Published in final edited form as:
Clin Psychol Rev. 2005 May ; 25(3): 307–339. doi:10.1016/j.cpr.2004.12.002.

Distinctions between bipolar and unipolar depression

Amy K. Cuellar*, **Sheri L. Johnson**, and **Ray Winters**
University of Miami, United States

Abstract

This is a review of the studies comparing unipolar and bipolar depression, with focus on the course, symptomatology, neurobiology, and psychosocial literatures. These are reviewed with one question in mind: does the evidence support diagnosing bipolar and unipolar depressions as the same disorder or different? The current nomenclature of bipolar and unipolar disorders has resulted in research that compares these disorders as a whole, without considering depression separately from mania within bipolar disorder. Future research should investigate two broad categories of depression and mania as separate disease processes that are highly comorbid.

Keywords

Bipolar disorder; Major depression; Diagnostic; Nomenclature

1. Distinctions between bipolar and unipolar depression

This review focuses on depression within bipolar disorder and the evidence concerning whether bipolar depression and unipolar depression appear unique or parallel in their etiology, symptoms, and course. Over the past 100 years, conceptions of depression within bipolar disorder have varied widely, and the changes in conceptualization have been reflected in fundamental changes in the diagnostic nomenclature.

Mania and depression have been seen as distinct, yet related, phenomena since ancient Greece (Angst & Marneros, 2001). Only in recent history have mood disorders been divided into syndromes of mania and depression. As the father of current psychiatric nosology, Kraeplin was one of the first to distinguish individuals with mania into those with and without depression. From Kraeplin through DSM-II (APA, 1968), the syndromes were labeled as mood disorders with the subtypes of recurrent mania, recurrent depression, recurrent mania and depression, and affective disorders with mixed states. Of note, recurrent mania was differentiated from recurrent mania with depression. Early descriptions of affective disorders conceptualized monopolar mania as separate from other mood disorders (Leonard, 1957). Psychiatric nosology since the DSM-III has classified major depressive disorder separately from bipolar disorder, defined by the presence of mania. Several issues guided the move to label bipolar disorder and unipolar disorder as distinct illnesses. Among these, increasing evidence supported the biological etiology and more severe lifetime course of mania compared to depression.

With the move to distinguish bipolar disorder from unipolar depression, substantial changes were made in the categorization of depression that accompanied mania. Depression and mania within bipolar disorder were viewed as part of a unitary illness, reflecting dysregulation along a single dimension. Indeed, the presence or absence of a history of depression within bipolar

*Corresponding author. Tel.: +1 305 284 1587; fax: +1 305 284 3402. akizer@umiami.ir.miami.edu (A.K. Cuellar).

disorder was no longer included in the diagnostic subtypes. This unitarian view of bipolar disorder codified a distinction between bipolar depression and unipolar depression, even though episodes of depression are common to bipolar and unipolar disorders. This assumption that bipolar and unipolar depressions are distinct has continued to guide research for almost 30 years. At this point it is easy to forget the controversy surrounding the creation of a separate bipolar classification. Hoche, one of Kraepelin's critics, pointed out, "If the term 'manic–depressive' is meant as a theoretical expression of the close internal relationship of the two opposite poles of affectivity, then there are no objections to raise against it. But the name is to be rejected as a disease-entity and consequently as a designation of diagnostic and prognostic value." (p. 273, in Jackson, 1986).

Given the increase in available evidence, it appears wise to question whether this bipolar–unipolar distinction, as it applies to *depressive* episodes, continues to garner support. That is, do depressions within bipolar disorder reflect unique disease processes compared to depressions within unipolar disorder? Indeed, a recent biological review has suggested that it may be more fruitful to consider conceptualizing bipolar and unipolar depression as the same illness (Joffe, Young, & MacQueen, 1999). This review, however, was focused on simply the biological evidence. Here, we broaden the question to include the evidence from studies of course and of psychosocial triggers. We believe that this broader focus is important, given the burgeoning literature on psychosocial antecedents and correlates of episodes of bipolar disorder.

Before continuing with the review of bipolar depression, it is worth noting that bipolar disorder does not necessarily imply a history of depression. Diagnostic criteria for bipolar I disorder require only one lifetime manic episode, but do not require an episode of depression (APA, 1994). Current research appears to support the existence of monopolar mania. Twenty-five to 33% of individuals with bipolar disorder in nontreatment samples do not report ever having a major depressive episode (Depue & Monroe, 1978; Karkowski & Kendler, 1997; Kessler, Rubinow, Holmes, Abelson, & Zhao, 1997; Weissman & Myers, 1978). In addition, a long-term study demonstrated that seven cases of unipolar mania remained free of depressive episodes during a 20-year follow-up (Solomon et al., 2003). Because depression may be more strongly related to treatment-seeking than mania (Johnson, in preparation), treatment samples tend to underestimate the prevalence of monopolar mania.

There is also evidence that mania and depression can be viewed as two separate continuums, rather than opposite ends of the same dimension. Perhaps the strongest evidence on this front stems from the evidence for high rates of mixed episodes, reflecting simultaneous full-blown episodes of mania and depression (Bauer, Whybrow, Gyulai, Gonnel, & Yeh, 1994). Indeed, the depressive symptoms demonstrated during periods with and without mania appear comparable (Johnson & Darcy, in preparation). Further, within individuals, fluctuations in depressive and manic symptoms are not correlated over time (Johnson & Darcy, in preparation). Hence, simple descriptive psychopathology evidence suggests that mania and depression can be disentangled, and do not appear to be opposites on the same pole.

Finally, it is of note that the psychosocial variables that predict bipolar depression are not consistently robust predictors of mania (Johnson, Meyer, Winett, & Small, 2000; Johnson, Winett, Meyer, Greenhouse, & Miller, 1999; Johnson, Sandrow et al., 2000; Miklowitz et al., 2000). Instead, a distinct set of biological (Chiaroni et al., 2000; El-Mallakh, Li, Worth, & Peiper, 1996; Johnson, Winters, & Meyers, in press), personality (Meyer, Johnson, & Carver, 1999; Strakowski, Stoll, Tohen, Faedda, & Goodwin, 1993; von Zerssen, 1996; Young et al., 1995), and life event (Johnson, Sandrow et al., 2000; Malkoff-Schwartz et al., 1998) variables appear to predict mania.

In sum, not all people with a lifetime episode of mania experience depression. Mania and depression appear to reflect separate symptom dimensions, which are predicted by distinct sets of psychosocial variables. In this context, we thought it was an important time within the field to review whether bipolar and unipolar depressions appear parallel.

This simple variability in whether individuals experience depression is one reason that authors have questioned whether we might want to consider diagnostic subtypes of mania with and without lifetime depression. The answer to this question, though, seems dependent on the uniqueness of depression for individuals with and without a history of mania. This article aims to compare episodes of unipolar depression to bipolar depression. Before beginning a review of the literature, we define theoretical models that may help organize the research literature. At a fundamental level, one can conceptualize two simple models: (1) bipolar depression and unipolar depression reflect distinct disorders, or (2) bipolar depression and unipolar depression reflect the same disorder. We briefly highlight each model below.

2. Unipolar and bipolar depression: different disorders

The prevailing model is that the depressions within unipolar and bipolar disorders are qualitatively different in etiology and phenomenology. This type of duality is exemplified in the DSM diagnostic system, with unipolar and bipolar disorders categorized as separate branches on the mood disorder diagnostic tree. This separate branch includes both mania and bipolar depression on the bipolar “branch,” rather than depression without mania, depression and mania, and monopolar mania. Drawing on the strong evidence that mania is biologically driven, bipolar depression has been seen as more endogenous than unipolar depression. As a consequence of this dichotomy in the diagnostic nomenclature, research in mood disorders tends to focus on either bipolar disorder as a whole, failing to account for episode polarity in bipolar disorder, or unipolar depression. Few researchers have directly compared unipolar and bipolar depression.

