaging studies have also been numerous and have generated a variety of findings. In a recent meta-analysis of functional neuroimaging in bipolar disorder that identified 55 studies (57), subjects with bipolar disorder had limbic hyperactivity and frontal hypoactivity in comparison to control subjects. This pattern was present in euthymic and depressed states but was most prominent in manic states.

4.3.5. Secondary Mania

Krauthammer and Klerman (58) thoroughly reviewed the literature on secondary mania, and required specific criteria for mania. The majority of reported causes were neurologic conditions such as neoplasm, epilepsy, head injury, cerebrovascular lesions, drugs, metabolic or endocrine disturbances, infections, or other systemic conditions.

Reviews of differences between organic and non-organic mania (59–61) have shown that patients with induced mania are frequently older at illness onset, their mood is more often irritable than manic, and they are less frequently psychotic. Their family histories are also more frequently negative, and they respond preferentially to anticonvulsants.

Mania may develop after a closed head injury (62–64). In a comparison of a large number of patients with bipolar disorder to well controls, those with a history of head injury were clearly overrepresented in the former (65). This relationship only existed for those whose injuries had occurred within 5 years of their admission for mania and was most prominent for admissions that had occurred within 1 year.

The relationship between stroke and the onset of mood disorders has also been well studied (66, 67). In a meta-analysis of 49 reports, the typical patient that developed mania following a stroke was a male with a right-sided infarction and without a personal or family history of psychiatric disorder (68).

4.4. Epidemiology

Because of the inclusion of BP II, estimates of the prevalence of bipolar disorder have increased since those reported by Boyd and Weissman (69) and by the ECA studies (70). Lifetime prevalence rates for DSM IV bipolar disorders (I and II) from the National Comorbidity Survey Replication were 3.9% (71). Rates varied inversely by age. Although prevalence rates for schizophrenia were not measured in these studies, bipolar illness is clearly the more common illness. Moreover, the cited rates did not include all of the cases of MDD that would later switch to bipolar disorder. Some authors contend that Major Depression and Bipolar Disorders may be nearer to equal in prevalence, mainly because of the BP II individuals embedded in the MDD group (72, 73). In most studies the distribution of males to females is balanced in BP I but is 2:1 female to male in BP II.

There are no racial differences in the incidence or prevalence of this illness. Evidence exists that both Hispanics and blacks with bipolar affective disorder are more likely to be misdiagnosed as having schizophrenia (74–76). In the ECA study (70), there were no differences in the lifetime prevalence of mania by race and mania was equally prevalent in urban or rural residents.

A relationship between bipolar disorder and creativity has long been appreciated (77). Studies of probands and relatives in the past several decades have likewise associated bipolar disorder with high educational and occupational achievement, but this appears to be true of the relatives of bipolar probands, rather than the probands themselves (78–80). The advantage in bipolar family members was particularly strong in the relatives who themselves had bipolar disorder, however. This suggests that, though the diathesis toward bipolar illness carries with it traits that promote higher achievement, the disability associated with those cases of bipolar disorder that necessitate treatment at tertiary care centers may overwhelm this advantage.

4.5. Diagnostic Stability

A recent review of follow-up studies that used structured interview at baseline showed a median conversion rate to bipolar I or bipolar II diagnoses of 15% (15). Follow-up studies that derived baseline diagnoses of MDD from chart review often reported considerably higher conversion rates than did those based on structured diagnostic interviews. This illustrates the frequent failure to appreciate past episodes of mania or hypomania that occurs in typical clinical settings. In the study that combined a high-surveillance intensity with a particularly lengthy follow-up of up to 31 years, the conversion rate was 1 in 5 (19.6%). For switches specifically to bipolar II disorder and to bipolar I disorder, rates were 12.2% and 7.5%, respectively (15). Patients with an early age of onset, with psychotic features, or with a family history of bipolar disorder have higher rates of switching (15, 81). Any admixture of manic symptoms with a depressive syndrome, particularly those of decreased need for sleep or increases in energy or activity, substantially raises the risk of an eventual bipolar diagnosis (15).

It should also be remembered that individuals who appear to have bipolar disorder are at risk for an eventual diagnosis of schizophrenia. In a carefully executed study of diagnostic stability over 10 years, Bromet et al. (82) found that a change in diagnosis of bipolar disorder to schizophrenia (14/95 = 14.7%) was more than three times more likely than a diagnostic change in the opposite direction (5/126 = 4.0%, $p < 0.005$).

4.6. Course

Though numerous reports have described tendencies for adverse life events to precede both manic and depressive episodes (83), most that have taken care to focus only on those adverse events that were likely to be independent of symptoms have found adverse events to be no more common before than after manic episodes (84). On the other hand, life events that disrupt social rhythms, particularly those resulting in sleep loss, do appear to trigger manic episodes (85, 86). This observation has led to efforts to stabilize social rhythms as a part of the long-term management of bipolar disorders (87).

Parturition is clearly a trigger. All studies have confirmed the postpartum period as a risk period for mania in known bipolar patients (88–90), and in patients with serious previous depression (81). Women who experience post-partum episodes are likely to develop them again following one or more subsequent deliveries.

Numerous studies have indicated that, in the teenage years, bipolar illness can be seen as schizophrenia, antisocial personality, or borderline personality disorder. Akiskal (81) indicated that the clinical presentation of adolescents with bipolar disorders are, in decreasing frequency, psychosis, alcohol and drug problems, moodiness, suicidal ideation or attempt, academic failure, philosophic brooding, obsessional brooding, somatic complaints, school phobia, "hyperactivity," stupor, and flagrant antisocial behavior.

The literature on late-onset (more than 50 years of age) bipolar illness is confusing because some of the patients discussed had episodes of depression before the age of 50 but did not become manic until after age 50. A study of manic episodes in older people indicated that a mean of 10 years had elapsed between the first depressive episode and the first manic episode (91). Late onsets should trigger a search for an underlying medical condition but there are onsets after 50 that are not associated with organic pathology (92–95). Since this age group is enlarging we should see more.

Periodicity of this illness exists for some patients, with fall/winter depression and spring/summer mania being most frequently described. Sayer et al. (96) confirmed in the southern hemisphere what had been reported in the northern hemisphere (97), that hospital admissions for mania have a spring/summer peak. A lengthy study of week-to-week mood ratings similarly found a peak for depressive symptoms in winter, but also a peak for hypomanic symptoms near the fall equinox (44).

Such observations have led to the concept of seasonal affective disorder (SAD) (98, 99), and many with this condition have bipolar disorder. Indeed, a community study concluded that bipolar patients experience greater seasonality than those with depression or healthy controls (100). The recognition of such patterns may be important for the management of certain patients.

4.7. Clinical Picture

4.7.1. Onset

More than one-third of patients first develop symptoms consistent with bipolar disorder in the teenage years (88, 101). Although there are conflicting reports (102), most researchers agree that the majority of patients, particularly women, begin with depressive episodes (103–106). Bipolar disorder most often starts with an episode of pure depression. Angst (103) reported that the ratio of depression to mania in the first episode was 3:1 for women and 3:2 for men.

It is well established that the mean age of onset for bipolar disorder is earlier than that for unipolar disorder. Moreover, many age-of-onset admixture analyses have been done to refine groups for genetics studies and most have identified three groups.

Early, middle, and late onset groups usually fall in the ranges of 20 or less, 21–29, and 30 or greater, respectively (101). An early age of onset is, according to substantial evidence, indicative of poorer outcomes. Such patients have longer index episodes (107), more depressive morbidity over time (102, 108, 109), a higher likelihood of psychotic features, lesser responses to treatment (110), and a greater likelihood of rapid cycling (111–113). They also make more suicide attempts (102, 111–113) and are more likely to abuse substances (114). Aging itself, when tracked within subjects, seems to bring more time in depressive episodes but not more manic or hypomanic morbidity (115).

The type of initial phase with cycling episodes also has prognostic value. In comparison with patients who began with a depressive phase, those with mania as their first phase tend to show better responses to lithium (116–120) and to have shorter episodes generally (121).

4.7.2. Symptoms

Mania can begin suddenly with the development of a full-blown syndrome over hours, or it may appear more gradually, and develop over days. It seldom takes weeks to develop. A history of a change in the patient's behavior is usual although, unless the onset is sudden, close relatives may miss the first indications. Early in the course of illness, mania can be preceded by life events, including bereavement, but later episodes do not appear to follow life events as often (122). There are no data to suggest that unipolar mania differs from the bipolar mania. Kraepelin (5) originally reported that 17% of his 900 manic-depressive patients were exclusively manic. In the Jorvi Bipolar Study (JoBS) only 4.4% of these recently diagnosed inpatients and outpatients reported having mania only (106). In the CDS, 14 (8.6%) of 163 bipolar I patients who had at least 15 years of follow-up gave a history of only manic episodes at their intake evaluation (123) but this number dwindled to 7 (4.3%) over the course of follow-up.

The picture can vary from an excited, talkative, loud, over-reactive, somewhat amusing individual to a completely disorganized, intrusive, and psychotic one. The mood is, by definition, elated, angry, or irritable. Patients often appear overly confident, bragging, self-aggrandizing, and happy but become irritable when their ideas are not enthusiastically endorsed. Frequently they become most angry at those who are closest to them, particularly their spouses. They interrupt conversations but dislike being interrupted themselves. They are distractible, and racing thoughts, pressured speech, circumstantiality, irrelevancies, and flight of ideas characterize their thoughts and language. Decreased need for sleep, an increase in sexual thoughts, and an increase in alcohol intake are all common in the manic patient. During the full-blown syndrome, there may be periods of depression lasting from minutes to hours. Grandiose ideas and delusions are common and are often the basis for the symptoms of excessive telephone calls, extravagances, and excessive writing. One or two themes usually predominate and may be religious, political, financial, sexual, or persecutory. Catatonic features during manic episodes have been well documented (124, 125).

All varieties of psychotic symptoms have been reported in the manic patient (126, 127). One of the better descriptions of this is the Carlson and Goodwin study on the evolution of manic episodes (128). They described patients admitted to research units at the NIMH, where, because of participation in various protocols, manic episodes were often allowed to evolve fully before treatment began. At the height of manic episodes, patients exhibited unusual psychomotor activities, incoherent thought processes, and delusions and hallucinations that were bizarre and idiosyncratic. They found symptoms of hyperactivity, extreme verbosity, pressured speech, grandiosity, irritability, euphoria, mood lability, hypersexuality, and flight of ideas. Seventy-five percent had delusions that were either of control or had sexual, persecutory, or religious themes; 75% exhibited assaultive or threatening behavior; 60% were intrusive; 55% had some delusions; 45% had regressive behavior (urinating or defecating inappropriately and exposing themselves); 40% had auditory and visual hallucinations; and 35% were confused. Confusion is, in fact, a well-documented symptom of acute mania. In one chart review, 58% of 31 manic patients were reported either to be disoriented or to have memory lapses (126). Kraepelin (5) used the term delirious mania for this condition.

Pope and Lipinski (129) emphasized that between 20 and 50% of well-validated bipolar patients have psychotic symptoms, including hallucinations, delusions, catatonia symptoms, and Schneiderian first-rank symptoms. The presence of formal thought disorder either during a manic episode, or more especially, at some time outside of a manic episode, is a predictor of persistent delusional thinking after 5 years of follow-up (130).

Andreasen (131–133) studied thought disorder in mania and found that, besides being over-inclusive, manic patients were tangential and had derailment, incoherence, and illogicality that was as prominent as it was in schizophrenic patients. Manic patients were more likely to have pressured speech, distractibility, and circumstantiality, while the schizophrenics more frequently had poverty of both speech and content of speech. Some have found that at follow-up, though it is in partial remission, many continue to have thought pathology (134, 135).

Many studies have compared bipolar depression to unipolar depression by symptoms. Differences have been inconsistent (136) but an excess in bipolar depression of psychomotor retardation (137, 138) and psychotic features have been among the most replicable (139–141). Other distinctions that have distinguished the depression of bipolar II patients from that of bipolar I patients include more anxiety (137, 142) and a greater likelihood of rapid cycling (143, 144) in the former.

4.7.3. Course

It should be remembered that nearly all descriptions of course in bipolar illness have used samples recruited from inpatient settings and that little is known of the typical outcome of bipolar I and bipolar II patients who might be sampled in outpatient settings. Individuals with relatively severe or refractory illnesses are more likely to be found in inpatient settings and, of course, such patients would be expected to follow on average a more malignant course. The body of follow-up studies nevertheless allows the use of a number of features in making useful prognostic estimates.

The most consistently reported difference in course between bipolar and unipolar disorders, other than in the likelihood of manic or hypomanic episodes, is the shorter time to relapse and shorter cycle lengths in the former (122, 145–149). Follow-up studies published over the past 50 years show single episode cases of bipolar disorder to be quite rare (1, 148–151).

Bipolar I and bipolar II disorders differ markedly in the likelihood of future manic episodes (152). In comparison to patients with bipolar I, those with bipolar II disorder experience more weeks with depressive symptoms, both above and below the threshold for a major depressive episode (153). This observation is in harmony with the tendency of bipolar II patients to exhibit higher levels of borderline, histrionic, and schizotypal traits (154).

Evolution in cycle length has been a topic of conflicting reports. A number have described a shortening of cycle length as episodes accumulate (148, 155) and this has spurred speculation that episodes themselves produce brain changes that result in an increased propensity to new episodes (the kindling hypothesis) (156). Nearly all of these studies were entirely, or at least largely, retrospective in design and therefore shaped by the tendency to remember more recent episodes and to forget those in the distant past. Other descriptions that were entirely prospective in their tracking of episodes have revealed no evidence that cycles decrease in length (121, 157, 158).

The presence of psychotic features, whether in depressive or manic phases, portends greater symptom morbidity and psychosocial impairment in the long term (159–161). Psychotic features that are mood-incongruent appear to predict even greater psychosocial impairment (162–164).

Anxiety symptoms during bipolar depressive phases comprise another feature with sustained prognostic import. It is not clear which types of anxiety symptoms are most important, but their presence in general is associated with a higher likelihood of switching (165, 166), shorter euthymic periods (160), poorer treatment response (163, 167), more suicide attempts (160), and a longer time to remission (168). A high level of anxiety appears to mark a type of depressive illness rather than to simply characterize a given episode. The degree of difference in morbidity over time between anxious and non-anxious individuals does not lessen over decades of follow-up (115).

Cycling within a given episode indicates a longer time to remission (169, 170), a greater likelihood of subsequent rapid cycling (143) and more morbidity in the ensuing years (121, 171). Cycling (121) and mixed episodes (172) also increase the likelihood of such episodes in the future. Those who tend to present with single phases of mania have, on average, much better long-term outcomes (173, 174).

Rapid cycling is the more extreme form of cycling and its poor prognostic implications are well appreciated (175–177). Some patients exhibit this pattern chronically but the majority with a prospectively observed onset of rapid cycling ceased to have rapid cycling within 1–2 years of its development (143, 175).

The reported frequency of mixed states varies with the number of symptoms of the other pole that are required to define it. Some reports combine mixed and cycling episodes, which elevates the percentage identified as having a mixed state (174, 178–181). In any event, those with mixed onsets are more likely to develop rapid cycling (182).