If the model of bipolar depression as unique is true, one would expect that biological evidence would be more pronounced in bipolar than unipolar depression. As an example, one might find a stronger genetic contribution to bipolar depression than unipolar depression. Second, one might expect the course of disorder to differ between bipolar and unipolar depression. Third, one would expect that psychosocial triggers of depression would be less pronounced in bipolar than unipolar depression. That is, if unipolar and bipolar depression were different disorders, one would expect there to be observable differences in biology, course, symptomatology, or psychosocial antecedents.

3. Unipolar and bipolar depression: same disorder

One relatively parsimonious idea is that bipolar disorder can be conceptualized as mania, with or without comorbid depression. In parallel, depression with and without mania could be seen as the same disorder. Mania and depression could be conceptualized as highly comorbid conditions, as are anxiety and depression. In the literature on anxiety and depression, most individuals conceptualize noncomorbid and comorbid depressions as parallel, with additional risk factors explaining the presence of comorbid anxiety. A similar model could be applied to depression and mania, with depression conceptualized as the same disorder regardless of the lifetime presence of mania. Support for the “same disorder” model would be drawn from an absence of replicable differences in biology, course, symptomatology, or psychosocial antecedents of bipolar and unipolar depression.

4. Methodological issues

Although much research has compared unipolar and bipolar disorders, the majority of these studies have focused on bipolar disorder as a whole, without differentiating mania and depression. Because these studies are comparing two different phenomena within the same disorder (i.e., mania and depression) with one phenomenon in unipolar disorder (i.e., depression), this literature does little to shed light on depressions in the two disorders. As such, we focus our review on articles that specifically compare episodes of depression within unipolar and bipolar disorders. Although this would seem to be a simple mission, a number of issues complicate comparisons of bipolar and unipolar depression. We summarize problems confronting researchers in sample definition, symptom measurement, and design.

4.1. Sample definition

Perhaps one of the most unresolved issues in this field of research is the choice of which diagnostic groups to include. To date, little evidence is available about how schizoaffective disorder, bipolar II disorder, and bipolar I disorder compare on many of the dimensions studied within this review. It is worth noting that although the criteria for bipolar I disorder do not require an episode of depression, the criteria for bipolar II disorder require at least one episode of depression. Klerman (1987) was one of the first to subdivide bipolar disorder into the subtypes of III through VI, with the subtypes primarily indicating subtypes of mania. For example, bipolar IV was defined as mania or hypomania precipitated by antidepressants and bipolar V as depression with a family history of mania. Akiskal and Pinto (1999) and Angst (1978) and have taken the extra step of defining several subtypes of bipolar disorder, such as mania and mild depression or bipolar I 1/2 (protracted hypomania) and bipolar II 1/2 (cyclothymic temperament and major depression). There is little consensus on which groups should be included in studies. Rather than labeling one strategy as “correct,” we flag this issue as it may influence the ability to compare findings across studies.

Beyond defining diagnostic inclusion criteria, there are other problems likely to plague researchers in this area. Individuals with bipolar and unipolar depression may vary on a range of characteristics as a result of the mania. One would expect manic episodes to be associated with more severe psychosocial impairment, broader use of mood stabilizing medications, and higher risk for suicidality. Doctors may also be more cautious about the use of anti-depressant medications in bipolar disorder, such that anti-depressant medication will be prescribed less frequently and at lower doses for individuals with bipolar disorder compared to unipolar disorder (Goldberg, 2004). Given these systematic differences in unipolar and bipolar treatment and course, well-matched samples may be difficult to find, and even when available, may not provide generalizable results. Nonetheless, it will be important for studies to control for these important illness and treatment parameters statistically.

4.2. Measuring symptom patterns

A fundamental issue involves measurement of episodes and their duration. Especially in case-register studies, data are often limited to the number and duration of hospitalizations, and these indices are assumed to index number and duration of episodes. A variety of factors beyond symptom status influences the decision to hospitalize patients, such as the quality of social support networks or ongoing relationships with mental health care providers. Indeed, Roy-Byrne, Post, Uhde, Porcu, and Davis (1985) found no relationship between number of episodes and number of hospitalizations.

A more precise evaluation might measure episodes, using structured symptom interviews and standardized cut-offs, such as those for remission, recovery, relapse, and recurrence (Frank et al., 1991). Many studies in this field, including our initial publications, have focused on

episodes. These studies are helpful in planning treatment, as they provide information regarding the percentage of individuals who recover or relapse within a given time period. These studies would also seem relevant for understanding processes involved in the generation and maintenance of depressive and manic symptoms, as separate analyses can be conducted to contrast mania versus depression. However, categorizing an episode as manic or depressive may obscure a surprisingly significant degree of symptoms from the opposite pole. For example, previous findings have suggested that 22% of individuals hospitalized for mania display at least 3 accompanying depressive symptoms (Akiskal et al., 1998; McElroy et al., 1992). Polarity change within the same episode is also a common occurrence; even if an episode begins with pure mania, many depressive symptoms can appear before recovery. Categorizing episodes by polarity, then, might obscure relatively common depressive symptoms within a 'manic' episode. Therefore, assessing the *degree* of change in depressive and manic symptoms will be more precise than simply comparing episodes.

4.3. Design issues

At a broad level, studies can be categorized into retrospective, cross-sectional, and prospective studies. With the exception of intervention studies and some recent psychosocial research, most studies are cross-sectional or retrospective. At this stage, the field remains focused on identifying correlates of episodes, which are then hoped to help reveal mechanisms that will guide course.

Although the problems with retrospective and cross-sectional designs are well established with other psychopathologies (cf. Coyne, 2000), these problems are magnified for the study of depression and mania within bipolar disorder.

Cross-sectional studies will suffer from a logical issue in deciphering the contributions of vulnerability to mania and depression. That is, vulnerability factors for both mania and depression are presumed to be fairly constant. Hence, for a person with a history of mania, vulnerability factors that contribute to mania are likely to remain present, even during an episode of depression. Given this, a key question becomes which variables predict the course of mania versus depression.

Other issues are likely to handicap the interpretation of retrospective studies. Depressive episodes tend to last much longer than manic episodes (APA, 1994). Given this, retrospective studies of triggers of episode onset require recall of more extended time periods for depression than for mania. Although there is evidence that indicates severe life events can be recalled for 1 year, (Brown & Harris, 1982), small shifts in routines and minor life events are forgotten quickly. Given these problems in retrospective studies, prospective designs can provide a needed alternative for the investigation of mood episode triggers.

With these methodological issues in mind, we turn towards the empirical literature. To evaluate the degree of similarity between bipolar and unipolar depression, we consider three broad literatures: the biological correlates, clinical phenomenology, and psychosocial variables associated with depression. We begin with a discussion of clinical phenomenology, with separate consideration of the course of disorder and symptomatology.

5. Biological vulnerability

One possible difference between bipolar and unipolar depression is genetic predisposition. Bipolar depression is often thought of as more "genetic" due to the well-established genetic vulnerability for the disorder as a whole. Some of the most convincing evidence for differences in genetic vulnerability comes from twin studies, in which the average concordance rate for bipolar I disorder in MZ twins is 33% to 80% and for DZ twins 30% to 80%, yielding heritability

rates of 30% to 80% (National Institute of Mental Health, 1998). Because DSM-IV defines bipolar disorder strictly on the basis of one lifetime episode of mania, these studies measure the transmission of mania instead of depression. Of those MZ twins concordant for affective disorders, the concordance rate for mania has been found to be 80% (Akiskal, 1983). Nevertheless, sweeping statements about bipolar being a more "genetic disorder" might be too simplistic a biological model. Kelsoe (2003) proposes a model of unipolar disorder, bipolar disorder, schizophrenia, and their spectrum disorders as being overlapping phenotypes. In this model, some genetic vulnerabilities are shared and others are disorder-specific. In other words, some genes might lead to the development of bipolar disorder, whereas others might lead to either bipolar disorder *or* unipolar disorder, depending on environmental influences.

Unfortunately, these studies do not distinguish between bipolar disorder with and without depression. To date, only one twin study is available that has considered whether the heritability of depression and mania within bipolar disorder are separable. In a recent study of 67 twins, McGuffin et al. (2003) tested models of heritability. They found one model which best fit the data. In this model, genetic vulnerability to mania and depression were correlated, but separable.

5.1. Imaging studies

One way in which genetic vulnerability may manifest itself is in brain pathology associated with mood disorders. Indeed, neuroimaging studies suggest a great deal of overlap in the brain regions involved in unipolar and bipolar depression. Both unipolar and bipolar depression have been associated with reduced blood flow to the cerebral cortex (Videbech, 2000), especially in the prefrontal cortex ventral to the genu of the corpus callosum (Drevets et al., 1997), as well as abnormal phosophorus metabolism in the frontal lobes (Deicken, Fein, & Weiner, 1995) and abnormal metabolism in the amygdala and prefrontal areas connected with the amygdala (Drevets, 1999). In a comparison of PET scans of patients with unipolar and bipolar depression, psychomotor-anhedonia symptoms on the Beck Depression Inventory were associated with higher metabolism in the anterior cingulate and lower metabolism in the right insula, claustrum, basal ganglia, and temporal cortex in both bipolar and unipolar depression. Also, in a review of neuroimaging findings in bipolar disorder, bipolar depression has been associated with decreased activity in the prefrontal cortex compared to controls (Stoll, Renshaw, Yurgelun-Todd, & Cohen, 2000). That is, both unipolar and bipolar depression seem parallel in their links with decreased prefrontal cortex activity, as well as changes in amygdala activity. Only one study provides evidence to suggest any differences (Buchsbaum, Someya, Wu, Tang, & Bunney, 1997).

Functional imaging studies also support strong parallels in the brain activity during processing of emotion-relevant stimuli. Several studies now suggest that when both bipolar and unipolar depression are associated with increased amygdalar activity (Abercrombie et al., 1998; Drevets, 1999; Drevets et al., 1992), particularly when viewing or making judgements about faces with sad or threatening facial expressions (Sheline et al., 2001; Yurgelun-Todd et al., 2000). In sum, the bulk of imaging studies suggests strong parallels between bipolar and unipolar depression.

5.2. Comparison of neurotransmitter activity in bipolar depression and unipolar depression

Several studies have identified distinct biological correlates of mania. These include increased dopamine activity (Kaplan & Sadock, 1998), hyperpolarization in transmembrane potentials (El-Mallakh et al., 1996), and changes in dopamine sub-3 receptor mechanisms (Chiaroni et al., 2000). However, here we focus on the correlates of bipolar depression, as compared to unipolar depression. Although there have been many recent gains in the procedures for studying neurotransmitter regulation, including studies of genetic transporter mechanisms,

amphetamine-challenge studies, and for some neuro-transmitters, spectroscopy, these novel approaches have not been applied to direct comparisons of bipolar and unipolar depression.

Both theory and empirical observations of mood disorders point to the importance of regulatory deficits involving dopamine or norepinephrine (Depue & Zald, 1993; Ebert & Berger, 1998; Gottschalk, Bauer, & Whybrow, 1998; Howland & Thase, 1999; Prange, Wilson, Lynn, Alltop, & Stikeleather, 1974; Spoont, 1992; Winters, Scott, & Beavers, 2000). There are two broad classes of theories of why this dysregulation occurs: (1) theories which posit deficiencies in extracellular regulation of monoamine neurotransmission, such as deficits of serotonergic regulation of dopamine (DA) and norepinephrine (NE) systems and (2) theories which assert that regulatory deficiencies are due to abnormalities in intracellular signal transduction systems within monoamine neurons. Support for both classes of theories have been obtained within unipolar and bipolar depression (Howland & Thase, 1999). The regulatory strength of a neurobiological system can be assessed by determining the ability to maintain control in the face of environmental challenge. Differences in regulatory strength would be reflected in the intensity of responses to system challenges such as life events, drugs, or sleep deprivation. We begin by describing the literature on dopamine and norepinephrine activity in unipolar and bipolar depression, and then describe evidence regarding the regulation of these transmitters.[1]

5.2.1. Dopamine—A focal structure in theories of affective disorders is the DA-secreting neurons of the ventral tegmental area that project to the nucleus accumbens and the cerebral cortex (mesocorticolimbic dopaminergic system; behavioral activation system, (BAS; Depue & Zald, 1993). This system is the key because of its modulatory role in appetive motivation and goal-directed behaviors. Excessively low DA activity is posited to be the hallmark of depression, and considerable evidence supports this perspective in unipolar depression, including recent studies using a D-amphetamine challenge (see Naranjo, Tremblay, & Busto, 2001, for a review).

DA activity appears to be similar in unipolar and bipolar depression. The results of 11 out of 12 studies indicate that bipolar and unipolar depression are associated with comparable CSF levels of the DA metabolite, homovanillic acid (HVA) (Goodwin & Jamison, 1990; Koslow et al., 1983). In addition, anomalies in the dopamine 4 (D4) receptor gene have been associated with both bipolar disorder and unipolar depression (Manki et al., 1996). In sum, there is little evidence that dopamine activity differs between unipolar and bipolar depression. Rather, dopamine activity appears to be disturbed for both unipolar and bipolar depression.

5.2.2. Norepinephrine—It is important to note some issues in the measurement of norepinephrine (NE). For many years, inconsistent findings have emerged in the unipolar literature, with some authors finding lower levels of NE and others finding higher levels of NE associated with depression (Beckmann & Goodwin, 1975; Maas, 1975; Schildkraut, 1974). The NE system has been conceptualized as one part of the hypothalamic-pituitary-adrenocortical stress response system. This system is increasingly recognized as changing over the life course in response to cumulative stress exposure as well as immediate stressful circumstances. Given this, understanding the role of NE requires accounting for medication exposure, chronicity, and stress exposure.

[1]We note, however, that a range of other neurotransmitters have been implicated in the pathogenesis of BP disorder compared to MDD. Yatham et al. (2000) reviewed 80 studies addressing biological differences in unipolar and bipolar depression such as platelet imipramine binding, monoamine oxydase activity, catechol-*o*-methyltransferase activity, plasma levels of GABA, plasma cortisol, and insulin tolerance, among others. They concluded that biological differences between unipolar and bipolar disorder remain elusive, as most findings could not be replicated.

Importantly, when recurrence rates are similar, plasma NE and MHPG levels, urinary MHPG levels, and neuroendocrine abnormalities associated with the hypothalamic-pituitary-adrenocortical axis are remarkably similar in bipolar II and unipolar depression (Altshuler et al., 1995; Dunner, 1993; Schatzberg & Schildkraut, 1995).

5.2.3. Serotonin (5-HT)—As described above, neurobiological theories of affective disorders focus on deficits in the regulation of the catecholamines DA and NE. There is substantial evidence for a critical role of serotonin in the regulation of catecholamines (Depue & Zald, 1993; Prange et al., 1974; Spoont, 1992).