Patients with mixed mania also have poorer responses to acute treatment (178, 179) and worse outcomes on follow-up (161, 183, 184). Depressive episodes with mixed features last longer on average, feature more intense dysphoria and both carry a higher likelihood of suicidal thinking and behavior and feature dysphoria that is more intense (185, 186).

Two early studies (88, 187), with follow-ups averaging 2 years and 6 years, respectively found that nearly 30% in both never achieved full remission. Welner et al. (188) later reviewed a large number of studies of bipolar illness and indicated that chronicity, if defined as presence of symptoms, social decline, or both, occurred in at least one-third of the bipolar patients. Chronic mania, however, is uncommon.

An analysis of the weekly status of bipolar I and II patients, most of whom who were hospitalized at the beginning of a lengthy follow-up, showed that the average patient with bipolar I disorder was ill for 47% of weeks (189) while those with bipolar II disorder were in episodes for 54% of weeks (190, 191). Sub-syndromal residual symptoms are an important problem for bipolar patients (191). Disability resulting from both depressive and manic symptoms increase steadily with increases in symptom number (192) and relapse into a full syndrome is much more likely in the presence of even mild subthreshold symptoms (193).

There are several more favorable outcome studies. One was Petterson (194) who observed the clinical, social, and genetic aspects of 123 patients in Sweden for approximately 5 years. At the end of the study, a large number of patients showed more satisfactory work capacity and better social adaptation. This was a group treated by a single investigator. Similarly, Miller et al. (195) also reported that their carefully treated patients were asymptomatic 59% of the time in a 23.7 month follow-up. So perhaps with complete and vigorous treatment in a stable clinical setting, the course is more favorable.

4.7.4. Consequences

4.7.4.1. Psychosocial Impairment

Bipolar disorder may cost twice as much in lost productivity as major depression disorder (196). It is estimated that each US worker with bipolar disorder averaged 66 lost workdays in a year compared to 27 for major depression.

Some have indicated that the marriage of bipolar patients end in divorce more frequently than those of unipolar patients or appropriate controls (197). In the CDS, patients with bipolar disorders were twice as likely to be divorced as were unipolar patients (198). Bipolar patients who were married, however, were only half as likely as were married unipolar patients to rate the relationship with their spouse as poor or very poor. Well spouses may have a different view though. In one report, 53% of well spouses compared with 5% of the bipolar patients indicated that they would not have married the spouse, and 47% of the well spouses, compared with 5% of the patients, would not have had children had they known about the bipolar illness before making these decisions (199). Thus, the illness has an impact on marriage, job, child rearing, and all aspects of life (200).

4.7.4.2. Suicide

A review of 27 studies of bipolar disorder showed a median suicide rate of 0.4 per 100 person-years (201). The 13 reports that included standardized mortality ratios had a median value of 22, indicating that individuals with bipolar disorder have a 22-fold greater likelihood of eventual suicide than do age- and sex-matched individuals from the general population.

In a 40–44 year follow-up of patients hospitalized for a mood disorder, 10.2% of those with bipolar disorder died by suicide (202, 203). Even though it was the more seriously ill patients who got treatment, the suicide rate was much reduced in those who were treated compared to those who were not. Outpatients have lower suicide rates in most studies (194, 204, 205).

Bipolar patients die by suicide in the depressed phase of their illness. One of the first psychological autopsy studies showed that although the most frequent diagnosis was one of a mood disorder, no patient was manic at the time of the suicide (206).

Findings have been uneven regarding whether risks for completed suicide are higher for patients with bipolar disorder than for those with MDD. In many reports, and particularly in retrospective studies, bipolar patients were more likely to have made suicide attempts (137, 169, 207). In prospective studies bipolar patients appear to have the same risk factors for suicide attempts and completions, as do MDD patients (208).

4.7.4.3. Cardiovascular Morbidity and Mortality

There are also links between bipolar disorder and excess cardiovascular mortality (209, 210). The increase in risk appears to be higher in bipolar illness than in MDD (211–213) and may be especially strong when the illness is not treated (202, 214, 215). The few studies that have compared bipolar I and bipolar II groups found significantly higher risks for cardiovascular morbidity in the former (208). The cumulative time already spent in manic or hypomanic episodes appeared to drive this risk (216).

4.7.4.4. Other Morbidity

Bipolar illness is associated with increased risk for dementia (217) as is MDD. Some of this association can be attributed to mood symptoms that are a prodrome of dementia, but a number of reports have described robust associations with mood disorders with onsets that have preceded the onset of dementia by many years.

Most mental disorders increase risks for alcohol use disorders, but the risk is highest in bipolar I and bipolar II disorders (218), and, relative to the general population, is much greater for women than men (219). Alcoholism may develop before or after bipolar illness first appears, and this order has some prognostic significance. Bipolar disorder which develops after alcoholism is established has a later onset and entails less affective morbidity over time (220, 221) The outcome for the alcoholism is poorer, however (220). This suggests that, when the onset of either bipolar disorder or alcoholism is facilitated by the presence of the other disorder, the course of the illness with later onset may be less malignant. Ongoing alcoholism or substance abuse, however, appears to predispose to mixed bipolar episodes (222, 223).

Some researchers have concluded that, in remission, manics evaluate themselves in a positive way (199, 224, 225). Others have emphasized the achievement-oriented personality of the bipolar patients (226, 227) and still others have found that bipolar patients who are well or stabilized on lithium have personalities similar to those of controls (228, 229). Some have suggested rather that lithium mutes underlying cyclothymia and causes bipolar patients to test more like unipolar patients (230).

A more recent look at distinct temperaments in 98 bipolar I, 64 bipolar II, and 251 unipolar major depressive disorder patients found that bipolar I patients described themselves as near normal whereas bipolar II patients emerged as mood labile, energetic, and assertive yet sensitive and brooding (231). Bipolar I patients were low on neuroticism and bipolar II patients were high,

mostly because of their mood lability. Angst and Clayton (232) compared premorbid personality traits in young men who went on to develop bipolar illness with those who remained well, and found no differences. Unfortunately, the personality test did not measure obsessionality—the trait, as reported by Klein and Depue (233), that may be associated with risk for bipolar disorder in the offspring of bipolar probands.

Rates of comorbidity in general are probably higher in bipolar disorders than in any other prevalent DSM IV disorder and this certainly extends to the personality disorders. Bipolar II disorder is more likely to be accompanied by personality disorders than is bipolar I disorder. Many patients with bipolar illness have high levels of impulsivity, a trait that worsens during episodes but then appears to remain higher than those of normal controls, even between episodes (221, 234).

With regard to criminality, Petterson's (194) patients had fewer convictions than expected in comparison with the general population, a finding replicated in other studies. An interesting set of studies (235), however, indicates that symptoms of mania are more common in forensic settings than was generally thought. Among patients admitted to St. Elizabeth's Hospital in Washington, DC, 11 of the 13 attempted crimes against the presidents of the USA, so-called White House cases, were perpetrated by people diagnosed as having an affective disorder, and the majority of them were bipolar.

There is also an association between pathologic gambling and a bipolar diagnosis (236). Pathologic gamblers have high rates of comorbidity, especially with bipolar disorder (237). In a large family study, the relatives of pathological gamblers were more likely to have bipolar disorder than were the relatives of control probands. This remained true when the effect of bipolar illness in the proband was controlled (238).

4.8. Differential Diagnosis

As indicated, there are other disorders that share many features with bipolar disorder. The distinction between bipolar disorder and some of these disorders is particularly problematic.

4.8.1. Schizophrenia

Schizophrenia and mania are alike in many ways. The symptoms of a current episode can be similar in mania and schizophrenia. There is not one symptom that is pathognomonic for either, although the mood of merriment, elation, ecstasy, or even irritability is much more likely to occur in mania than in schizophrenia. A study of diagnostic criteria for mania indicated that the triad of symptoms—manic mood, rapid or pressured speech, and hyperactivity—is relatively specific for mania (239). Thus, the presence of this triad should heavily tilt a differential diagnosis toward mania. In patients partially treated with lithium or other anti-manic drugs, these symptoms may be muted, and the prominent symptoms may only be psychotic symptoms.

Mania, for the most part, should have a relatively sudden onset, with the only extended prodromal symptoms being a depressive syndrome, and should be characterized as a clear change from the person's premorbid self. Schizophrenia is usually more insidious in onset, but it, too, can begin with depression or anxiety. Again, the other indications of a manic syndrome, such as increases in activity and decreased need for sleep, previous episodes, an acute onset, and family history, should help to differentiate patients. Prominent delusional thinking or hallucinations may overshadow manic symptoms in an acutely psychotic individual. In these cases a careful questioning of family members may reveal that manic symptoms were apparent in the lead up to fulminant psychosis.

The course of the illnesses can be similar. At least one-third of bipolar patients have either social disabilities or symptoms that may be more than just low-grade depressive symptoms. Still, all studies show significantly better follow-up outcome in manic individuals than in schizophrenics. Both have high suicide rates, with 10–15% dying by suicide. An important difference in these two illnesses is the family history. Although both are hereditable, at least 50% of manic patients have some family history of an affective disorder (mania or depression). Studies of schizophrenics show a significant but less striking increase in schizophrenia in their families but no increase in affective disorder over the population prevalence.

4.8.2. Catatonic Schizophrenia

Patients who present with catatonic symptoms are more likely to have bipolar disorder than any other diagnosis. All patients in whom the diagnosis of catatonic schizophrenia is entertained should be evaluated carefully for depressive and manic symptoms in the period preceding the onset of catatonic symptoms, for previous episodes, and for family history. Some manics become mute when their thoughts go so fast that they cannot speak. The amytal interview may still be useful in uncovering depressive delusions, disjointed manic thoughts, or disorientation (organicity) (240).

4.8.3. Schizoaffective Disorder

As is discussed in the chapter on schizoaffective disorder, this term has been given many definitions and its boundaries have varied accordingly as has its prognostic position between mood disorders and schizophrenia. Probably the most important component of the criteria in DSM-IV and DSM-5 is the requirement that, at some point, psychotic features have been manifest for at least 2 weeks in the absence of a mood episode. Many clinicians disregard this when they assign a schizoaffective disorder diagnosis.

4.8.4. Organic Mental Disorders

Because at least one-third of manic patients have either disorientation or some memory deficits during an episode, it might be easy to think of mania as a toxic state. Although certain drugs can precipitate manic episodes, usually even these syndromes are treated with neuroleptics or lithium, or both. A first episode in an elderly patient can be quite problematic and it is most difficult in a catatonic stupor. Previous history and family history should be useful in confirming a diagnosis. In younger patients it is important not to be sidetracked by the confusion of mania and to delay treatment for a long time while completing extensive organic workups.

4.8.5. Personality Disorders (Antisocial, Borderline) and Alcohol and Drug Abuse

There are many presentations of bipolar disorder. In the teenage years, a change in behavior would be the key to distinguishing the manic from the typical sociopath. It is easy if the sociopathic behavior is manic—that is, stealing with some grandiose plan in mind—but less easy if it is typical of all adolescent antisocial acts. The same can be said of alcohol or drug problems, school phobia, and borderline personality diagnoses. Here again, this should be a clear change in behavior that could not have been expected or anticipated. Depressive symptoms or, less commonly, previous manic symptoms should be present if inquired about. These things, coupled with a family history of affective disorder, should help in making the proper diagnosis.

Bipolar disorder shares the trait of impulsivity in particular with borderline personality disorder. Many other features overlap as well, including rapid mood shifts, propensity to substance abuse, frequently unstable interpersonal relationships, periods of striking irritability, a high risk for suicide attempts, and an often chronic course with early onset. As a consequence many patients with borderline personality disorder are misdiagnosed as having bipolar disorder and treated accordingly (241, 242). The relationship between borderline personality disorder and bipolar disorder is controversial and some believe they exist on a continuum (243).

4.8.6. Attention Deficit Hyperactivity Disorder in Children and Adolescents

The debate over the comorbidity of bipolar disorder and attention deficit disorder continues (244). Children who meet criteria for bipolar disorder are very likely to do so for ADHD as well (245). The two disorders share the symptoms of irritable mood, accelerated speech, distractibility, and high energy level (246). Symptoms that are relatively specific to bipolar disorder are grandiosity, elation, decreased need for sleep, and hypersexuality (247). Individuals who are comorbid for those disorders are more likely to have anxiety and substance use disorder and to have a criminal history (248). Notably, family studies have shown either bipolar disorder or ADHD to raise the risk of having the other disorder in relatives (249, 250). This opens the possibility that their coexistence represents a subtype of bipolar disorder.

4.9. Treatment

4.9.1. Acute Mania and Mixed Episodes

Little psychosocial management can be accomplished with a patient in the manic state. The patient is talkative, both irritable and irritating, sexually aroused, confident, expansive, and completely lacking in insight or good judgment. Because of the uplifted mood, the patient feels no need of treatment and refuses with vehemence offers of assistance. Hospitalization is necessary and frequently entails commitment. The patient must be protected against the serious social and medical consequences of this state. Because of the manic patient's intrusiveness and potential for creating conflict, it is almost always possible to think of that person as being dangerous to himself or herself. If there are other illnesses, such as hypertension, that are controlled by medication, these get out of control as the manic individual neglects medications, creating another reason for hospitalization.

When manic patients are hospitalized, their excessive energy is easy to handle if they are given space to roam and are not confined to a locked room. This does not mean that they can be on an unlocked unit, since they are capable of excessive spending even while in the hospital. Manic patients are also intrusive and speak in an uncensored way, so they can provoke arguments anywhere, including the hospital. In addition, enormous bills and bad feelings can result if telephone use is not restricted. The relatives, who are worn down and exasperated by the manic patient's behavior and relieved to know that he or she is being protected in the hospital, also often welcome hospitalization. The patient may also be super alert such that they hear and overinterpret everything they see and hear. It is best to maintain them in an environment with as little stimulation as possible; groups, occupational therapy, and television should be minimized until the illness is remitting.

In treating manic patients, physicians should always remember that certain interpersonal traits are part of the manic illness. Janowsky et al. (251, 252) outlined a series of interpersonal behaviors that they had originally thought were part of the manic's premorbid personality but that were later discovered to be symptoms of the manic episode. In addition to the classic manic symptoms of hyperactivity, push of speech, flight of ideas, irritability, distractibility, poor judgment, and increased social contact, they found that manic behavior included such things as the testing of limits, flattery, shifting responsibility for their actions to others, exploiting other's soft spots, dividing the staff, and provoking anger. These traits may lead to marked interpersonal, marital, and ward conflict. Therefore, in treating the manic patient, one must take into consideration these symptoms and behaviors and respond to them as if they were part of the illness. Setting limits in an unambivalent, firm, arbitrary way best does this.

The efficacy of lithium for acute mania is well accepted. With this in mind, the following choices are available, although the order may be debatable and may depend on the severity of the presenting symptoms: (1) lithium, (2) atypical antipsychotics or older antipsychotics (3) anticonvulsants such as valproate or carbamazepine alone or in combination with lithium, or (4) electroconvulsive therapy (ECT). Early studies comparing lithium with chlorpromazine or lithium, chlorpromazine, and haloperidol indicated that lithium was superior to the others in terms of earlier discharge. These studies, however, indicated that chlorpromazine, haloperidol, and other such neuroleptics control the hyperactivity/excitement of the acutely manic patient more quickly than does lithium. Some maintained that, clinically, the end result was superior with lithium alone, whereas others felt that haloperidol alone was sufficient for the acute illness. Because there have been some reports that the combination of haloperidol and lithium can produce adverse side effects (253–255), and because bipolar illness may increase risks for tardive dyskinesia (256–258), the newer second generation of antipsychotics, such as olanzapine, risperidone, quetiapine, ziprasidone, and aripiperazole, may be preferable for the treatment of acute mania.

Before beginning treatment with lithium, the patient's evaluation should include a physical examination, tests for thyroid and renal function (blood urea nitrogen and creatinine), a white blood cell count, and electrocardiography. Other medications should be recorded, particularly the use of diuretics. While the proper dose is being determined inpatients should be monitored daily for symptoms of toxicity, such as tremor, nausea, vomiting, diarrhea, and confusion. In general, if the dose is raised gradually, toxicity can be avoided. Skin rash, usually acneiform, is another potential problem.

The usual starting dose of lithium in acute mania is 300 mg three times a day, which is gradually raised until a blood level of 1.0–1.2 mEq/L is achieved. Lithium's half-life requires an unchanging dose for 5 days before measurement of steady state concentrations. Changes made on the basis of shorter intervals may overestimate doses and result in toxicity. Lower starting dose and smaller dose increments are appropriate for those over 50 years old (259). Once the patient has shown the ability to tolerate the lithium, the regimen should be switched to a single evening dose. That may be better for the kidneys. Improvement typically occurs in 8–10 days.

Unfortunately, patients are often discharged from the hospital long before a manic episode has sufficiently resolved only to be followed by readmission shortly afterward. Before discharge the manic patient should have a marked decrease in symptoms and some insight into the illness and show a willingness to continue lithium (260). In addition, the patient's family should be educated to have an understanding of the illness and the importance of maintenance therapy.

4.9.2. Other Treatment Therapies

All the second-generation antipsychotics except lurasidone have FDA indications for the treatment of mania. It is desirable to weigh the patient, measure waistline and obtain a metabolic panel before these medicines are started. The doses recommended are as follows: risperidone, 2–6 mg/day, olanzapine 10–20 mg/day, quetiapine 400–800 mg in divided doses, ziprasidone 80–160 mg/day, again in divided doses, asenapine 100 mg twice daily, and aripiprazole 30 mg/day. The side effect profiles of each are different, as are the presumed modes of action. The major drawback to some of them is weight gain, metabolic syndrome, and the onset of diabetes, but as we have already noted, there seems to be some relationship between bipolar illness and diabetes, independent of medications.

Double-blind, placebo-controlled studies (261–264) have also shown valproic acid to be effective in the treatment of acute mania. Before beginning, a complete blood count and liver function tests are recommended. Depakote (enteric coated divalproex sodium) is a delayed-release tablet that causes less nausea. The goal is to achieve a blood level between 60 and 120 ng/mL (265).

Giving 20–30 mg/kg from the outset can approximate the dose necessary for therapeutic plasma levels. Beginning at this dose apparently results in a shorter time to improvement than does a conventional tapering regimen and entails no greater side effect burden (266). Poorer responses have been demonstrated for plasma levels below 60 ng/mL and, because protein binding begins to become saturated at doses exceeding 100 ng/mL, concentrations of the unbound portion may rise much more rapidly with increasing plasma levels beyond that point (267). Doses should be adjusted if used with other mood stabilizers like lamotrigine.

Carbamazepine XR as well is useful in the treatment of acute mania (268–272) and placebo-controlled studies have shown it to be an effective antidepressant (273, 274). The average daily dose varies across studies from 200 to 800 mg bid, and the average blood level to be achieved varies between 6 and 12 ng/mL. The use of loading doses is not recommended. Before beginning, a complete blood count and liver function tests are desirable because carbamazepine too can produce elevations of liver function tests and reductions in white blood cell and platelet counts in a dose-related fashion. Dose, however, does not predict the rarely seen aplastic anemia or agranulocytosis. Carbamazepine induces its own metabolism, causing the blood concentrations to drop after several weeks so that an upward adjustment of medication is often necessary. Because it induces liver enzymes, carbamazepine may lower valproate levels and these may, in turn, increase if carbamazepine is discontinued. Other drugs also may have their concentrations reduced during treatment with carbamazepine, notably birth control pills and many of the antipsychotics.

The broad efficacy of valproate and carbamazepine does not extend to other anticonvulsants. There is no published evidence that lamotrigine is effective in acute mania and placebo-controlled studies provide no support for gabapentin (275) or topiramate (276).

Although it is said that the anticonvulsants are particularly useful for mixed or dysphoric mania (277–280), one study that compared lithium to valproate did not find this (281). These drugs should be used when a patient is nonresponsive to lithium or when the side effects of lithium are disturbing, particularly in the face of polyuria, weight gain, or acne. Psoriasis can make the use of lithium quite difficult.

McCabe (282, 283) found that both ECT and chlorpromazine were far superior to no treatment in acute mania, when measured by duration of hospitalization, condition at discharge, and social recovery. There were no significant differences between the two treatments, however. He did not have a comparison group of patients treated with lithium, but Black et al. (284) retrospectively compared ECT and lithium and found that patients treated with ECT (unilateral or bilateral) were significantly more likely to show marked improvement, especially in cases of schizoaffective disorder, manic type. A randomized comparison (285) of lithium and bilateral ECT found ECT outcomes to be better in the first 8 weeks but not in the later outcomes. Finally, Mukherjee and Debsikdar (286) reported a very favorable outcome in India in 30 manic patients treated with unmodified ECT. It seemed particularly good for dysphoric mania, severe cases and those featuring catatonia.

4.9.3. Treatment of the Depressive Episode

Various meta-analyses on this topic have reached conflicting conclusions. The controlled trials at this point most strongly support fluoxetine and quetiapine as monotherapy, and combinations of lamotrigine with lithium and of fluoxetine with olanzapine (OFC) (287). Viewed in terms of a ratio of number needed to treat (remission) to number needed to harm (adverse events), a meta-analysis has shown a value of 9 for aripiprazole, for quetiapine and for risperidone. It showed a value of 19 for OFC (288).

Second generation antidepressant monotherapy may be sufficient for bipolar II patients (289–292). For bipolar I patients, antidepressants should be accompanied by a mood stabilizer.

Controlled trials have shown little evidence that the use of SSRI antidepressants with mood stabilizers increase risks for switching (293, 294). On the other hand, evidence from such trials for the efficacy of antidepressants in bipolar disorder is thin (295) though it is present (296). A consensus is developing, that TCA's and SNRI's pose a greater risk for switching than do SSRI's (294, 297, 298).

4.9.4. Maintenance Therapy

Lithium is clearly an effective prophylactic agent and is the "gold standard for maintenance therapy" (299, 300). Not only does it significantly decrease the number of manic episodes, but it also decreases the number of depressive episodes and the likelihood of suicide. This may occur because lithium decreases the number of manic episodes and, since the illness is frequently biphasic or triphasic, it automatically decreases the potential for depressive episodes. Also, the quality of the episodes that do occur is changed (shorter, less severe), and hospitalization is more often avoided. Because mood swings still occur, however, patients on maintenance lithium need to be followed regularly so that the physician can add antipsychotics, an antidepressant, or other drugs if necessary. Lithium can be given in a single bedtime dose that can be either lithium carbonate or a sustained-release lithium. There is some evidence that this reduces lithium's impact on the kidney (301) and it is likely to improve compliance.

The preventative effects of lithium for mania appear to increase steadily at least up to a level of 1.2 mEq/L (302). Prophylaxis against depressive episodes requires a minimum of 0.6 mEq/L.

When manic symptoms reappear during lithium treatment the treating physician should attempt to determine whether they occur despite adequate plasma levels. This may be difficult with an acute admission for mania since symptom breakthrough may have occurred with adequate levels but then resulted in noncompliance. In any event, a single breakthrough does not necessarily signify lithium's ineffectiveness. Mirror image studies have shown that episodes are less severe and frequent after lithium is started than during a period of similar length before it is started (303).

Carbamazepine and valproic acid are also good maintenance therapies, and here, too, the dose for maintenance is the same as that necessary to treat the acute attack. Lamotrigine is more effective against depressive than against manic occurrences and is therefore complimentary to lithium which is more protective against manic than against depressive episodes (304, 305). The side effect profiles of lithium and lamotrigine do not overlap so their use in combination has unique benefits.

The previous course of illness has bearing on prophylactic treatment selection. As anticonvulsants may be more effective than lithium for acute mixed mania, this selectivity may extend to prophylaxis (306). A family history of mania has been associated with better lithium prophylaxis (307–309).

Patients with a rapid cycling pattern are more likely to experience recurrences during prophylaxis than are those with sustained periods between episodes. Because early studies were focused on lithium as the sole prophylactic agent, rapid cycling has come to be regarded as a predictor of poor response to lithium per se (307, 310). However, most comparisons of prophylaxis success rates between those for lithium and those for anticonvulsants have not found a difference (311–313).

All data show that there is a high risk of recurring episodes if lithium maintenance is discontinued, particularly if it is done abruptly, so a sudden cessation of lithium is hazardous (314, 315). As might be expected, those who had been without episodes for the longest period before lithium discontinuation were the least likely to experience relapse. Even with a pregnancy, lithium should be discontinued gradually and the patient followed very closely.

On maintenance lithium, thyroid and renal functions need to be monitored. With carbamazepine and valproate, blood counts and liver function should be monitored. Blood levels should be done one to two times a year.

Jamison and Goodwin (316) have outlined the therapeutic issues surrounding maintenance therapy with lithium, including patient and physician compliance. O'Connell et al. (317) also discussed the relevance of family and psychosocial factors in the outcome of lithium-maintained bipolar patients, as did Clarkin et al. (318). It is important to address these issues when the literature on maintenance therapy is reviewed, there are far more relapses in collaborative treatment studies of multiple investigators than in studies reported by individual therapists treating a cohort of patients. It is definitely a disorder in which the quality of therapy and management make a difference.

It should be noted that stereotactic tractotomy is still being used for the most resistant cases (319–321). Increasing knowledge of the neurocircuitry underlying mood disorder has resulted in a variety of targets for both tractotomy and deep brain stimulation (321).

4.9.5. Side Effects of Antimanic Drugs

The side effects of lithium may be numerous and disturbing to the patient but seldom deleterious to his or her health. Many complain of tremor while on lithium, and this can be treated with 30–80 mg of propranolol in divided doses (322). Improvement, if it occurs, can be seen in 24 hours. Plasma levels correlate with degree of tremor so dosage adjustments may be helpful. Weight gain is also a frequent problem. Almost 50% of patients gain some weight, and weight gains of up to 30 kg have been reported. Patients who develop hypothyroidism, edema, polydipsia, or an increased appetite are more likely to experience weight gain, but it is less likely with plasma levels below 0.8 mEq/L. Patients should be warned not to treat an increased thirst with calorie-laden drinks. Nausea is more likely with rapid increases in plasma levels and may be improved with divided doses taken with meals or with a delayed release preparation. The latter choice may result in diarrhea.

Polyuria and polydipsia are common and concomitant use of SSRI antidepressants raises the risk of these problems (323, 324). The avoidance of multiple dosing may be helpful for this (301, 325). Likewise, polyuria may improve with amiloride at 5 mg twice daily (326). In the long term, usually after 10 years of lithium treatment, tubulointerstitial fibrosis may develop. Risks for this do not appear to be dose related. It is reversible in early stages and these can be detected from increasing creatinine levels. This adds to the importance of at least annual monitoring.

Hypothyroidism is more likely in females, in older patients, in those with early weight gain or with a family history of thyroid disease. Cognitive impairment is more highly correlated with TSH values than with lithium concentrations. Moreover thyroid functioning in the hypothyroid half of the normal range is associated with more affective morbidity (327–330).

Some patients complain of effects on cognitive performance. A meta-analysis has shown that lithium results in small but significant impairment in immediate verbal learning and memory (331). The effects of long-term lithium treatment on psychomotor performance appear to be larger difficulties.

Valproate causes at least as much weight gain as does lithium (304). If this threatens compliance, the alternatives of lamotrigine or carbamazepine are typically weight neutral. Nausea is not infrequent and a histamine-2 blocker may be helpful (332). Increases in ammonia levels are also common (333, 334) and may result in fatigue, cognitive slowing, or sedation. This may progress to an encephalopathy regardless of plasma levels (335–337) so ammonia levels should be checked if such complaints are prominent after therapeutic plasma levels are established.

Women may experience menstrual disturbances (338) and possibly polycystic ovary disease (339) though there has been some controversy over this. Use of valproate during pregnancy carries a much higher risk for congenital malformation than does the use of lithium. Hair loss is also more frequent than with other anticonvulsants. Stevens-Johnson syndrome is no less common than with lamotrigine if recommendations for lamotrigine dose tapering are closely followed (340).

Leukopenia is more likely with carbamazepine than with valproate or lamotrigine (341). Notably, concomitant lithium treatment may serve to correct this (342). Hyponatremia is also more frequently seen with carbamazepine (343).

The metabolic side effects of the atypical antipsychotics are well recognized and a metabolic panel at the onset of treatment is now a standard of care. Aripiprazole and ziprasidone appear to carry the least risks for significant weight gain, followed by risperidone, quetiapine, olanzapine, and clozapine, in that order.

4.9.6. Psychosocial Treatment

Pharmacotherapy has been the principle focus of the research into the management of bipolar disorders. Recognition of the extent to which residual symptoms and psychosocial impairment persist despite the use of mood stabilizers has increased interest in psychotherapeutic approaches. Such therapies have sought principally to stabilize day-to-day activities and to improve coping skills, medication compliance, and the recognition of prodromal symptoms.

The largest number of randomized controlled trials has tested cognitive-behavioral therapy (CBT) modified for application to the bipolar disorders. A recent meta-analysis showed low to moderate effect sizes for clinical symptoms ($d=0.44$), quality of life ($d=0.36$), and treatment adherence ($d=.53$) at the end of treatment (344). Effect sizes for clinical symptoms remained at 6–12 months for treatment ($d=0.43$) but were nonsignificant for the other four clinical outcome categories listed. At no point did CBT significantly increase or decrease treatment costs.

4.9.7. Advantages of Lithium

A recent meta-analysis of 31 studies conclusively showed that the risks of completed and attempted suicide were consistently lower, by approximately 80%, during treatment of bipolar and other major affective disorder patients with lithium compared to those not treated with lithium (345). A significant advantage for lithium treatment persisted when trials were limited to those that were randomized and controlled. Moreover, the ratio of attempted to completed suicide was 2.5 times higher than in lithium treated patients indicating that, when suicide attempts occurred, they had lower lethality in patients who were taking lithium. A randomized, placebo-controlled trial undertaken to assess the anti-suicidal effects of lithium found a strong trend in the expected direction for suicide attempts and a significant difference for completed suicide (346).