Several investigators (Depue & Zald, 1993; Hestenes, 1992; Howland & Thase, 1999; Prange et al., 1974) have emphasized the importance of deficits in 5-HT regulation of dopamine and/or norepinephrine in the etiology of mood disorders. There is substantial evidence for abnormalities in serotonin (5-HT) functioning in both unipolar and bipolar depressions. Low concentrations of the 5-HT metabolite 5-Hydroxyindoleacetic acid (5-HIAA) have been observed post-mortem in the brainstems of patients who died during unipolar (Traskman, Asberg, Bertilsson, & Sjostrand, 1981), and bipolar depressive episodes (Young et al., 1994). Post-mortem studies of 5-HT uptake sites in the frontal cortex revealed lower concentrations of 5-HT uptake sites in patients with unipolar and bipolar depression (Leake, Fairbairn, McKeith, & Ferrier, 1991). Similarly, CSF levels of the 5-HT metabolite 5-HIAA of patients with both unipolar and bipolar depression were significantly lower than healthy controls matched for sex, age, and body weight (Asberg et al., 1984).

Subsensitivity of the serotonin system is posited to be a correlate of unipolar (Maes & Meltzer, 1995) and bipolar disorder (Depue & Zald, 1993; Howland & Thase, 1999; Prange et al., 1974). Both postmortem and antemortem studies reveal altered 5-HT receptor sensitivity and/or density (see review by Markou, Kosten, & Koob, 1998; Yatham et al., 2000). Dietary depletion of 5-HT can induce symptoms of depression in patients treated with SSRIs (Delgado et al., 1990). Neuroendocrine challenge studies provide evidence for 5-HT subsensitivity in bipolar patients as well. D-fenfluramine induced prolactin release is considered to be a measure of net CNS 5-HT activity (Shiah, Yatham, & Baker, 2000). Blunted prolactin responses to D-fenfluramine challenge have been found in one sample of patients with bipolar disorder (Thakore, O'Keane, & Dinan, 1996). These results provide evidence that net 5-HT activity is low in bipolar disorder and that this low level is due to reduced 5-HT availability in CNS 5-HT synapses. These findings are consistent with the view that reduced 5-HT functioning which appears to be critically involved in unipolar depression is also involved in bipolar depression.

5.3. Intracellular differences between unipolar disorder and bipolar disorder

Virtually all antidepressant medications and mood stabilizers affect second messenger systems, and mood stabilizers alter the activity of all three intracellular second messenger systems (Ackenheil, 2001). Second messenger systems are involved in many cellular processes, including the release, synthesis, and degradation of neurotransmitters so abnormalities in these intracellular systems may underlie regulatory deficits in monoamine systems. NE, 5-HT, and DA exert their effects via postsynaptic receptors, which are coupled to guanine nucleotide-binding proteins (G-proteins).

Research provides evidence for differences in the intracellular signal transduction system in bipolar disorder compared to unipolar depression (Ackenheil, 2001; Suzuki, Kusumi, Sasaki, & Koyama, 2001). G-protein functioning is most commonly studied on lymphocytes and platelets of individuals with bipolar disorder. Increased activity of G-proteins connected to the production of cyclic AMP has been documented in individuals with bipolar disorder relative to individuals with unipolar disorder or controls (Manji et al., 1995; Mathews, Li, Young, Kisk, & Warsh, 1997; Mitchell, Manji, & Chen, 1997; Perez et al., 1995; Schreiber, Avissar, Danon,

& Belmarker, 1991; Young et al., 1994). Enhanced protein kinase C (PKC) activities in platelet or central nervous system also have been observed in some (Friedman, Wang, Levinson, Connel, & Singh, 1993; Wang, Markowitz, Levinson, Undie, & Friedman, 1999), but not all studies (Pandey et al., 2002). Increased intracellular calcium concentration and mobilization has also been documented (Emamghoreishi et al., 1997; Okamoto, Kagaya, Shinno, Motohashi, & Yamawaki, 1994;). Similarly, observed serotonin-induced increases in platelet intracellular calcium in bipolar disorder relative to unipolar disorder has been interpreted to reflect enhanced post-receptor mechanisms in bipolar disorder (Suzuki et al., 2001). In sum, many, but not all, studies have found that people with a history of mania evidence hyperfunctionality within intracellular signal transduction systems, leading to poor regulatory strength overall.

Studies on intracellular systems, however, defined samples on the basis of a lifetime episode of mania, and have not noted any deficits that were specific to depressive episodes within bipolar disorder. Given this, it seems reasonable to assume that the highly sensitized intracellular signal transduction systems in bipolar disorder is linked to the presence of mania rather than a reflection of bipolar depression.

5.4. Regulatory challenge research

One way to assess regulatory strength in patients with affective disorders is to provide a challenge to the underlying neurobiological systems; low regulatory strength would be reflected in a larger response to challenge. Possible challenges include drug treatment, sleep deprivation, and psychosocial stressors. Perhaps the cleanest available evidence comes from sleep deprivation studies. Sleep deprivation elevates mood and leads to a temporary remission of symptoms in about 60% of patients with unipolar depression (e.g., Albert, Merz, Schubert, & Ebert, 1998; Wu & Bunney, 1991); these individuals are referred to as *SD responders*. Both preclinical and clinical studies suggest that dopamine activity increases in response to sleep deprivation. That is, nimal studies provide evidence for increased dopamine release and behavioral sensitization to dopamine agonists following sleep deprivation (Demontis, Fadda, Devoto, Martellotta, & Fratta, 1990; Gessa, Pani, Serra, & Fratta, 1995; Nunes, Tufik, & Nobrega, 1994). Single photon emission computed tomography studies in unipolar depressed patients reveal a greater dopamine D_2 receptor occupancy in SD responders relative to non-responders; this finding also suggests an enhanced dopamine release in SD responders (Ebert, Feistel, Barocks, Kaschka, & Pirner, 1994). Also, plasma levels of prolactin, which is inhibited by dopamine, have been observed to decrease after total sleep deprivation in SD responders relative to non-responders (Baumgartner, Riemann, & Berger, 1990; Kasper et al., 1988). Taken together, these studies suggest that sleep deprivation is a challenge to the regulation of functional dopamine activity and changes in dopamine activity underlie, at least in part, the elevation in mood that is observed in SD responders.

To the extent that sleep deprivation provides a challenge to the dopamine system, such studies may provide insight into regulatory strength in unipolar versus bipolar depression. Barbini et al. (1998) found that repeated sleep deprivation over a 7-night period produced greater abatement in depressive symptoms among individuals with bipolar disorder compared to those with unipolar disorder. This finding supports the view that regulatory strength is weaker in bipolar disorder than in unipolar depression.

6. Summary of biological facets

Genetic evidence suggests that one can disentangle the biological vulnerability to mania from that of depression. Comparisons of bipolar and unipolar depression are not common, but nonetheless, some data is available. Functional imaging studies suggest remarkable parallels in that both bipolar and unipolar depression are characterized by increased activation of the amygdala and other limbic regions when individuals are exposed to sad stimuli (Yurgelun-

Todd et al., 2000). At a neurotransmitter level, bipolar and unipolar depressive episodes are characterized by similar levels of dopamine and serotonin. When matched for number of recurrences, bipolar II depressive episodes are associated with comparable levels of norepinephrine to unipolar depressive episodes. Despite the many parallels, one set of striking differences emerges. Studies of both intracellular mechanisms and sleep deprivation suggest that people with a lifetime history of mania may have deficits in the ability to regulate neurotransmitters in the face of a challenge. Such regulatory deficits would be expected to be manifested in more rapid course changes, as well as increased vulnerability to environmental challenges. We turn towards a review of course parameters and psychosocial triggers next.

7. Course of disorder

In this section, we examine different course parameters, such as age of onset, episode frequency, duration, and severity. For the current questions, there is a need to examine the course of depression within bipolar disorder as compared to unipolar disorder. We consider the relatively few studies that provide polarity-specific information within bipolar disorder.

7.1. Studies of bipolar depression and unipolar depression

In one large-scale, case-register study including data from 38000 participants internationally, the age of onset for bipolar disorder was 6 years younger than for that of unipolar depression (Weissman et al., 1996). Nevertheless, the onset of depression was not examined separately.

Evidence from a retrospective study suggests that bipolar disorder is characterized by more depressive episodes than unipolar disorder is (Roy-Byrne et al., 1985). Several studies suggest that bipolar depressions are shorter and quicker to onset than unipolar depression (Furukawa et al., 2000; Mitchell et al., 1992; Roy-Byrne et al., 1985). Nevertheless, findings are not consistent in this area, with two large-scale studies finding no difference between unipolar and bipolar depression in episode length (Coryell, Andreason, Endicott, & Keller, 1987; Kessing & Mortensen, 1999).

Cross-study differences in results might be due to changes in gender or episode length over time. Parallel with the gender ratio in unipolar depression, bipolar depression is more common among women than men (Leibenluft, 2000). One retrospective study reported that the length of bipolar depressive episodes shortened over a 15-year period (Berghöfer, Kossmann, & Müller-Oerlinghausen, 1996).

Beyond the temporal characteristics of course, other studies have focused on severity. Here, we focus on research that has measured severity using symptom interviews, as hospitalization rates have been shown to be influenced by a broad range of parameters that may or may not reflect the severity of depressive symptoms. Ahearn and Carroll (1996) reported no significant differences in episode severity as measured using symptom interviews between bipolar and unipolar depression, with the exception of bipolar depressed participants exhibiting greater short-term mood variability. In addition, a comparison of currently depressed unipolar and bipolar patients revealed no differences in terms of symptom severity or social impairment (Dorz, Borgherini, Conforti, Scarso, & Magni, 2003).

In sum, compared to unipolar depression, bipolar depression appears associated with a younger age of onset, more frequent episodes, and greater short-term mood variability. No consistent differences have been found between episode length, although some studies suggest a shorter episode length of bipolar depressions compared to unipolar depressions. Depression severity appears comparable between bipolar and unipolar disorders.

8. Symptomatology

Beyond the course of disorder, another comparison includes an assessment of the specific depression symptoms in bipolar and unipolar depression. Early studies indicated that unipolar depression was characterized by more typical vegetative and psychomotor symptoms than bipolar disorder, such as greater weight loss (Abrams & Taylor, 1980) and initial insomnia (Brockington, Altman, Hillier, Meltzer, & Nand, 1982). In contrast, bipolar depression was associated with more atypical symptoms, such as hypersomnia (for a review, see Depue & Monroe, 1978). Unipolar depression also was thought to be characterized by more affective symptoms, such as anxiety, anger, and agitation, than bipolar depression (Katz, Robins, Croughan, Secunda, & Swann, 1982).

Nevertheless, more recent findings have been much more inconsistent. Indeed, two literature reviews have examined differences between bipolar and unipolar depression for specific symptoms. These reviews have noted no consistent differences across groups for sleep (Goodwin & Jamison, 1990) or suicidality (Lester, 1993). Despite these slim results, some might argue that the failure to identify group differences is due to methodological issues. To examine the role of control over confounding variables, we sorted articles by key methodological features. As shown in Table 1, we classified studies from least to greatest methodological control. The most stringent studies were those that involve control over medication (i.e., a drug washout period or comparison of medications used by participants) and some control over confounding demographic variables. The next group of studies includes those that either matched participants on key demographic variables (i.e., age and sex) or depression subtype (i.e., melancholic or endogenous), without control over medications. A less stringent group of studies ensured that no significant differences were found between groups on demographic variables or course of illness (i.e., age of onset), but often did not test equivalence of medication approaches. The least stringent studies did not control for or assess potential group differences on demographic, symptom, or treatment characteristics.

Across all studies, there are only 4 symptoms that appear to consistently differentiate groups: people with unipolar depression have been characterized by more anxiety, activity, and somatization, and by less anhedonia compared to people with bipolar depression. The strongest methodology, however, is to include a drug wash-out period before symptom assessment, to ensure that symptoms are not merely the manifestation of the differing drug treatments used for bipolar and unipolar disorders. Although few studies are available within those that control over medications, group differences in anxiety, activity, and somatization consistently have been found in drug wash-out studies (Beigel & Murphy, 1971; Katz et al., 1982; Kuhs & Reschke, 1992; Kupfer et al., 1974). Although results across methodologies were not consistent, appetite loss (Gurpegui, Casanova, & Cervera, 1985) and agitation (Beigel & Murphy, 1971; Katz et al., 1982) have each been found to be more prevalent in unipolar depression than bipolar depression within three studies that included a drug washout period.

Nevertheless, results for other symptoms are not as clear. Findings for sleep (Brockington et al., 1982; Giles, Rush, & Roffwarg, 1986; Kuhs & Reschke, 1992; Mitchell et al., 2001), anger (Beigel & Murphy, 1971; Brockington et al., 1982; Gurpegui et al., 1985), psychomotor retardation (Mitchell et al., 1992, 2001; Parker, Roy, Wilhelm, Mitchell, & Hadzi-Pavlovi, 2000), psychosis (Beigel & Murphy, 1971; Black & Nasrallah, 1989; Breslau & Meltzer, 1998; Brockington et al., 1982; Guze, Woodruff, & Clayton, 1975; Mitchell et al., 2001; Parker et al., 2000), melancholia (Coryell et al., 1989; Endicott et al., 1985; Parker et al., 2000), and mood reactivity (Brockington et al., 1982; Mitchell et al., 2001; Parker et al., 2000) were not consistent across studies.

Although conclusions are limited by problems in measurement instruments, sample definition, and statistical approaches, many differences between unipolar and bipolar depression are not consistent. Most studies have found no differences between unipolar and bipolar depression on characteristics traditionally ascribed to bipolar depression, such as atypical vegetative symptoms. Differences in symptom severity are equally unclear. Indeed, the strong inconsistencies suggest one possible interpretation of this literature. Most studies perform a large number of separate statistical tests, comparing each individual symptom between unipolar and bipolar depression. Typically, this is done without correcting alpha levels. The resultant high risk of type I errors could contribute to inflated reports of symptom differences. Despite these limitations to the literature, some differences between unipolar and bipolar depression appear to emerge. Specifically, unipolar depression is associated with more prevalent anxious mood states, activity, and somatization, suggesting a pattern of greater anxiety.

9. Psychosocial antecedents to depression

Another area of research that could indicate differences between bipolar and unipolar depression is in their reactivity to the social environment. For many years, the assumption was that unipolar depression is a reaction to life stressors, whereas bipolar depression is an unfolding of endogenous, biological processes. However, a recently growing field has documented the influence of psychosocial antecedents on the course of bipolar disorder. Nevertheless, most studies have not studied mania and depression separately when examining their impact. Two large areas of psychosocial research in bipolar disorder have focused on the role of expressed emotion and negative life events, both of which are associated with an increased risk of relapse (Ellicott, 1989; Johnson & Roberts, 1995; Miklowitz, Goldstein, Nuechterlein, & Snyder, 1988; Priebe, Wildgrube, & Muller-Oerlinghausen, 1989). In addition to social variables, such as family environment and life stressors, psychological variables, such as personality and cognition, are correlated with symptom severity in bipolar disorder (cf., Hammen, Ellicott, & Gitlin, 1992; Hammen, Ellicott, Gitlin, & Jamison, 1989). Given that psychosocial variables seem to play a key role in the course of bipolar disorder, how do the psychosocial triggers of bipolar and unipolar depression overlap?