References

1. Angst J, Gamma A, Benazzi F, Ajdacic V, Eich D, Rössler W. Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. J Affect Disord 2003;73:133–146.
2. Menninger K, Mayman M, Pruyser P. The vital balance: the life process in mental health and illness. New York: Penguin; 1977.
3. Sedler MJ. Falret's discovery: the origin of the concept of bipolar affective illness (trans: Sedler MJ, Dessain EC). Am J Psychiatry 1983;140:1127–1133.
4. Kahlbaum K. Die Kataonie oder das Spannugsirresein. Berlin; 1874.
5. Kraepelin E. Manic-depressive insanity and paranoia. Edinburgh: E & S Livingstone; 1921.
6. Lange C. Periodiske Depressioner. Copenhagen; 1895.
7. Pederson A, Poort R, Schou H. Periodical depression as an independent nosological entity. Acta Psychiatr Neurol 1947;23:285–319.
8. Leonhard K. Aufteilung der Endogenen Psychosen. Berlin: Akademie Verlag; 1957.
9. Perris C. A study of bipolar (manic depressive) and unipolar recurrent depressive psychoses. Acta Psychiatr Scand Suppl 1966;42: 1–188.
10. Angst J. Zur ätiologie und nosologie endogener depressiver Psychosen. Monographien aus dem Gesamtgebiete der Neurologie und Psychiatric. Berlin: Springer; 1966.
11. Winokur G, Clayton P. Family history studies: 1. Two types of affective disorders separated according to genetic and clinical factors. In: Wortis J, editor. Recent advances in biological psychiatry. New York: Plenum Press; 1967.

12. Cassano GB, Rucci P, Frank E, Fagiolini A, Dell'Osso L, Shear MK, Kupfer DJ. The mood spectrum in unipolar and bipolar disorder: arguments for a unitary approach. Am J Psychiatry 2004;161:1264–1269.
13. Akiskal HS, Benazzi F. The DSM-IV and ICD-10 categories of recurrent [major] depressive and bipolar II disorders: evidence that they lie on a dimensional spectrum. J Affect Disord 2006;92:45–54.
14. Craddock N, Jones I. Genetics of bipolar disorder. J Med Genet 1999;36:585–594.
15. Fiedorowicz JG, Endicott J, Leon AC, Solomon DA, Keller MB, Coryell WH. Subthreshold hypomanic symptoms in progression from unipolar major depression to bipolar disorder. Am J Psychiatry 2011;168:40–48.
16. Coryell W, Zimmerman M, Pfohl B. Short-term prognosis in primary and secondary major depression. J Affect Disord 1985;9:265–270.
17. Spitzer RL, Endicott J, Robins E. Research diagnostic criteria: rationale and reliability. Arch Gen Psychiatry 1978;35:773–782.
18. Coryell W, Endicott J, Reich T, Andreasen N, Keller M. A family study of bipolar II disorder. Br J Psychiatry 1984;145:49–54.
19. Joyce PR, Doughty CJ, Wells JE, Walsh AE, Admiraal A, Lill M, Olds RJ. Affective disorders in the first-degree relatives of bipolar probands: results from the South Island Bipolar Study. Compr Psychiatry 2004;45:168–174.
20. Rice JP, McDonald-Scott P, Endicott J, Coryell W, Grove WM, Keller MB, Altis D. The stability of diagnosis with an application to bipolar II disorder. Psychiatry Res 1986;19:285–296.
21. Mendlewicz J, Rainer JD. Adoption study supporting genetic transmission in manic–depressive illness. Nature 1977;268:327–329.
22. Wender PH, Kety SS, Rosenthal D, Schulsinger F, Ortmann J, Lunde I. Psychiatric disorders in the biological and adoptive families of adopted individuals with affective disorders. Arch Gen Psychiatry 1986;43:923–929.
23. Shih RA, Belmonte PL, Zandi PP. A review of the evidence from family, twin and adoption studies for a genetic contribution to adult psychiatric disorders. Int Rev Psychiatry 2004;16:260–283.
24. Bertelsen A, Harvald B, Hauge M. A Danish twin study of manic-depressive disorders. Br J Psychiatry 1977;130:330–351.
25. Cardno AG, Marshall EJ, Coid B, Macdonald AM, Ribchester TR, Davies NJ, Venturi P, Jones LA, Lewis SW, Sham PC, Gottesman II, Farmer AE, McGuffin P, Reveley AM, Murray RM. Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. Arch Gen Psychiatry 1999;56:162–168.
26. Goodwin FK, Jamison KR. Manic-depressive illness: bipolar disorders and recurrent depression. 2nd ed. New York: Oxford University Press; 2007.
27. Major Depressive Disorder Working Group of the Psychiatric, GWAS Consortium, Ripke S, Wray NR, Lewis CM, Hamilton SP, Weissman MM, Breen G, Byrne EM, Blackwood DH, Boomsma DI, Cichon S, Heath AC, Holsboer F, Lucae S, Madden PA, Martin NG, McGuffin P, Muglia P, Noethen MM, Penninx BP, Pergadia ML, Potash JB, Rietschel M, Lin D, Müller-Myhsok B, Shi J, Steinberg S, Grabe HJ, Lichtenstein P, Magnusson P, Perlis RH, Preisig M, Smoller JW, Stefansson K, Uher R, Kutalik Z, Tansey KE, Teumer A, Viktorin A, Barnes MR, Bettecken T, Binder EB, Breuer R, Castro VM, Churchill SE, Coryell WH, Craddock N, Craig IW, Czamara D, De Geus EJ, Degenhardt F, Farmer AE, Fava M, Frank J, Gainer VS, Gallagher PJ, Gordon SD, Goryachev S, Gross M, Guipponi M, Henders AK, Herms S, Hickie IB, Hoefels S, Hoogendijk W, Hottenga JJ, Iosifescu DV, Ising M, Jones I, Jones L, Jung-Ying T, Knowles JA, Kohane IS, Kohli MA, Korszun A, Landen M, Lawson WB, Lewis G, Macintyre D, Maier W, Mattheisen M, McGrath PJ, McIntosh A, McLean A, Middeldorp CM, Middleton L, Montgomery GM, Murphy SN, Nauck M, Nolen WA, Nyholt DR, O'Donovan M, Oskarsson H, Pedersen N, Scheftner WA, Schulz A, Schulze TG, Shyn SI, Sigurdsson E, Slager SL, Smit JH, Stefansson H, Steffens M, Thorgeirsson T, Tozzi F, Treutlein J, Uhr M, van den Oord EJ, Van Grootheest G, Völzke H, Weilburg JB, Willemsen G, Zitman FG, Neale B, Daly M, Levinson DF, Sullivan PF. A mega-analysis of genome-wide association studies for major depressive disorder. Mol Psychiatry 2013;18:497–511.
28. Craddock N, Sklar P. Genetics of bipolar disorder. Lancet 2013;381:1654–1662.
29. Zhang X, Zhang C, Wu Z, Wang Z, Peng D, Chen J, Hong W, Yuan C, Li Z, Yu S, Fang Y. Association of genetic variation in CACNA1C with bipolar disorder in Han Chinese. J Affect Disord 2013;150:261–265.
30. Casamassima F, Hay AC, Benedetti A, Lattanzi L, Cassano GB, Perlis RH. L-type calcium channels and psychiatric disorders: a brief review. Am J Med Genet B Neuropsychiatr Genet 2010;153B:1373–1390.
31. Cross-Disorder Group of the Psychiatric Genomics Consortium, Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH, Mowry BJ, Thapar A, Goddard ME, Witte JS, Absher D, Agartz I, Akil H, Amin F, Andreassen OA, Anjorin A, Anney R, Anttila V, Arking DE, Asherson P, Azevedo MH, Backlund L, Badner JA, Bailey AJ, Banaschewski T, Barchas JD, Barnes MR, Barrett TB, Bass N, Battaglia A, Bauer M, Bayés M, Bellivier F, Bergen SE, Berrettini W, Betancur C, Bettecken T, Biederman J, Binder EB, Black DW, Blackwood DH, Bloss CS, Boehnke M, Boomsma DI, Breen G, Breuer R, Bruggeman R, Cormican P, Buccola NG, Buitelaar JK, Bunney WE, Buxbaum JD, Byerley WF, Byrne EM, Caesar S, Cahn W, Cantor RM, Casas M, Chakravarti A, Chambert K, Choudhury K, Cichon S, Cloninger CR, Collier DA, Cook EH, Coon H, Cormand B, Corvin A, Coryell WH, Craig DW, Craig IW, Crosbie J, Cuccaro ML, Curtis D, Czamara D, Datta S, Dawson G, Day R, De Geus EJ, Degenhardt F, Djurovic S, Donohoe GJ, Doyle AE, Duan J, Dudbridge F, Duketis E, Ebstein RP, Edenberg HJ, Elia J, Ennis S, Etain B, Fanous A, Farmer AE, Ferrier IN, Flickinger M, Fombonne E, Foroud T, Frank J, Franke B, Fraser C, Freedman R, Freimer NB, Freitag CM, Friedl M, Frisén L, Gallagher L, Gejman PV, Georgieva L, Gershon ES, Geschwind DH, Giegling I, Gill M, Gordon SD, Gordon-Smith K, Green EK, Greenwood TA, Grice DE, Gross M, Grozeva D, Guan W, Gurling H, De Haan L, Haines JL, Hakonarson H, Hallmayer J, Hamilton SP, Hamshere ML, Hansen TF, Hartmann AM, Hautzinger M, Heath AC, Henders AK, Herms S, Hickie IB, Hipolito M, Hoefels S, Holmans PA, Holsboer F, Hoogendijk WJ, Hottenga JJ, Hultman CM, Hus V, Ingason A, Ising M, Jamain S, Jones EG, Jones I, Jones L, Tzeng JY, Kähler AK, Kahn RS, Kandaswamy R, Keller MC, Kennedy JL, Kenny E, Kent L, Kim Y, Kirov GK, Klauck SM, Klei L, Knowles JA, Kohli MA, Koller DL, Konte B, Korszun A, Krabbendam L, Krasucki R, Kuntsi J, Kwan P, Landén M, Långström N, Lathrop M, Lawrence J, Lawson WB,

Leboyer M, Ledbetter DH, Lee PH, Lencz T, Lesch KP, Levinson DF, Lewis CM, Li J, Lichtenstein P, Lieberman JA, Lin DY, Linszen DH, Liu C, Lohoff FW, Loo SK, Lord C, Lowe JK, Lucae S, MacIntyre DJ, Madden PA, Maestrini E, Magnusson PK, Mahon PB, Maier W, Malhotra AK, Mane SM, Martin CL, Martin NG, Mattheisen M, Matthews K, Mattingsdal M, McCarroll SA, McGhee KA, McGough JJ, McGrath PJ, McGuffin P, McInnis MG, McIntosh A, McKinney R, McLean AW, McMahon FJ, McMahon WM, McQuillin A, Medeiros H, Medland SE, Meier S, Melle I, Meng F, Meyer J, Middeldorp CM, Middleton L, Milanova V, Miranda A, Monaco AP, Montgomery GW, Moran JL, Moreno-De-Luca D, Morken G, Morris DW, Morrow EM, Moskvina V, Muglia P, Mühleisen TW, Muir WJ, Müller-Myhsok B, Murtha M, Myers RM, Myin-Germeys I, Neale MC, Nelson SF, Nievergelt CM, Nikolov I, Nimgaonkar V, Nolen WA, Nöthen MM, Nurnberger JI, Nwulia EA, Nyholt DR, O'Dushlaine C, Oades RD, Olincy A, Oliveira G, Olsen L, Ophoff RA, Osby U, Owen MJ, Palotie A, Parr JR, Paterson AD, Pato CN, Pato MT, Penninx BW, Pergadia ML, Pericak-Vance MA, Pickard BS, Pimm J, Piven J, Posthuma D, Potash JB, Poustka F, Propping P, Puri V, Quested DJ, Quinn EM, Ramos-Quiroga JA, Rasmussen HB, Raychaudhuri S, Rehnström K, Reif A, Ribasés M, Rice JP, Rietschel M, Roeder K, Roeyers H, Rossin L, Rothenberger A, Rouleau G, Ruderfer D, Rujescu D, Sanders AR, Sanders SJ, Santangelo SL, Sergeant JA, Schachar R, Schalling M, Schatzberg AF, Scheftner WA, Schellenberg GD, Scherer SW, Schork NJ, Schulze TG, Schumacher J, Schwarz M, Scolnick E, Scott LJ, Shi J, Shilling PD, Shyn SI, Silverman JM, Slager SL, Smalley SL, Smit JH, Smith EN, Sonuga-Barke EJ, St Clair D, State M, Steffens M, Steinhausen HC, Strauss JS, Strohmaier J, Stroup TS, Sutcliffe JS, Szatmari P, Szelinger S, Thirumalai S, Thompson RC, Todorov AA, Tozzi F, Treutlein J, Uhr M, van den Oord EJ, Van Grootheest G, Van Os J, Vicente AM, Vieland VJ, Vincent JB, Visscher PM, Walsh CA, Wassink TH, Watson SJ, Weissman MM, Werge T, Wienker TF, Wijsman EM, Willemsen G, Williams N, Willsey AJ, Witt SH, Xu W, Young AH, Yu TW, Zammit S, Zandi PP, Zhang P, Zitman FG, Zöllner S; International Inflammatory Bowel Disease Genetics Consortium (IIBDGC), Devlin B, Kelsoe JR, Sklar P, Daly MJ, O'Donovan MC, Craddock N, Sullivan PF, Smoller JW, Kendler KS, Wray NR. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet. 2013;45:984–994.