The role of psychosocial variables in the course of unipolar depression is supported by a vast literature. Some of the variables associated with the course of unipolar depression include expressed emotion, negative life events, and marital conflict (Brown & Harris, 1978, 1989; Butzlaff & Hooley, 1998; Davila & Bradbury, 1998). In addition, extensive research has linked personality traits and cognitive styles to the course of unipolar disorder (Clark, Watson, & Mineka, 1994; Coyne & Whiffen, 1995; Klein, Durbin, Shankman, & Santiago, 2002). The next sections compare the specific psychosocial findings in unipolar and bipolar depression.

9.1. Socio-environmental variables

Many studies have focused on life events and episodes in bipolar disorder, but few of these have been prospective, and few have differentiated independent events, defined as those that were not caused by symptoms or pathology (see Johnson & Roberts, 1995, for a review). Further, many studies have looked exclusively at mania, thus not shedding light on depression in bipolar disorder. In regard to bipolar depression, three studies found that approximately 0–8% of participants had a severe, independent life event before euthymic periods, whereas approximately 11–28% of participants experienced such an event before a depressive episode (Hunt, Bruce-Jones, & Silverstone, 1992; Malkoff-Schwartz et al., 1998; McPherson, Herbison, & Romans, 1993). Hence, rates of life events do appear elevated before the onset of bipolar depressive episodes. A more sensitive and controlled design, though, involves assessing whether symptoms change within the same individuals after a life event (see Norman & Malla, 1993, for a more detailed discussion). An important advantage of such within-subject designs is that it allows for control over differences in individual vulnerability to episodes. Prospective

designs are also advantageous in that with typically shorter time intervals for assessment, they are less likely to be associated with errors in memory than are retrospective designs. In prospective studies, negative life events have been found to predict depressive symptoms (Johnson et al., 1999), as well as episode onset (Ellicott, Hammen, Gitlin, Brown, & Jamison, 1990; Malkoff-Schwartz et al., 1998). Hence, in both cross-sectional and prospective analyses, severe negative life events appear related to bipolar depression.

Do life events exert the same magnitude of effect for bipolar and unipolar depression? Less is known. Participants with bipolar disorder and unipolar disorder have been found to report severe, independent life events prior to a depressive episode. Nevertheless, differences in methodologies make comparisons across studies difficult. Seminal work on depression and life events suggests that 50% of people with unipolar depression experienced a severe independent life event in the period preceeding the episode (Brown & Harris, 1978). In a sample with bipolar depression, Malkoff-Schwartz et al. (1998) found that in participants with bipolar disorder, severe life events were more frequent prior to the onset of a depressive episode than during the control period. Not surprisingly, people with bipolar disorder experience more stressful events across the lifespan than people with unipolar disorder do (Bidzinska, 1984; Hall, Dunner, Zeller, & Fieve, 1977; Perris, 1984). A more central question is whether bipolar depression is equally likely to be triggered by life events as unipolar depression. In the two studies which examined this question, life events appeared to be equally common triggers of depression for unipolar and bipolar depression (Hirschfeld & Cross, 1982; Perris, 1966). In a novel method of examining life stress, Isometsa, Heikinen, Henriksson, Aro, and Lonnquist (1995) report that next of kin interviews following completed suicides suggest that bipolar and unipolar persons who committed suicide appeared to have experienced comparable levels of stress prior to the suicide (Isometsa et al., 1995). Low social support is associated with more frequent episodes of depression in both unipolar and bipolar depression. In bipolar depression, social support showed a medium effect size in buffering life events (r^2=0.07; Johnson et al., 1999). Similarly, in unipolar disorder, after controlling for age and chronicity, social support was significantly more associated with recovery from a depressive episode (Veiel, Kuehner, Brill, & Ihle, 1992).

In sum, negative life events and social support appear to be important factors in bipolar depression, as well as unipolar depression. To date, no study has directly examined whether individuals with a history of bipolar and unipolar depression are equally sensitive to relapse following a life event. Such a design would be another way of considering whether bipolar and unipolar disorders are equivalent or not in regulatory strength following a challenge. One might expect an individual with lower regulatory strength in their underlying biology might be more vulnerable after a life event. Prospective, within-subject designs are needed to assess these questions.

9.2. Personality traits

The role of personality in bipolar disorder has been a topic of interest since the early days of psychodynamic theory. An intriguing question is whether personality traits predict the course of illness in bipolar depression. Two studies found that over time, neuroticism is associated with increasing depressive symptoms, but is unrelated to manic symptoms (Heerlein, Richter, Gonzalez, & Santander, 1998; Lozano & Johnson, 2001). Such findings are consistent with the unipolar depression literature, which has consistently found neuroticism to be the personality variable most associated with unipolar depression (Gunderson, Triebwasser, Phillips, & Sullivan, 1999). In sum, neuroticism appears to be associated with increases in depressive symptoms, regardless of whether the depression is within unipolar or bipolar disorder.

9.3. Cognitive styles

An early study of rapid cycling bipolar disorder found a correlation between the affective valence of autobiographical memories and the polarity of episode (Weingartner, Cohen, Murphy, Martello, & Gert, 1981). A similar effect was elicited in response to the induction of positive and negative moods in non-clinical samples, with mood-congruent memories found to be more easily accessible (Teasdale & Fogarty, 1979; Teasdale, Taylor, & Fogarty, 1980). These studies launched a series of studies examining mood-congruent and mood-dependent memory (Blaney, 1986; Bower, 1981). Further research replicated the findings that mood episodes influence the valence of autobiographical recall in bipolar disorder (Eich, Macaulay, & Lam, 1997). In recent years, there has been a return to the area, fueled by cognitive models (Leahy, 1999) and therapy manuals for bipolar disorder (Basco & Rush, 1996; Newman, Leahy, Beck, Reilly-Harrington, & Gyulai, 2002; Scott, 1995). In the following sections, we review the current research on cognitive styles, with a focus on those styles associated with depression, rather than mania. We divide studies into those that focus on cognitive styles during depression, during remission, and cognitive styles that predict depression.

9.4. Cognition during depressive episodes

When cognition is assessed during a depressive episode, bipolar disorder, comparable to unipolar disorder, is associated with a negative cognitive style, as measured by the Attributional Style Questionnaire (Seligman et al., 1988), the Automatic Thoughts Questionnaire (Hill, Oei, & Hill, 1989; Hollon, Kendall, & Lumry, 1986), and the Dysfunctional Attitudes Scale (Hollon et al., 1986; Scott & Pope, 2003). Similar to patients with unipolar depression, patients with bipolar depression exhibit low self-esteem (Ashworth, Blackburn, & McPherson, 1982; Roy, 1991; Scott & Pope, 2003). In addition, attributions of failure are correlated with depression severity in both unipolar and bipolar depression (Seligman et al., 1988). People with current episodes of unipolar and those with current bipolar depression appear to be comparable on measures of negative attributions about events and interference from negative words on the Stroop color naming task (Lyon, Startup, & Bentall, 1999).

9.5. Cognition during remission

Like unipolar depression, the negative cognitions diminish during euthymic periods for people with bipolar depression (see Johnson & Kizer, 2002 for a review). Few studies have directly compared remitted bipolar and unipolar groups during remission, though. In one study, participants with remitted bipolar disorder reported higher self-esteem than remitted participants with unipolar depression (Ashworth, Blackburn, & McPherson, 1985). These findings would suggest slim evidence for negative cognitions as a stable facet of bipolar disorder. However, there are a set of methodological issues that may have precluded the ability to accurately assess maladaptive cognitive styles during remission.