32. Van Snellenberg JX, de Candia T. Meta-analytic evidence for familial coaggregation of schizophrenia and bipolar disorder. Arch Gen Psychiatry 2009;66:748–755.
33. Janowsky DS, Risch SC, Judd LL. Behavioral and neuroendocrine effects of physostigmine in affective disorder patients. In: Clayton P, Barrett JE, editors. Treatment of depression: old controversies and new approaches. New York: Raven; 1983.
34. Olfson M. An old treatment for mania. Lancet 1987;2:221–222.
35. Zarate C Jr, Machado-Vieira R, Henter I, Ibrahim L, Diazgranados N, Salvadore G. Glutamatergic modulators: the future of treating mood disorders? Harv Rev Psychiatry 2010;18:293–303.
36. Sachar EJ, Hellman L, Roffwarg HP, Halpern FS, Fukushima DK, Gallagher TF. Disrupted 24-hour patterns of cortisol secretion in psychotic depression. Arch Gen Psychiatry 1973;28:19–24.
37. Carroll BJ, Feinberg M, Greden JF, Tarika J, Albala AA, Haskett RF, James NM, Kronfol Z, Lohr N, Steiner M, de Vigne JP, Young E. A specific laboratory test for the diagnosis of melancholia. Standardization, validation, and clinical utility. Arch Gen Psychiatry 1981;38:15–22.
38. Stetler C, Miller GE. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. Psychosom Med 2011;73:114–126.
39. Wehr TA, Wirz-Justice A, Goodwin FK, Duncan W, Gillin JC. Phase advance of the circadian sleep-wake cycle as an antidepressant. Science 1979;206:710–713.
40. Souêtre E, Salvati E, Pringuey D, Plasse Y, Savelli M, Darcourt G. Antidepressant effects of the sleep/wake cycle phase advance. Preliminary report. J Affect Disord 1987;12:41–46.
41. Colombo C, Lucca A, Benedetti F, Barbini B, Campori E, Smeraldi E. Total sleep deprivation combined with lithium and light therapy in the treatment of bipolar depression: replication of main effects and interaction. Psychiatry Res 2000;95:43–53.
42. Terman M, Terman JS, Quitkin FM, McGrath PJ, Stewart JW, Rafferty B. Light therapy for seasonal affective disorder. A review of efficacy. Neuropsychopharmacology 1989;2:1–22.
43. Beauchemin KM, Hays P. Sunny hospital rooms expedite recovery from severe and refractory depressions. J Affect Disord 1996;40:49–51.
44. Akhter A, Fiedorowicz JG, Zhang T, Potash JB, Cavanaugh J, Solomon DA, Coryell WH. Seasonal variation of manic and depressive symptoms in bipolar disorder. Bipolar Disord 2013;15:377–384.
45. Jauhar P, Weller MP. Psychiatric morbidity and time zone changes: a study of patients from Heathrow airport. Br J Psychiatry 1982;140:231–235.
46. Young DM. Psychiatric morbidity in travelers to Honolulu, Hawaii. Compr Psychiatry 1995;36:224–228.
47. Svendsen K. Sleep deprivation therapy in depression. Acta Psychiatr Scand 1976;54:184–192.
48. Benedetti F, Barbini B, Fulgosi MC, Colombo C, Dallaspezia S, Pontiggia A, Smeraldi E. Combined total sleep deprivation and light therapy in the treatment of drug-resistant bipolar depression: acute response and long-term remission rates. J Clin Psychiatry 2005;66:1535–1540.
49. Benedetti F, Colombo C, Barbini B, Campori E, Smeraldi E. Ongoing lithium treatment prevents relapse after total sleep deprivation. J Clin Psychopharmacol 1999;19:240–245.
50. Baxter Jr LR, Liston EH, Schwartz JM, Altshuler LL, Wilkins JN, Richeimer S, Guze BH. Prolongation of the antidepressant response to partial sleep deprivation by lithium. Psychiatry Res 1986;19:17–23.
51. Benedetti F, Barbini B, Lucca A, Campori E, Colombo C, Smeraldi E. Sleep deprivation hastens the antidepressant action of fluoxetine. Eur Arch Psychiatry Clin Neurosci 1997;247:100–103.
52. Benedetti F, Colombo C, Pontiggia A, Bernasconi A, Florita M, Smeraldi E. Morning light treatment hastens the antidepressant effect of citalopram: a placebo-controlled trial. J Clin Psychiatry 2003;64:648–653.

53. Elsenga S, van den Hoofdakker RH. Clinical effects of sleep deprivation and clomipramine in endogenous depression. J Psychiatr Res 1982;17:361–374.
54. Kempton MJ, Geddes JR, Ettinger U, Williams SC, Grasby PM. Meta-analysis, database, and meta-regression of 98 structural imaging studies in bipolar disorder. Arch Gen Psychiatry 2008;65:1017–1032.
55. Kempton MJ, Salvador Z, Munafò MR, Geddes JR, Simmons A, Frangou S, Williams SC. Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. Arch Gen Psychiatry 2011;68:675–690.
56. Germaná C, Kempton MJ, Sarnicola A, Christodoulou T, Haldane M, Hadjulis M, Girardi P, Tatarelli R, Frangou S. The effects of lithium and anticonvulsants on brain structure in bipolar disorder. Acta Psychiatr Scand 2010;122:481–487.
57. Kupferschmidt DA, Zakzanis KK. Toward a functional neuroanatomical signature of bipolar disorder: quantitative evidence from the neuroimaging literature. Psychiatry Res 2011;193:71–79.
58. Krauthammer C, Klerman GL. Secondary mania: manic syndromes associated with antecedent physical illness or drugs. Arch Gen Psychiatry 1978;35:1333–1339.
59. Cook BL, Shukla S, Hoff AL, Aronson TA. Mania with associated organic factors. Acta Psychiatr Scand 1987;76:674–677.
60. Larson EW, Richelson E. Organic causes of mania. Mayo Clin Proc 1988;63:906–912.
61. Starkstein SE, Boston JD, Robinson RG. Mechanisms of mania after brain injury. 12 case reports and review of the literature. J Nerv Ment Dis 1988;176:87–100.
62. Shukla S, Cook BL, Mukherjee S, Godwin C, Miller MG. Mania following head trauma. Am J Psychiatry 1987;144:93–96.
63. Clark AF, Davison K. Mania following head injury. A report of two cases and a review of the literature. Br J Psychiatry 1987;150:841–844.
64. Pope HG Jr, McElroy SL, Satlin A, Hudson JI, Keck PE Jr, Kalish R. Head injury, bipolar disorder, and response to valproate. Compr Psychiatry 1988;29:34–38.
65. Mortensen PB, Mors O, Frydenberg M, Ewald H. Head injury as a risk factor for bipolar affective disorder. J Affect Disord 2003; 76:79–83.
66. Robinson RG, Kubos KL, Starr LB, Rao K, Price TR. Mood changes in stroke patients: relationship to lesion location. Compr Psychiatry 1983;24:555–566.
67. Robinson RG, Boston JD, Starkstein SE, Price TR. Comparison of mania and depression after brain injury: causal factors. Am J Psychiatry 1988;145:172–178.
68. Santos CO, Caeiro L, Ferro JM, Figueira ML. Mania and stroke: a systematic review. Cerebrovasc Dis 2011;32:11–21.
69. Boyd JH, Weissman MM. Epidemiology of affective disorders. A reexamination and future directions. Arch Gen Psychiatry 1981;38:1039–1046.
70. Robins LN, Helzer JE, Weissman MM, Orvaschel H, Gruenberg E, Burke JD Jr, Regier DA. Lifetime prevalence of specific psychiatric disorders in three sites. Arch Gen Psychiatry 1984;41:949–958.
71. Kessler RC, Berglund P, Borges G, Nock M, Wang PS. Trends in suicide ideation, plans, gestures, and attempts in the United States, 1990–1992 to 2001–2003. JAMA 2005;293:2487–2495.
72. Angst J, Gamma A. A new bipolar spectrum concept: a brief review. Bipolar Disord 2002;4:11–14.
73. Carta MG, Angst J. Epidemiological and clinical aspects of bipolar disorders: controversies or a common need to redefine the aims and methodological aspects of surveys. Clin Pract Epidemiol Ment Health 2005;1:4.
74. Jones BE, Gray BA, Parson EB. Manic-depressive illness among poor urban blacks. Am J Psychiatry 1981;138:654–657.
75. Jones BE, Gray BA, Parson EB. Manic-depressive illness among poor urban Hispanics. Am J Psychiatry 1983;140:1208–1210.
76. Keisling R. Underdiagnosis of manic-depressive illness in a hospital unit. Am J Psychiatry 1981;138:672–673.
77. Andreasen NC. Creativity and mental illness: prevalence rates in writers and their first-degree relatives. Am J Psychiatry 1987;144:1288–1292.
78. Coryell W, Endicott J, Keller M, Andreasen N, Grove W, Hirschfeld RM, Scheftner W. Bipolar affective disorder and high achievement: a familial association. Am J Psychiatry 1989;146:983–988.
79. Verdoux H, Bourgeois M. Social class in unipolar and bipolar probands and relatives. J Affect Disord 1995;33:181–187.
80. Tsuchiya KJ, Agerbo E, Byrne M, Mortensen PB. Higher socio-economic status of parents may increase risk for bipolar disorder in the offspring. Psychol Med 2004;34:787–793.
81. Akiskal HS, Walker P, Puzantian VR, King D, Rosenthal TL, Dranon M. Bipolar outcome in the course of depressive illness. Phenomenologic, familial, and pharmacologic predictors. J Affect Disord 1983;5:115–128.
82. Bromet EJ, Kotov R, Fochtmann LJ, Carlson GA, Tanenberg-Karant M, Ruggero C, Chang SW. Diagnostic shifts during the decade following first admission for psychosis. Am J Psychiatry 2011;168:1186–1194.
83. Ambelas A. Life events and mania. A special relationship? Br J Psychiatry 1987;150:235–240.
84. Johnson SL, Cuellar AK, Ruggero C, Winett-Perlman C, Goodnick P, White R, Miller I. Life events as predictors of mania and depression in bipolar I disorder. J Abnorm Psychol 2008;117:268–277.
85. Malkoff-Schwartz S, Frank E, Anderson B, Sherrill JT, Siegel L, Patterson D, Kupfer DJ. Stressful life events and social rhythm disruption in the onset of manic and depressive bipolar episodes: a preliminary investigation. Arch Gen Psychiatry 1998;55:702–707.
86. Wehr TA, Sack DA, Rosenthal NE. Sleep reduction as a final common pathway in the genesis of mania. Am J Psychiatry 1987;144:201–204.
87. Frank E, Kupfer DJ, Thase ME, Mallinger AG, Swartz HA, Fagiolini AM, Grochocinski V, Houck P, Scott J, Thompson W, Monk T. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. Arch Gen Psychiatry 2005;62:996–1004.

88. Winokur G, Clayton PJ, Reich T. Manic depressive illness. St. Louis, MO: Mosby; 1969.
89. Freeman M, Gelenberg AJ. Bipolar disorder in women: reproductive events and treatment considerations. Acta Psychiatr Scand 2005;112:88–96.
90. Kendell RE, Chalmers JC, Platz C. Epidemiology of puerperal psychoses. Br J Psychiatry 1987;150:662–673.
91. Shulman K, Post F. Bipolar affective disorder in old age. Br J Psychiatry 1980;136:26–32.
92. Yassa R, Nair NP, Iskandar H. Late-onset bipolar disorder. Psychiatr Clin North Am 1988;11:117–131.
93. Rubin EH. Aging and mania. Psychiatr Dev 1988;6:329–337.
94. Stone K. Mania in the elderly. Br J Psychiatry 1989;155:220–224.
95. Young RC, Klerman GL. Mania in late life: focus on age at onset. Am J Psychiatry 1992;149:867–876.
96. Sayer HK, Marshall S, Mellsop GW. Mania and seasonality in the southern hemisphere. J Affect Disord 1991;23:151–156.
97. Carney PA, Fitzgerald CT, Monaghan CE. Influence of climate on the prevalence of mania. Br J Psychiatry 1988;152:820–823.
98. Rosenthal NE, Sack DA, Gillin JC, Lewy AJ, Goodwin FK, Davenport Y, Mueller PS, Newsome DA, Wehr TA. Seasonal affective disorder. A description of the syndrome and preliminary findings with light therapy. Arch Gen Psychiatry 1984;41:72–80.
99. Rosenthal NE, Wehr TA. Chronobiology: seasonal affective disorders. Psychiatr Ann 1987;17:640–674.
100. Shin K, Schaffer A, Levitt AJ, Boyle MH. Seasonality in a community sample of bipolar, unipolar and control subjects. J Affect Disord 2005;86:19–25.
101. Coryell W, Fiedorowicz JG, Solomon D, Leon AC, Rice JP, Keller MB. Effects of anxiety on the long-term course of depressive disorders. Br J Psychiatry 2012;200:210–215.
102. Perlis RH, Miyahara S, Marangell LB, Wisniewski SR, Ostacher M, DelBello MP, Bowden CL, Sachs GS, Nierenberg AA, STEP-BD Investigators. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry 2004;55:875–881.
103. Angst J. The course of affective disorders. II. Typology of bipolar manic-depressive illness. Arch Psychiatr Nervenkr 1978;226:65–73.
104. Perris C. The separation of bipolar (manic-depressive) from unipolar recurrent depressive psychoses. Behav Neuropsychiatry 1969; 1:17–24.
105. Angst J. Discussion: classification and prediction of outcome of depression. In: Angst J, editor. Symposia Medica Hoechst 8. New York: F.K. Schattauer Verlag; 1974.
106. Mantere O, Suominen K, Leppämäki S, Valtonen H, Arvilommi P, Isometsä E. The clinical characteristics of DSM-IV bipolar I and II disorders: baseline findings from the Jorvi Bipolar Study (JoBS). Bipolar Disord 2004;6:395–405.
107. Bromet EJ, Finch SJ, Carlson GA, Fochtmann L, Mojtabai R, Craig TJ, Kang S, Ye Q. Time to remission and relapse after the first hospital admission in severe bipolar disorder. Soc Psychiatry Psychiatr Epidemiol 2005;40:106–113.
108. Bellivier F, Golmard JL, Henry C, Leboyer M, Schürhoff F. Admixture analysis of age-at-onset in bipolar I affective disorder. Arch Gen Psychiatry 2001;58:510–512.
109. Coryell W, Fiedorowicz JG, Solomon D, Leon AC, Rice JP, Keller MB. Effects of anxiety on the long-term course of depressive disorders. Br J Psychiatry 2012;200:210–215.
110. Schurhoff F, Schürhoff F, Bellivier F, Jouvent R, Mouren-Siméoni MC, Bouvard M, Allilaire JF, Leboyer M. Early and late onset bipolar disorders: two different forms of manic-depressive illness? J Affect Disord 2000;58:215–221.
111. Lin PI, McInnis MG, Potash JB, Willour V, MacKinnon DF, DePaulo JR, Zandi PP. Clinical correlates and familial aggregation of age-at-onset in bipolar disorder. Am J Psychiatry 2006;163:240–246.
112. Hamshere ML, Gordon-Smith K, Forty L, Jones L, Caesar S, Fraser C, Hyde S, Tredget J, Kirov G, Jones I, Craddock N, Smith DJ. Age-at-onset in bipolar-I disorder: mixture analysis of 1369 cases identifies three distinct clinical subgroups. J Affect Disord 2009;116:23–29.
113. Carter TD, Mundo E, Parikh SV, Kennedy JL. Early age-at-onset as a risk factor for poor outcome of bipolar disorder. J Psychiatr Res 2003;37:297–303.
114. Kennedy N, Everitt B, Boydell J, Van Os J, Jones PB, Murray RM. Incidence and distribution of first-episode mania by age: results from a 35-year study. Psychol Med 2005;35:855–863.
115. Coryell W, Fiedorowicz J, Solomon D, Endicott J. Age transitions in the course of bipolar I disorder. Psychol Med 2009;39:1247–1252.
116. Kukopulos A, Reginaldi D, Laddomada P, Floris G, Serra G, Tondo L. Course of the manic-depressive cycle and changes caused by treatment. Pharmakopsychiatr Neuropsychopharmakol 1980;13:156–167.
117. Koukopoulos A, Reginaldi D, Tondo L, Visioli C, Baldessarini RJ. Course sequences in bipolar disorder: depressions preceding or following manias or hypomanias. J Affect Disord 2013;151:105–110.
118. Haag H, Heidorn A, Haag M, Greil W. Sequence of affective polarity and lithium response: preliminary report on Munich sample. Prog Neuropsychopharmacol Biol Psychiatry 1987;11:205–208.
119. Grof P. Admission rates and lithium therapy. Br J Psychiatry 1987;150:264–265.
120. Maj M, Pirozzi R, Starace F. Previous pattern of course of the illness as a predictor of response to lithium prophylaxis in bipolar patients. J Affect Disord 1989;17:237–241.
121. Turvey CL, Coryell WH, Solomon DA, Leon AC, Endicott J, Keller MB, Akiskal H. Long-term prognosis of bipolar I disorder. Acta Psychiatr Scand 1999;99:110–119.
122. Angst J, Baastrup P, Grof P, Hippius H, Pöldinger W, Weis P. The course of monopolar depression and bipolar psychoses. Psychiatr Neurol Neurochir 1973;76:489–500.
123. Solomon DA, Leon AC, Endicott J, Coryell WH, Mueller TI, Posternak MA, Keller MB. Unipolar mania over the course of a 20-year follow-up study. Am J Psychiatry 2003;160:2049–2051.

124. Abrams R, Taylor MA. Catatonia. A prospective clinical study. Arch Gen Psychiatry 1976;33:579–581.
125. Fein S, McGrath MG. Problems in diagnosing bipolar disorder in catatonic patients. J Clin Psychiatry 1990;51:203–205.
126. Clayton PJ, Pitts FN Jr. Affect disorder. IV. Mania. Compr Psychiatry 1965;6:313–322.
127. Abrams R, Taylor MA. Importance of schizophrenic symptoms in the diagnosis of mania. Am J Psychiatry 1981;138:658–661.
128. Carlson GA, Goodwin FK. The stages of mania. A longitudinal analysis of the manic episode. Arch Gen Psychiatry 1973;28:221–228.
129. Pope HG Jr, Lipinski JF Jr. Diagnosis in schizophrenia and manic-depressive illness: a reassessment of the specificity of 'schizophrenic' symptoms in the light of current research. Arch Gen Psychiatry 1978;35:811–828.
130. Coryell W, Keller M, Lavori P, Endicott J. Affective syndromes, psychotic features, and prognosis. II. Mania. Arch Gen Psychiatry 1990;47:658–662.
131. Andreasen NC. Thought, language, and communication disorders. II. Diagnostic significance. Arch Gen Psychiatry 1979;36:1325–1330.
132. Andreasen NC. Thought, language, and communication disorders. I. Clinical assessment, definition of terms, and evaluation of their reliability. Arch Gen Psychiatry 1979;36:1315–1321.
133. Andreasen NJ, Powers PS. Overinclusive thinking in mania and schizophrenia. Br J Psychiatry 1974;125:452–456.
134. Harrow M, Grossman LS, Silverstein ML, Meltzer HY. Thought pathology in manic and schizophrenic patients. Its occurrence at hospital admission and seven weeks later. Arch Gen Psychiatry 1982;39:665–671.
135. Brockington IF, Hillier VF, Francis AF, Helzer JE, Wainwright S. Definitions of mania: concordance and prediction of outcome. Am J Psychiatry 1983;140:435–439.
136. Mitchell PG, Parker G, Jamieson K, Wilhelm K, Hickie I, Brodaty H, Boyce P, Hadzi-Pavlovic D, Roy K. Are there any differences between bipolar and unipolar melancholia? J Affect Disord 1992;25:97–105.
137. Dunner DL, Gershon ES, Goodwin FK. Heritable factors in the severity of affective illness. Biol Psychiatry 1976;11:31–42.
138. Andreasen NC, Shore D, Burke JD Jr, Grove WM, Lieberman JA, Oltmanns TF, Pettegrew JW, Pulver AE, Siever LJ, Tsuang MT, Wyatt RJ. Clinical phenomenology. Schizophr Bull 1988;14:345–363.
139. Coryell W, Endicott J, Andreasen N, Keller M. Bipolar I, bipolar II, and nonbipolar major depression among the relatives of affectively ill probands. Am J Psychiatry 1985;142:817–821.
140. Black DW, Nasrallah A. Hallucinations and delusions in 1,715 patients with unipolar and bipolar affective disorders. Psychopathology 1989;22:28–34.
141. Guze SB, Woodruff RA Jr, Clayton PJ. The significance of psychotic affective disorders. Arch Gen Psychiatry 1975;32:1147–1150.
142. Judd LL, Akiskal HS, Schettler PJ, Coryell W, Maser J, Rice JA, Solomon DA, Keller MB. The comparative clinical phenotype and long term longitudinal episode course of bipolar I and II: a clinical spectrum or distinct disorders? J Affect Disord 2003;73:19–32.
143. Coryell W, Endicott J, Keller M. Rapidly cycling affective disorder. Demographics, diagnosis, family history, and course. Arch Gen Psychiatry 1992;49:126–131.
144. Maj M, Pirozzi R, Formicola AM, Tortorella A. Reliability and validity of four alternative definitions of rapid-cycling bipolar disorder. Am J Psychiatry 1999;156:1421–1424.
145. Coryell W, Keller M, Endicott J, Andreasen N, Clayton P, Hirschfeld R. Bipolar II illness: course and outcome over a five-year period. Psychol Med 1989;19:129–141.
146. Angst J. The course of affective disorders. Psychopathology 1986;19:47–52.
147. Angst J. Course of unipolar depressive, bipolar manic-depressive, and schizoaffective disorders. Results of a prospective longitudinal study (author's transl). Fortschr Neurol Psychiatr Grenzgeb 1980;48:3–30.
148. Zis AP, Grof P, Webster M, Goodwin FK. Prediction of relapse in recurrent affective disorder. Psychopharmacol Bull 1980;16:47–49.
149. Perris C. The course of depressive psychoses. Acta Psychiatr Scand 1968;44:238–248.
150. Carlson GA, Kotin J, Davenport YB, Adland M. Follow-up of 53 bipolar manic-depressive patients. Br J Psychiatry 1974;124: 134–139.
151. Keller MB, Lavori PW, Coryell W, Endicott J, Mueller TI. Bipolar I: a five-year prospective follow-up. J Nerv Ment Dis 1993;181: 238–245.
152. Coryell W, Endicott J, Maser JD, Mueller T, Lavori P, Keller M. The likelihood of recurrence in bipolar affective disorder: the importance of episode recency. J Affect Disord 1995;33:201–206.
153. Judd LL, Schettler PJ, Akiskal HS, Maser J, Coryell W, Solomon D, Endicott J, Keller M. Long-term symptomatic status of bipolar I vs. bipolar II disorders. Int J Neuropsychopharmacol 2003;6:127–137.
154. Joyce PR, Doughty CJ, Wells JE, Walsh AE, Admiraal A, Lill M, Olds RJ. Affective disorders in the first-degree relatives of bipolar probands: results from the South Island Bipolar Study. Compr Psychiatry 2004;45:168–174.
155. Roy-Byrne P, Post RM, Uhde TW, Porcu T, Davis D. The longitudinal course of recurrent affective illness: life chart data from research patients at the NIMH. Acta Psychiatr Scand Suppl 1985;317:1–34.
156. Post RM, Rubinow DR, Ballenger JC. Conditioning and sensitisation in the longitudinal course of affective illness. Br J Psychiatry 1986;149:191–201.
157. Baldessarini RJ, Salvatore P, Khalsa HM, Imaz-Etxeberria H, Gonzalez-Pinto A, Tohen M. Episode cycles with increasing recurrences in first-episode bipolar-I disorder patients. J Affect Disord 2012;136:149–154.
158. Winokur G, Coryell W, Akiskal HS, Endicott J, Keller M, Mueller T. Manic-depressive (bipolar) disorder: the course in light of a prospective ten-year follow-up of 131 patients. Acta Psychiatr Scand 1994;89:102–110.
159. Coryell W, Leon AC, Turvey C, Akiskal HS, Mueller T, Endicott J. The significance of psychotic features in manic episodes: a report from the NIMH Collaborative Study. J Affect Disord 2001;67:79–88.

160. Simon NM, Otto MW, Wisniewski SR, Fossey M, Sagduyu K, Frank E, Sachs GS, Nierenberg AA, Thase ME, Pollack MH. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2004;161:2222–2229.
161. Tohen M, Waternaux CM, Tsuang MT. Outcome in mania. A 4-year prospective follow-up of 75 patients utilizing survival analysis. Arch Gen Psychiatry 1990;47:1106–1111.
162. Marneros A, Röttig S, Röttig D, Tscharntke A, Brieger P. Bipolar I disorder with mood-incongruent psychotic symptoms: a comparative longitudinal study. Eur Arch Psychiatr Clin Neurosci 2009;259:131–136.
163. Feske U, Frank E, Kupfer DJ, Shear MK, Weaver E. Anxiety as a predictor of response to interpersonal psychotherapy for recurrent major depression: an exploratory investigation. Depress Anxiety 1998;8:135–141.
164. Tohen M, Tsuang MT, Goodwin DC. Prediction of outcome in mania by mood-congruent or mood-incongruent psychotic features. Am J Psychiatry 1992;149:1580–1584.
165. MacKinnon DF, Zandi PP, Cooper J, Potash JB, Simpson SG, Gershon E, Nurnberger J, Reich T. Comorbid bipolar disorder and panic disorder in families with a high prevalence of bipolar disorder. Am J Psychiatry 2002;159:30–35.
166. Nwulia EA, Zandi PP, McInnis MG, DePaulo JR Jr, MacKinnon DF. Rapid switching of mood in families with familial bipolar disorder. Bipolar Disord 2008;10:597–606.
167. Frank E, Cyranowski JM, Rucci P, Shear MK, Fagiolini A, Thase ME, Cassano GB, Grochocinski VJ, Kostelnik B, Kupfer DJ. Clinical significance of lifetime panic spectrum symptoms in the treatment of patients with bipolar I disorder. Arch Gen Psychiatry 2002; 59:905–911.
168. Otto MW, Simon NM, Wisniewski SR, Miklowitz DJ, Kogan JN, Reilly-Harrington NA, Frank E, Nierenberg AA, Marangell LB, Sagduyu K, Weiss RD, Miyahara S, Thase ME, Sachs GS. Pollack MH; STEP-BD Investigators. Prospective 12-month course of bipolar disorder in out-patients with and without comorbid anxiety disorders. Br J Psychiatry 2006;189:20–25.
169. Coryell W, Andreasen NC, Endicott J, Keller M. The significance of past mania or hypomania in the course and outcome of major depression. Am J Psychiatry 1987;144:309–315.
170. Solomon DA, Leon AC, Coryell WH, Endicott J, Li C, Fiedorowicz JG, Boyken L, Keller MB. Longitudinal course of bipolar I disorder: duration of mood episodes. Arch Gen Psychiatry 2010;67:339–347.
171. Maj M, Pirozzi R, Bartoli L, Magliano L. Long-term outcome of lithium prophylaxis in bipolar disorder with mood-incongruent psychotic features: a prospective study. J Affect Disord 2002;71:195–198.
172. Cassidy F, Ahearn E, Carroll BJ. A prospective study of inter-episode consistency of manic and mixed subtypes of bipolar disorder. J Affect Disord 2001;67:181–185.
173. Coryell W, Solomon DA, Fiedorowicz JG, Endicott J, Schettler PJ, Judd LL. Anxiety and outcome in bipolar disorder. Am J Psychiatry 2009;166:1238–1243.
174. Keller MB, Lavori PW, Coryell W, Andreasen NC, Endicott J, Clayton PJ, Klerman GL, Hirschfeld RM. Differential outcome of pure manic, mixed/cycling, and pure depressive episodes in patients with bipolar illness. JAMA 1986;255:3138–3142.
175. Coryell W, Solomon D, Turvey C, Keller M, Leon AC, Endicott J, Schettler P, Judd L, Mueller T. The long-term course of rapid-cycling bipolar disorder. Arch Gen Psychiatry 2003;60:914–920.
176. Maj M, Magliano L, Pirozzi R, Marasco C, Guarneri M. Validity of rapid cycling as a course specifier for bipolar disorder. Am J Psychiatry 1994;151:1015–1019.
177. Goldberg JF, Harrow M. Kindling in bipolar disorders: a longitudinal follow-up study. Biol Psychiatry 1994;35:70–72.
178. Secunda SK, Swann A, Katz MM, Koslow SH, Croughan J, Chang S. Diagnosis and treatment of mixed mania. Am J Psychiatry 1987;144:96–98.
179. Prien RF, Himmelhoch JM, Kupfer DJ. Treatment of mixed mania. J Affect Disord 1988;15:9–15.
180. Post RM, Rubinow DR, Uhde TW, Roy-Byrne PP, Linnoila M, Rosoff A, Cowdry R. Dysphoric mania. Clinical and biological correlates. Arch Gen Psychiatry 1989;46:353–358.
181. Bauer MS, Crits-Christoph P, Ball WA, Dewees E, McAllister T, Alahi P, Cacciola J, Whybrow PC. Independent assessment of manic and depressive symptoms by self-rating. Scale characteristics and implications for the study of mania. Arch Gen Psychiatry 1991; 48:807–812.
182. Perugi G, Micheli C, Akiskal HS, Madaro D, Socci C, Quilici C, Musetti L. Polarity of the first episode, clinical characteristics, and course of manic depressive illness: a systematic retrospective investigation of 320 bipolar I patients. Compr Psychiatry 2000;41: 13–18.
183. Tohen M, Zarate CA Jr, Hennen J, Khalsa HM, Strakowski SM, Gebre-Medhin P, Salvatore P, Baldessarini RJ. The McLean-Harvard First-Episode Mania Study: prediction of recovery and first recurrence. Am J Psychiatry 2003;160:2099–2107.
184. Cohen S, Khan A, Cox G. Demographic and clinical features predictive of recovery in acute mania. J Nerv Ment Dis 1989;177:638–642.
185. Fawcett J, Scheftner W, Clark D, Hedeker D, Gibbons R, Coryell W. Clinical predictors of suicide in patients with major affective disorders: a controlled prospective study. Am J Psychiatry 1987;144:35–40.
186. Judd LL, Schettler PJ, Akiskal H, Coryell W, Fawcett J, Fiedorowicz JG, Solomon DA, Keller MB. Prevalence and clinical significance of subsyndromal manic symptoms, including irritability and psychomotor agitation, during bipolar major depressive episodes. J Affect Disord 2012;138:440–448.
187. Bratfos O, Haug JO. The course of manic-depressive psychosis. A follow up investigation of 215 patients. Acta Psychiatr Scand 1968;44:89–112.