First, the psychodynamic lore of the “manic defense” (cf. Klein, 1994) continues to receive attention and suggests some important assessment issues. That is, many cognitive theorists have postulated that assessment is complicated by defensiveness among individuals with bipolar disorder. Although people with bipolar disorder do not obtain elevated scores on standard measures of defensiveness (Donnelly & Murphy, 1973; Donnelly, Murphy, & Goodwin, 1976), some have argued that measures of attributional style, or how an individual would interpret negative life events, may invoke less defensiveness (Lyon et al., 1999). In one set of findings consistent with this idea, people with remitted bipolar disorder reported higher self-esteem on overt measures, but when asked to describe their attributions for hypothetical negative events, their pattern of answers was comparable to participants with a history of unipolar depression (Winters & Neale, 1985). Nonetheless, other studies have found that remitted bipolar depression, compared to remitted unipolar depression, is associated with less stable attributions about negative events (Tracy, Bauwens, Martin, Pardoen, & Mendlowicz,

1992). Hence, although findings are not entirely consistent, it may be important to use measures that assess negative cognitions in a less overt manner.

Second, few studies have used procedures to activate schemas, such as mood induction protocols (Williams, Watts, MacLeod, & Mathews, 1997). Teasdale and Barnard (1994) have suggested that depression may be maintained by mood-state dependent cognitions in vulnerable populations. Studying cognition during sad moods appears to help identify information-processing biases among people with anxiety and depression (cf. Ingram, Bernet, & McLaughlin, 1994). In one study that used a self-focus task before measuring cognition, participants with remitted bipolar disorder demonstrated lower latency to both positively and negatively valenced words and greater DAS scores than controls (Lex, 2000). This study suggests that schema activation procedures might help identify both positive and negative information-processing biases among people with remitted bipolar disorder.

Finally, not all individuals with a history of mania will experience depression. One study supports the importance of examining history of depression. Among participants with a history of hypomania, those with no history of depression did not differ from normal controls in terms of negative cognitive style. In contrast, those with a history of depression did demonstrate negative cognitive styles (Alloy, Reilly-Harrington, Fresco, Whitehouse, & Zechmeister, 1999). Hence, selecting samples with a history of depression might help increase the consistency of findings for negative cognitive styles.

9.6. Summary of findings regarding cognitive styles during remission

Some methodological issues must be attended to in the study of cognitive vulnerabilities in bipolar disorder, particularly variability in depression history. In studies that have failed to account for these issues, the evidence for negative cognitive styles among persons with remitted bipolar disorder is quite limited. However, when researchers have focused on just those persons with a history of depression or have used schema activation procedures, findings have suggested that bipolar disorder in remission is characterized by a depressive cognitive style.

9.7. Cognitive styles as predictors of depression

Evidence suggests that at least some individuals with bipolar disorder have negative cognitive styles. Although cognitive styles do not appear to be universal among people with a history of unipolar depression, their presence is predictive of relapse (Segal, Gemar, & Williams, 1999). Several studies suggest a similar pattern in bipolar disorder. One such study found that among college students with a lifetime history of either unipolar disorder or a bipolar spectrum disorder, self-referential negative encoding in interaction with negative life events predicted 11.7% of the variance in depressive symptoms (combined across bipolar II and unipolar participants) one month later (Reilly-Harrington, Alloy, Fresco, & Whitehouse, 1999). A second study found that Negative Automatic Thoughts, Dysfunctional Attitudes, and less Positive Automatic thoughts predicted increases in depression over time in a bipolar I sample (Johnson & Fingerhut, 2004). Finally, low self-esteem has been found to predict increases in depression over time (Johnson, Meyer et al., 2000). It appears, then, that negative cognitive styles predict both unipolar and bipolar depression. Nevertheless, none of these studies compared the effects of cognitive variables for unipolar and bipolar depression. Hence, more research comparing the relative effects of cognition on unipolar and bipolar depression is needed.

10. Psychosocial treatment

Due to the cognitive and personality similarities between unipolar and bipolar depression, it would seem that psychosocial treatments for unipolar depression should be equally effective

for bipolar depression. Demonstrating equal efficacy becomes more important in light of the fact that mood stabilizers used to treat mania are not as effective for depression (Hlastala et al., 1997). Family and interpersonal psychotherapies, two well-studied interventions for bipolar disorder, have been found to alleviate depression, but not mania (Frank et al., 2000; Miklowitz et al., 2000). Similar treatments have been found to be effective for unipolar depression, suggesting that bipolar depression might be responsive to psychosocial interventions used for unipolar depression (DeRubeis & Crits-Christoph, 1998; Frank et al., 2000; Kolko, Brent, Baugher, Bridge, & Birmaher, 2000).

11. Summary and conclusions

Our review suggests that the literature that directly compares unipolar and bipolar depression is lamentably sparse, and in some areas, plagued with inconsistent results. As such, conclusions must be taken with some degree of caution. Fundamentally, we ask the question of whether bipolar and unipolar depression are discrete diagnostic categories, and whether these categories should be differentiated. A natural technology for exploring these questions would be the MAXCOV procedure postulated by Meehl and colleagues (Meehl, 1973; Meehl & Yonce, 1996) to determine taxonicity, or whether the latent concept is composed of a single or multiple groups (Meehl, 2004). We know of no investigation to date that has explored differentiation between bipolar and unipolar depression in this manner. Nevertheless, some commonalities appear to emerge between unipolar and bipolar depression. Arguing for commonalities potentially involves trying to “prove the null hypothesis,” a fatally flawed research approach. For example, much of the research on genetic vulnerabilities and neurotransmitter activity suggests no differences between unipolar and bipolar depression. Perhaps more importantly, however, beyond the studies that identify no differences, predictors within both unipolar and bipolar depression are also beginning to accumulate. These predictive studies go much further than trying to “prove the null hypotheses” by demonstrating parallel processes within both groups. For example, psychosocial antecedents such as negative life events, low social support, and maladaptive cognitive styles appear to predict both bipolar and unipolar depression. Given these predictors, it is not surprising that early evidence supports the applicability of psychological treatments developed for unipolar disorder in the treatment of bipolar depression. In sum, bipolar and unipolar depression appear comparably tied to psychosocial predictors and neurotransmitter correlates, pointing to a common etiology that would be amenable to similar psychosocial interventions.

Some suggest that the high comorbidity of depression and mania (cf. Kessler et al., 1997) and the increased risk of depression in relatives of probands with mania (cf. Plomin, DeFries, McClearn, & Rutter, 1997) could imply that manic and depressive episodes are opposite poles of the same disorder, rather than two separate processes. Do these data on co-occurrence of mania and depression within individuals and within families provide a strong rationale for considering these syndromes to be the result of one disease process? Given the strong parallels between unipolar and bipolar depression, a more accurate nosology might be to classify mania and depression as separate disorders that are sometimes comorbid. For example, McGuffin et al. (2003) suggests that the genetic influences for mania and depression are separable, but correlated. The strong genetic and comorbidity overlap between unipolar depression and anxiety may provide an excellent heuristic for contemplating the overlap between mania and depression. There are likely common and unique risk factors for depression and anxiety. Classifying depression and anxiety as separate disorders has benefited the understanding of the separate processes involved in each. If our nomenclature had categorized depression with anxiety as a single disorder, our knowledge about unique risk factors for each would be far less. Perhaps rather than dividing mood disorders into unipolar and bipolar depression, the field would be better served by examining depression, regardless of comorbid mania.

Currently, the most parsimonious conceptualization of bipolar disorder appears to be a model that involves the process of two distinct, yet highly comorbid, syndromes: mania and depression. Sadly, current nomenclature has shaped much of the research so profoundly that there have been relatively few attempts to empirically examine whether this is accurate. Further research should continue to test the extent to which unipolar and bipolar depression are similar, although this is a difficult task. Differences found between unipolar and bipolar depression might not be due to differences in the depressions per se, but rather in differences attributable to concurrent manic symptoms, scarring from previous manic episodes, or manic vulnerability. Despite methodological hurdles, however, distinguishing mania and depression as separate disorder processes would allow researchers to draw from the wealth of unipolar depression literature in designing treatments and etiological models of bipolar depression. The rich literature indicates that unipolar depression is a disorder with varied presentations and etiological influences, perhaps best conceptualized as a diverse set of subtypes. Almost no research has considered comparing subtype issues across unipolar and bipolar depressions. Similarly, despite rich examples in the unipolar literature of how fundamental recurrence is for understanding inheritance and neurobiology (cf. Dunner, 1993), the bipolar literature almost universally fails to consider the role of depression recurrence. We believe that the gaps in considering these fundamental dimensions of depression heterogeneity have been guided by the failure to label lifetime depression as a distinct feature from mania within bipolar disorder.