188. Welner A, Welner Z, Leonard MA. Bipolar manic-depressive disorder: a reassessment of course and outcome. Compr Psychiatry 1977;18:327–332.
189. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, Keller MB. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59:530–537.
190. Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, Solomon DA, Leon AC, Keller MB. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 2003;60:261–269.
191. Paykel ES, Abbott R, Morriss R, Hayhurst H, Scott J. Sub-syndromal and syndromal symptoms in the longitudinal course of bipolar disorder. Br J Psychiatry 2006;189:118–123.
192. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Leon AC, Solomon DA, Coryell W, Maser JD, Keller MB. Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. Arch Gen Psychiatry 2005;62:1322–1330.
193. Judd LL, Schettler PJ, Akiskal HS, Coryell W, Leon AC, Maser JD, Solomon DA. Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence. Arch Gen Psychiatry 2008;65:386–394.
194. Petterson U. Manic-depressive illness. A clinical, social and genetic study. Acta Psychiatr Scand Suppl 1977;1–93.
195. Miller IW, Uebelacker LA, Keitner GI, Ryan CE, Solomon DA. Longitudinal course of bipolar I disorder. Compr Psychiatry 2004;45:431–440.
196. Kessler RC, Akiskal HS, Ames M, Birnbaum H, Greenberg P, Hirschfeld RM, Jin R, Merikangas KR, Simon GE, Wang PS. Prevalence and effects of mood disorders on work performance in a nationally representative sample of U.S. workers. Am J Psychiatry. 2006;163:1561–1568.
197. Brodie HK, Leff MJ. Bipolar depression–a comparative study of patient characteristics. Am J Psychiatry 1971;127:1086–1090.
198. Coryell W, Scheftner W, Keller M, Endicott J, Maser J, Klerman GL. The enduring psychosocial consequences of mania and depression. Am J Psychiatry 1993;150:720–727.
199. Targum SD, Dibble ED, Davenport YB, Gershon ES. The Family Attitudes Questionnaire. Patients' and spouses' views of bipolar illness. Arch Gen Psychiatry 1981;38:562–568.
200. Matza L, de Lissovoy G, Sasane R, Pesa J, Mauskopf J. The impact of bipolar disorder on work loss. Drug Benefit Trends 2004;16: 476–481.
201. Tondo L, Isacsson G, Baldessarini R. Suicidal behaviour in bipolar disorder: risk and prevention. CNS Drugs 2003;17:491–511.
202. Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34–38 years. J Affect Disord 2002;68:167–181.
203. Angst J, Angst F, Gerber-Werder R, Gamma A. Suicide in 406 mood-disorder patients with and without long-term medication: a 40 to 44 years' follow-up. Arch Suicide Res 2005;9:279–300.
204. Khuri R, Akiskal HS. Suicide prevention: the necessity of treating contributory psychiatric disorders. Psychiatr Clin North Am 1983;6: 193–207.
205. Martin RL, Cloninger CR, Guze SB, Clayton PJ. Mortality in a follow-up of 500 psychiatric outpatients. II Cause-specific mortality Arch Gen Psychiatry 1985;42:58–66.
206. Robins E. The final months: A study of the lives of 134 persons who committed suicide. New York: Oxford Press; 1981.
207. Kupfer DJ, Carpenter LL, Frank E. Is bipolar II a unique disorder? Compr Psychiatry 1988;29:228–236.
208. Fiedorowicz JG, Solomon DA, Endicott J, Leon AC, Li C, Rice JP, Coryell WH. Manic/hypomanic symptom burden and cardiovascular mortality in bipolar disorder. Psychosom Med 2009;71:598–606.
209. Yates WR, Wallace R. Cardiovascular risk factors in affective disorder. J Affect Disord 1987;12:129–134.
210. Weeke A, Juel K, Vaeth M. Cardiovascular death and manic-depressive psychosis. J Affect Disord 1987;13:287–292.
211. Laursen TM, Munk-Olsen T, Nordentoft M, Mortensen PB. Increased mortality among patients admitted with major psychiatric disorders: a register-based study comparing mortality in unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia. J Clin Psychiatry 2007;68:899–907.
212. Black DW, Winokur G, Nasrallah A. Is death from natural causes still excessive in psychiatric patients? A follow-up of 1593 patients with major affective disorder. J Nerv Ment Dis 1987;175:674–680.
213. Osby U, Brandt L, Correia N, Ekbom A, Sparén P. Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry 2001;58:844–850.
214. Avery D, Winokur G. Mortality in depressed patients treated with electroconvulsive therapy and antidepressants. Arch Gen Psychiatry 1976;33:1029–1037.
215. Tsuang MT, Woolson RF. Mortality in patients with schizophrenia, mania, depression and surgical conditions. A comparison with general population mortality. Br J Psychiatry 1977;130:162–166.
216. Fiedorowicz JG, Coryell WH, Rice JP, Warren LL, Haynes WG. Vasculopathy related to manic/hypomanic symptom burden and first-generation antipsychotics in a sub-sample from the collaborative depression study. Psychother Psychosom 2012;81:235–243.
217. da Silva J, Goncalves-Pereira M, Xavier M, Mukaetova-Ladinska EB. Affective disorders and risk of developing dementia: systematic review. Br J Psychiatry 2013;202:177–186.
218. Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA 1990;264:2511–2518.
219. Frye MA, Altshuler LL, McElroy SL, Suppes T, Keck PE, Denicoff K, Nolen WA, Kupka R, Leverich GS, Pollio C, Grunze H, Walden J, Post RM. Gender differences in prevalence, risk, and clinical correlates of alcoholism comorbidity in bipolar disorder. Am J Psychiatry 2003;160:883–889.

220. Winokur G, Coryell W, Akiskal HS, Maser JD, Keller MB, Endicott J, Mueller T. Alcoholism in manic-depressive (bipolar) illness: familial illness, course of illness, and the primary-secondary distinction. Am J Psychiatry 1995;152:365–372.
221. Strakowski SM, Fleck DE, DelBello MP, Adler CM, Shear PK, Kotwal R, Arndt S. Impulsivity across the course of bipolar disorder. Bipolar Disord 2010;12:285–297.
222. Himmelhoch JM, Mulla D, Neil JF, Detre TP, Kupfer DJ. Incidence and signficiance of mixed affective states in a bipolar population. Arch Gen Psychiatry 1976;33:1062–1066.
223. Goldberg JF, Garno JL, Leon AC, Kocsis JH, Portera L. A history of substance abuse complicates remission from acute mania in bipolar disorder. J Clin Psychiatry 1999;60:733–740.
224. Jamison KR, Gerner RH, Hammen C, Padesky C. Clouds and silver linings: positive experiences associated with primary affective disorders. Am J Psychiatry 1980;137:198–202.
225. Bouman TK, de Vries J, Koopmans IH. Lithium prophylaxis and interepisode mood. A prospective longitudinal comparison of euthymic bipolars and non-patient controls. J Affect Disord 1992;24:199–206.
226. Akiskal HS, Hirschfeld RM, Yerevanian BI. The relationship of personality to affective disorders. Arch Gen Psychiatry 1983;40: 801–810.
227. Matussek P, Feil WB. Personality attributes of depressive patients. Arch Gen Psychiatry 1983;40:783–790.
228. MacVane JR, Lange JD, Brown WA, Zayat M. Psychological functioning of bipolar manic-depressives in remission. Arch Gen Psychiatry 1978;35:1351–1354.
229. Lumry AE, Gottesman II, Tuason VB. MMPI state dependency during the course of bipolar psychosis. Psychiatry Res 1982;7:59–67.
230. Bech P, Shapiro RW, Sihm F, Nielsen BM, Sørensen B, Rafaelsen OJ. Personality in unipolar and bipolar manic-malancholic patients. Acta Psychiatr Scand 1980;62:245–257.
231. Akiskal HS, Kilzieh N, Maser JD, Clayton PJ, Schettler PJ, Traci Shea M, Endicott J, Scheftner W, Hirschfeld RM, Keller MB. The distinct temperament profiles of bipolar I, bipolar II and unipolar patients. J Affect Disord 2006;92:19–33.
232. Angst J, Clayton P. Premorbid personality of depressive, bipolar, and schizophrenic patients with special reference to suicidal issues. Compr Psychiatry 1986;27:511–532.
233. Klein DN, Depue RA. Obsessional personality traits and risk for bipolar affective disorder: an offspring study. J Abnorm Psychol 1985;94:291–297.
234. Swann AC, Pazzaglia P, Nicholls A, Dougherty DM, Moeller FG. Impulsivity and phase of illness in bipolar disorder. J Affect Disord 2003;73:105–111.
235. London WP, Taylor BM. Bipolar disorders in a forensic setting. Compr Psychiatry 1982;23:33–37.
236. McCormick RA, Russo AM, Ramirez LF, Taber JI. Affective disorders among pathological gamblers seeking treatment. Am J Psychiatry 1984;141:215–218.
237. Zimmerman M, Chelminski I, Young D. Prevalence and diagnostic correlates of DSM-IV pathological gambling in psychiatric outpatients. J Gambl Stud 2006;22:255–262.
238. Black D, Coryell W, Crowe R, McCormick B, Shaw M, Allen J. A direct controlled blind family study of DSM-IV pathological gambling. J Clin Psychiatry 2014;75:215–221.
239. Young MA, Abrams R, Taylor MA, Meltzer HY. Establishing diagnostic criteria for mania. J Nerv Ment Dis 1983;171:676–682.
240. Dysken MW, Kooser JA, Haraszti JS, Davis JM. Clinical usefulness of sodium amobarbital interviewing. Arch Gen Psychiatry 1979;36:789–794.
241. Zimmerman M, Ruggero CJ, Chelminski I, Young D. Is bipolar disorder overdiagnosed? J Clin Psychiatry 2008;69:935–940.
242. Zimmerman M, Galione JN, Ruggero CJ, Chelminski I, Young D, Dalrymple K, McGlinchey JB. Screening for bipolar disorder and finding borderline personality disorder. J Clin Psychiatry 2010;71:1212–1217.
243. Perugi G, Angst J, Azorin JM, Bowden C, Vieta E, Young AH, BRIDGE Study Group. The bipolar-borderline personality disorders connection in major depressive patients. Acta Psychiatr Scand 2013;128:376–383.
244. Masi G, Perugi G, Toni C, Millepiedi S, Mucci M, Bertini N, Pfanner C. Attention-deficit hyperactivity disorder – bipolar comorbidity in children and adolescents. Bipolar Disord 2006;8:373–381.
245. Geller B, Zimerman B, Williams M, Bolhofner K, Craney JL, Delbello MP, Soutullo CA. Diagnostic characteristics of 93 cases of a prepubertal and early adolescent bipolar disorder phenotype by gender, puberty and comorbid attention deficit hyperactivity disorder. J Child Adolesc Psychopharmacol 2000;10:157–164.
246. Geller B, Williams M, Zimerman B, Frazier J, Beringer L, Warner KL. Prepubertal and early adolescent bipolarity differentiate from ADHD by manic symptoms, grandiose delusions, ultra-rapid or ultradian cycling. J Affect Disord 1998;51:81–91.
247. Geller B, Zimerman B, Williams M, Delbello MP, Bolhofner K, Craney JL, Frazier J, Beringer L, Nickelsburg MJ. DSM-IV mania symptoms in a prepubertal and early adolescent bipolar disorder phenotype compared to attention-deficit hyperactive and normal controls. J Child Adolesc Psychopharmacol 2002;12:11–25.
248. Nierenberg AA, Miyahara S, Spencer T, Wisniewski SR, Otto MW, Simon N, Pollack MH, Ostacher MJ, Yan L, Siegel R. Sachs GS; STEP-BD Investigators. Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. Biol Psychiatry 2005;57:1467–1473.
249. Faraone SV, Biederman J, Mennin D, Wozniak J, Spencer T. Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? J Am Acad Child Adolesc Psychiatry 1997;36:1378–1387. discussion 1387–1390.
250. Faraone SV, Biederman J, Wozniak J. Examining the comorbidity between attention deficit hyperactivity disorder and bipolar I disorder: a meta-analysis of family genetic studies. Am J Psychiatry 2012;169:1256–1266.

251. Janowsky DS. el-Yousef MK, Davis JM. Interpersonal maneuvers of manic patients. Am J Psychiatry 1974;131:250–255.
252. Janowsky DS, Leff M, Epstein RS. Playing the manic game. Interpersonal maneuvers of the acutely manic patient. Arch Gen Psychiatry 1970;22:252–261.
253. Garfinkel PE, Stancer HC, Persad E. A comparison of haloperidol, lithium carbonate and their combination in the treatment of mania. J Affect Disord 1980;2:279–288.
254. Dunner DL. Drug treatment of the acute manic episode. In: Grinspoon L, editor. Psychiatry update. Arlington, VA: American Psychiatric Association Publishing; 1983.
255. Marhold J, Zimanova J, Lachman M, Kral J, Vojtechovsky M. To the incompatibility of haloperidol with lithium salts. Act Nerv Super (Praha) 1974;16:199–200.
256. Rosenbaum AH, Niven RG, Hanson NP, Swanson DW. Tardive dyskinesia: relationship with a primary affective disorder. Dis Nerv Syst 1977;38:423–427.
257. Kane J, Struve FA, Weinhold P, Woerner M. Strategy for the study of patients at high risk for tardive dyskinesia. Am J Psychiatry 1980;137:1265–1267.
258. Rush M, Diamond F, Alpert M. Depression as a risk factor in tardive dyskinesia. Biol Psychiatry 1982;17:387–392.
259. Greil W, Stoltzenburg MC, Mairhofer ML, Haag M. Lithium dosage in the elderly. A study with matched age groups. J Affect Disord 1985;9:1–4.
260. Young RC, Nysewander RW, Schreiber MT. Mania ratings at discharge from hospital: a follow-up. J Nerv Ment Dis 1982;170:638–639.
261. McElroy SL, Keck PE Jr, Pope HG Jr, Hudson JI. Valproate in the treatment of bipolar disorder: literature review and clinical guidelines. J Clin Psychopharmacol 1992;12:42S–52S.
262. Prien RF, Gelenberg AJ. Alternatives to lithium for preventive treatment of bipolar disorder. Am J Psychiatry 1989;146:840–848.
263. Prien RF, Potter WZ. NIMH workshop report on treatment of bipolar disorder. Psychopharmacol Bull 1990;26:409–427.
264. Gerner RH, Stanton A. Algorithm for patient management of acute manic states: lithium, valproate, or carbamazepine? J Clin Psychopharmacol 1992;12:57S–63S.
265. Allen MH, Hirschfeld RM, Wozniak PJ, Baker JD, Bowden CL. Linear relationship of valproate serum concentration to response and optimal serum levels for acute mania. Am J Psychiatry 2006;163:272–275.
266. Hirschfeld RM, Baker JD, Wozniak P, Tracy K, Sommerville KW. The safety and early efficacy of oral-loaded divalproex versus standard-titration divalproex, lithium, olanzapine, and placebo in the treatment of acute mania associated with bipolar disorder. J Clin Psychiatry 2003;64:841–846.
267. Bowden CL, Janicak PG, Orsulak P, Swann AC, Davis JM, Calabrese JR, Goodnick P, Small JG, Rush AJ, Kimmel SE, Risch SC, Morris DD. Relation of serum valproate concentration to response in mania. Am J Psychiatry 1996;153:765–770.
268. Ballenger JC, Post RM. Carbamazepine in manic-depressive illness: a new treatment. Am J Psychiatry 1980;137:782–790.
269. Post RM. Use of the anticonvulsant carbamazepine in primary and secondary affective illness: clinical and theoretical implications. Psychol Med 1982;12:701–704.
270. Post RM, Uhde TW, Ballenger JC, Squillace KM. Prophylactic efficacy of carbamazepine in manic-depressive illness. Am J Psychiatry 1983;140:1602–1604.
271. Nolen WA. Carbamazepine, a possible adjunct or alternative to lithium in bipolar disorder. Acta Psychiatr Scand 1983;67:218–225.
272. Kishimoto A, Ogura C, Hazama H, Inoue K. Long-term prophylactic effects of carbamazepine in affective disorder. Br J Psychiatry 1983;143:327–331.
273. Zhang ZJ, Kang WH, Tan QR, Li Q, Gao CG, Zhang FG, Wang HH, Ma XC, Chen C, Wang W, Guo L, Zhang YH, Yang XB, Yang GD. Adjunctive herbal medicine with carbamazepine for bipolar disorders: A double-blind, randomized, placebo-controlled study. J Psychiatr Res 2007;41:360–369.
274. Zhang ZJ, Tan QR, Tong Y, Li Q, Kang WH, Zhen XC, Post RM. The effectiveness of carbamazepine in unipolar depression: a double-blind, randomized, placebo-controlled study. J Affect Disord 2008;109:91–97.
275. Obrocea GV, Dunn RM, Frye MA, Ketter TA, Luckenbaugh DA, Leverich GS, Speer AM, Osuch EA, Jajodia K, Post RM. Clinical predictors of response to lamotrigine and gabapentin monotherapy in refractory affective disorders. Biol Psychiatry 2002;51:253–260.
276. Kushner SF, Khan A, Lane R, Olson WH. Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials. Bipolar Disord 2006;8:15–27.
277. Freeman TW, Clothier JL, Pazzaglia P, Lesem MD, Swann AC. A double-blind comparison of valproate and lithium in the treatment of acute mania. Am J Psychiatry 1992;149:108–111.
278. Calabrese JR, Fatemi SH, Kujawa M, Woyshville MJ. Predictors of response to mood stabilizers. J Clin Psychopharmacol 1996;16:24S–31S.
279. Swann AC, Bowden CL, Morris D, Calabrese JR, Petty F, Small J, Dilsaver SC, Davis JM. Depression during mania. Treatment response to lithium or divalproex. Arch Gen Psychiatry 1997;54:37–42.
280. Bowden CL. Predictors of response to divalproex and lithium. J Clin Psychiatry 1995;56:25–30.
281. Clothier J, Swann AC, Freeman T. Dysphoric mania. J Clin Psychopharmacol 1992;12:13S–16S.
282. McCabe MS. ECT in the treatment of mania: a controlled study. Am J Psychiatry 1976;133:688–691.
283. McCabe MS, Norris B. ECT versus chlorpromazine in mania. Biol Psychiatry 1977;12:245–254.
284. Black DW, Winokur G, Nasrallah A. Treatment of mania: a naturalistic study of electroconvulsive therapy versus lithium in 438 patients. J Clin Psychiatry 1987;48:132–139.
285. Small JG, Klapper MH, Kellams JJ, Miller MJ, Milstein V, Sharpley PH, Small IF. Electroconvulsive treatment compared with lithium in the management of manic states. Arch Gen Psychiatry 1988;45:727–732.

286. Mukherjee S, Debsikdar V. Unmodified electroconvulsive therapy of acute mania: A retrospective naturalistic study. Convuls Ther 1992;8:5–11.
287. Fountoulakis KN, Kasper S, Andreassen O, Blier P, Okasha A, Severus E, Versiani M, Tandon R, Möller HJ, Vieta E. Efficacy of pharmacotherapy in bipolar disorder: a report by the WPA section on pharmacopsychiatry. Eur Arch Psychiatry Clin Neurosci 2012;262:1–48.
288. Spielmans GI, Berman MI, Linardatos E, Rosenlicht NC, Perry A, Tsai AC. Adjunctive atypical antipsychotic treatment for major depressive disorder: a meta-analysis of depression, quality of life, and safety outcomes. PLoS Med 2013;10:e1001403.
289. Amsterdam JD, Garcia-España F, Fawcett J, Quitkin FM, Reimherr FW, Rosenbaum JF, Schweizer E, Beasley C. Efficacy and safety of fluoxetine in treating bipolar II major depressive episode. J Clin Psychopharmacol 1998;18:435–440.
290. Amsterdam J. Efficacy and safety of venlafaxine in the treatment of bipolar II major depressive episode. J Clin Psychopharmacol 1998;18:414–417.
291. Amsterdam JD, Brunswick DJ. Antidepressant monotherapy for bipolar type II major depression. Bipolar Disord 2003;5:388–395.
292. Amsterdam JD, Shults J. Comparison of short-term venlafaxine versus lithium monotherapy for bipolar II major depressive episode: a randomized open-label study. J Clin Psychopharmacol 2008;28:171–181.
293. Ghaemi SN, Ostacher MM, El-Mallakh RS, Borrelli D, Baldassano CF, Kelley ME, Filkowski MM, Hennen J, Sachs GS, Goodwin FK, Baldessarini RJ. Antidepressant discontinuation in bipolar depression: a Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) randomized clinical trial of long-term effectiveness and safety. J Clin Psychiatry 2010;71:372–380.
294. Peet M. Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. Br J Psychiatry 1994;164:549–550.
295. Frye MA, Ha K, Kanba S, Kato T, McElroy SL, Özerdem A, Vázquez G, Vieta E. International consensus group on depression prevention in bipolar disorder. J Clin Psychiatry 2011;72:1295–1310.
296. Ghaemi SN, Wingo AP, Filkowski MA, Baldessarini RJ. Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks. Acta Psychiatr Scand 2008;118:347–356.
297. Post RM, Altshuler LL, Leverich GS, Frye MA, Nolen WA, Kupka RW, Suppes T, McElroy S, Keck PE, Denicoff KD, Grunze H, Walden J, Kitchen CM, Mintz J. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. Br J Psychiatry 2006;189:124–131.
298. Vieta E, Martinez-Arán A, Goikolea JM, Torrent C, Colom F, Benabarre A, Reinares M. A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers. J Clin Psychiatry 2002;63:508–512.
299. Prien RF. Long-term prophylactic pharmacologic treatment of bipolar illness. In: Grinspoon L, editor. Psychiatry update. Arlington, VA: American Psychiatric Association Publishing; 1983.
300. Muzina DJ, Calabrese JR. Maintenance therapies in bipolar disorder: focus on randomized controlled trials. Aust N Z J Psychiatry 2005;39:652–661.
301. Plenge P, Mellerup ET, Bolwig TG, Brun C, Hetmar O, Ladefoged J, Larsen S, Rafaelsen OJ. Lithium treatment: does the kidney prefer one daily dose instead of two? Acta Psychiatr Scand 1982;66:121–128.
302. Maj M, Starace F, Nolfe G, Kemali D. Minimum plasma lithium levels required for effective prophylaxis in DSM III bipolar disorder: a prospective study. Pharmacopsychiatry 1986;19:420–423.
303. Tondo L, Baldessarini RJ, Floris G. Long-term clinical effectiveness of lithium maintenance treatment in types I and II bipolar disorders. Br J Psychiatry Suppl 2001;41:s184–s190.
304. Bowden CL, Calabrese JR, McElroy SL, Gyulai L, Wassef A, Petty F, Pope HG Jr, Chou JC, Keck PE Jr, Rhodes LJ, Swann AC, Hirschfeld RM, Wozniak PJ. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group Arch Gen Psychiatry 2000;57:481–489.
305. Bowden CL, Calabrese JR, Sachs G, Yatham LN, Asghar SA, Hompland M, Montgomery P, Earl N, Smoot TM. DeVeaugh-Geiss J; Lamictal 606 Study Group. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. Arch Gen Psychiatry 2003;60:392–400.
306. Greil W, Kleindienst N, Erazo N, Muller-Oerlinghausen B. Differential response to lithium and carbamazepine in the prophylaxis of bipolar disorder. J Clin Psychopharmacol 1998;18:455–460.
307. Prien RF, Caffey EM Jr, Klett CJ. Factors associated with treatment success in lithium carbonate prophylaxis. Report of the Veterans Administration and National Institute of Mental Health Collaborative Study Group. Arch Gen Psychiatry 1974;31:189–192.
308. Grof P, Duffy A, Cavazzoni P, Grof E, Garnham J, MacDougall M, O'Donovan C, Alda M. Is response to prophylactic lithium a familial trait? J Clin Psychiatry 2002;63:942–947.
309. Grof P, Alda M, Grof E, Zvolsky P, Walsh M. Lithium response and genetics of affective disorders. J Affect Disord 1994;32:85–95.
310. Dunner DL, Fieve RR. Clinical factors in lithium carbonate prophylaxis failure. Arch Gen Psychiatry 1974;30:229–233.
311. Baldessarini RJ, Tondo L, Floris G, Hennen J. Effects of rapid cycling on response to lithium maintenance treatment in 360 bipolar I and II disorder patients. J Affect Disord 2000;61:13–22.
312. Okuma T. Effects of carbamazepine and lithium on affective disorders. Neuropsychobiology 1993;27:138–145.
313. Tondo L, Lepri B, Baldessarini RJ. Suicidal risks among 2826 Sardinian major affective disorder patients. Acta Psychiatrica Scandinavica 2007;116:419–428.
314. Strober M, Morrell W, Lampert C, Burroughs J. Relapse following discontinuation of lithium maintenance therapy in adolescents with bipolar I illness: a naturalistic study. Am J Psychiatry 1990;147:457–461.
315. Suppes T, Baldessarini RJ, Faedda GL, Tohen M. Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. Arch Gen Psychiatry 1991;48:1082–1088.
316. Jamison KR, Goodwin FK. Psychotherapeutic issues in bipolar illness. In: Grinspoon L, editor. Psychiatry update. Arlington, VA: American Psychiatric Association Publishing; 1983.

317. O'Connell RA, Mayo JA, Flatow L, Cuthbertson B, O'Brien BE. Outcome of bipolar disorder on long-term treatment with lithium. Br J Psychiatry 1991;159:123–129.
318. Clarkin JF, Glick ID, Haas GL, Spencer JH, Lewis AB, Peyser J, DeMane N, Good-Ellis M, Harris E, Lestelle V. A randomized clinical trial of inpatient family intervention. V. Results for affective disorders. J Affect Disord 1990;18:17–28.
319. Lovett LM, Shaw DM. Outcome in bipolar affective disorder after stereotactic tractotomy. Br J Psychiatry 1987;151:113–116.
320. Poynton A, Bridges PK, Bartlett JR. Resistant bipolar affective disorder treated by stereotactic subcaudate tractotomy. Br J Psychiatry 1988;152:354–358.
321. Lapidus KA, Shin JS, Pasculli RM, Briggs MC, Popeo DM, Kellner CH. Low-dose right unilateral electroconvulsive therapy (ECT): effectiveness of the first treatment. J ECT 2013;29:83–85.
322. Lipinski JF Jr, Zubenko GS, Cohen BM, Barreira PJ. Propranolol in the treatment of neuroleptic-induced akathisia. Am J Psychiatry 1984;141:412–415.
323. Movig KL, Baumgarten R, Leufkens HG, van Laarhoven JH, Egberts AC. Risk factors for the development of lithium-induced polyuria. Br J Psychiatry 2003;182:319–323.
324. Wilting I, Egberts AC, Movig KL, Laarhoven JH, Heerdink ER, Nolen WA. The association between concomitant use of serotonergic antidepressants and lithium-induced polyuria. A multicenter medical chart review study. Pharmacopsychiatry 2008;41:129–133.
325. Bowen RC, Grof P, Grof E. Less frequent lithium administration and lower urine volume. Am J Psychiatry 1991;148:189–192.
326. Batlle DC, von Riotte AB, Gaviria M, Grupp M. Amelioration of polyuria by amiloride in patients receiving long-term lithium therapy. N Engl J Med 1985;312:408–414.
327. Baumgartner A, von Stuckrad M, Muller-Oerlinghausen B, Graf KJ, Kurten I. The hypothalamic-pituitary-thyroid axis in patients maintained on lithium prophylaxis for years: high triiodothyronine serum concentrations are correlated to the prophylactic efficacy. J Affect Disord 1995;34:211–218.
328. Frye MA, Denicoff KD, Bryan AL, Smith-Jackson EE, Ali SO, Luckenbaugh D, Leverich GS, Post RM. Association between lower serum free T4 and greater mood instability and depression in lithium-maintained bipolar patients. Am J Psychiatry 1999;156:1909–1914.
329. Cole DP, Thase ME, Mallinger AG, Soares JC, Luther JF, Kupfer DJ, Frank E. Slower treatment response in bipolar depression predicted by lower pretreatment thyroid function. Am J Psychiatry 2002;159:116–121.
330. Frye MA, Yatham L, Ketter TA, Goldberg J, Suppes T, Calabrese JR, Bowden CL, Bourne E, Bahn RS, Adams B. Depressive relapse during lithium treatment associated with increased serum thyroid-stimulating hormone: results from two placebo-controlled bipolar I maintenance studies. Acta Psychiatr Scand 2009;120:10–13.
331. Wingo AP, Wingo TS, Harvey PD, Baldessarini RJ. Effects of lithium on cognitive performance: a meta-analysis. J Clin Psychiatry 2009;70:1588–1597.
332. Stoll A, Vuckovic A, McElroy S. Histamine subscript 2-receptor antagonists for the treatment of valproate induced gastrointestinal distress. Ann Clin Psychiatry 1991;301–304.
333. Raja M, Azzoni A. Valproate-induced hyperammonaemia. J Clin Psychopharmacol 2002;22:631–633.
334. Hjelm M, Oberholzer V, Seakins J, Thomas S, Kay JD. Valproate-induced inhibition of urea synthesis and hyperammonaemia in healthy subjects. Lancet 1986;2:859.
335. Cheng M, Tang X, Wen S, Yue J, Wang H. Valproate (VPA)-associated hyperammonemic encephalopathy independent of elevated serum VPA levels: 21 cases in China from May 2000 to May 2012. Compr Psychiatry 2013;54:562–567.
336. Eze E, Workman M, Donley B. Hyperammonemia and coma developed by a woman treated with valproic acid for affective disorder. Psychiatr Serv 1998;49:1358–1359.
337. Dealberto MJ. Valproate-induced hyperammonaemic encephalopathy: review of 14 cases in the psychiatric setting. Int Clin Psychopharmacol 2007;22:330–337.
338. Joffe H, Cohen LS, Suppes T, McLaughlin WL, Lavori P, Adams JM, Hwang CH, Hall JE, Sachs GS. Valproate is associated with new-onset oligoamenorrhea with hyperandrogenism in women with bipolar disorder. Biol Psychiatry 2006;59:1078–1086.
339. Isojärvi JI, Laatikainen TJ, Pakarinen AJ, Juntunen KT, Myllylä VV. Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. N Engl J Med 1993;329:1383–1388.
340. Rzany B, Correia O, Kelly JP, Naldi L, Auquier A, Stern R. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case–control study. Study Group of the International Case Control Study on Severe Cutaneous Adverse Reactions. Lancet 1999;353:2190–2194.
341. Castillo J, Baldessarini RJ, Zarate C Jr, Kando JC. Blood dyscrasias with carbamazepine and valproate: a pharmacoepidemiological study of 2,228 patients at risk. Am J Psychiatry 1995;152:413–418.
342. Brewerton TD. Lithium counteracts carbamazepine-induced leukopenia while increasing its therapeutic effect. Biol Psychiatry 1986;21:677–685.
343. Yassa R, Iskandar H, Nastase C, Camille Y. Carbamazepine and hyponatremia in patients with affective disorder. Am J Psychiatry 1988;145:339–342.
344. Szentagotai A, David D. The efficacy of cognitive-behavioral therapy in bipolar disorder: a quantitative meta-analysis. J Clin Psychiatry 2010;71:66–72.
345. Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. Bipolar Disord 2006;8:625–639.
346. Lauterbach E, Felber W, Müller-Oerlinghausen B, Ahrens B, Bronisch T, Meyer T, Kilb B, Lewitzka U, Hawellek B, Quante A, Richter K, Broocks A, Hohagen F. Adjunctive lithium treatment in the prevention of suicidal behaviour in depressive disorders: a randomised, placebo-controlled, 1-year trial. Acta Psychiatr Scand 2008;118:469–479.