Despite strong overlap in unipolar and bipolar depression, there are some variables that distinguish unipolar and bipolar depression. There is relatively consistent evidence that unipolar depression is characterized by more anxiety and agitation than bipolar depression is. Aside from this pattern, dysregulation appears to be a risk variable involved in both depression and mania, but more strongly tied to bipolar than unipolar disorder. This thesis emerges from the biological literature on intracellular messenger systems and responses to sleep deprivation, but is congruent with the findings on course parameters. That is, a poorly regulated biological system should be reflected in more rapid changes in symptoms; congruently, bipolar disorder is related to an earlier age of onset, more rapid recurrence, and mood variability than unipolar depression.

Although Hollon (1992) stated that dysregulation is important in understanding unipolar depression, dysregulation might be even more important for understanding the symptoms of bipolar depression. One prediction from this model is that bipolar disorder might be associated with a more exaggerated response to psychosocial stressors than unipolar depression is. Testing this will require more careful longitudinal research.

12. Future directions

The questions asked and the research designs used in this field have long been influenced by the decision to consider bipolar and unipolar depression as unique entities. Researchers often specialize in either unipolar or bipolar disorder, and cross-fertilization between these two areas has been slower than ideal, despite a few notable exceptions. We believe it is time to re-open the question of whether the depression within these two conditions is truly unique. Given how well research paradigms from the unipolar depression field have applied to bipolar depression, more careful research is needed to assess whether bipolar and unipolar depression are actually distinct. Based on the weight of currently available evidence, we agree with a recent proposal based on the biological literature (Joffe et al., 1999). That is, it is time to consider reorganizing nomenclature to assess mania with and without depression. We argue that future research should focus on the syndromes separately through the comparison of unipolar depression and unipolar mania. Rather than being merely an academic exercise, distinguishing mania and depression as separate syndromes is vital to improving research design. By studying mania

and depression as separate disorders, rather than as bipolar and unipolar disorders, the field can tease apart processes that are similar and unique between these phenomena that with the current nomenclature is not probable.

References

Abercrombie HC, Schaefer SM, Larson CL, Oakes TR, Lindgren KA, Holden JE, et al. Metabolic rate in the right amygdala predicts negative affect in depressed patients. NeuroReport: An International Journal for the Rapid Communication of Research in Neuroscience 1998;9:3301–3307.

Abrams R, Taylor MA. A comparison of unipolar and bipolar affective illness. American Journal of Psychiatry 1980;137:1084–1087. [PubMed: 6107049]

Ackenheil M. Neurotransmitters and signal transduction processes in bipolar affective disorders: A synopsis. Journal of Affective Disorders 2001;62:101–111. [PubMed: 11172877]

Ahearn EP, Carroll BJ. Short-term variability of mood ratings in unipolar and bipolar depressed patients. Journal of Affective Disorders 1996;36:107–115. [PubMed: 8821313]

Akiskal HS. Bipolar outcome in the course of depressive illness: Phenomenologic, familial, and pharmacologic predictors. Journal of Affective Disorders 1983;5:115–128. [PubMed: 6222091]

Akiskal HS, Hantouche EG, Bourgeois ML, Azorin JM, Sechter D, Allilaire JF, et al. Gender, temperament, and the clinical picture in dysphoric mixed mania: Findings from a French national study (EPIMAN). Journal of Affective Disorders 1998;50(2–3):175–186. [PubMed: 9858077]

Akiskal HS, Pinto O. The evolving bipolar spectrum. Prototypes I, II, III, and IV. Psychiatric Clinics of North America 1999;22(3):517–534. [PubMed: 10550853]

Albert R, Merz A, Scuert J, Ebert D. Sleep deprivation and subsequent sleep phase advance stabilizes the positive effect of sleep deprivation in depressive episodes. Nervenarzt 1998;69(1):66–69. [PubMed: 9522335]

Alloy LB, Reilly-Harrington N, Fresco DM, Whitehouse WG, Zechmeister JS. Cognitive styles and life events in subsyndromal unipolar and bipolar disorders: Stability and prospective prediction of depressive and hypomanic mood swings. Journal of Cognitive Psychotherapy 1999;13(1):21–40.

Altshuler LL, Curran JG, Hauser P, Mintz J, Denicoff K, Post R. T_2hyperintensities in bipolar disorder: Magnetic resonance imaging comparison and literature meta-analysis. American Journal of Psychiatry 1995;152:1139–1144. [PubMed: 7625460]

American Psychiatric Association. Diagnostic and statistical manual of mental disorder. 2. Washington, DC: Author; 1968.

American Psychiatric Association. Diagnostic and statistical manual of mental disorder. 4. Washington, DC: Author; 1994.

Angst J. The course of affective disorders: II. Typology of bipolar manic–depressive illness. Archiv fuer Psychiatrie und Nervenkrankheiten 1978;226(1):65–73.

Angst J, Marneros A. Bipolarity from ancient to modern times: Conception, birth, and rebirth. Journal of Affective Disorders 2001;67(1–3):3–19. [PubMed: 11869749]

Asberg M, Bertillsson L, Martensson B, Scalia-Tompa GP, Thoren P, Trakman-Bendz L. CSF monoamine metabolites in melancholia. Acta Psychiatrica Scandinavica 1984;69:201–219. [PubMed: 6201041]

Ashworth CM, Blackburn IM, McPherson FM. The performance of depressed and manic patients on some repertory grid measures: A cross-sectional study. British Journal of Medical Psychology 1982;55:247–255. [PubMed: 6982065]

Ashworth CM, Blackburn IM, McPherson FM. The performance of depressed and manic patients on some repertory grid measures: A longitudinal study. British Journal of Medical Psychology 1985;58:337–342. [PubMed: 4092016]

Barbini B, Colombo C, Benedetti F, Campori E, Bellodi L, Smeraldi E. The unipolar–bipolar dichotomy and the response to sleep deprivation. Psychiatry Research 1998;79:43–50. [PubMed: 9676825]

Basco, MR.; Rush, AJ. Cognitive–behavioral therapy for bipolar disorder. New York, NY: The Guilford Press; 1996.

Bauer MS, Whybrow PC, Gyulai L, Gonnel J, Yeh HS. Testing definitions of dysphoric mania and hypomania: Prevalence, clinical characteristics and inter-episode stability. Journal of Affective Disorders 1994;32:201–211. [PubMed: 7852662]

Baumgartner A, Riemann D, Berger M. Neuroendocrinological investigations during sleep deprivation in depression: II. Longitudinal measurement of thyrotropin, TH, cortisol, prolactin, GH, and LH during sleep and sleep deprivation. Biological Psychiatry 1990;28:569–587. [PubMed: 2171684]

Beckmann H, Goodwin FK. Antidepressant response to tricyclics and urinary MHPG in unipolar patients: Clinical response to impipramine or amitriptyline. Archives of General Psychiatry 1975;32:17–21. [PubMed: 1089399]

Beigel A, Murphy DL. Unipolar and bipolar affective illness: Differences in clinical characteristics accompanying depression. Archives of General Psychiatry 1971;24:215–230. [PubMed: 5100617]

Berghöfer A, Kossmann B, Müller-Oerlinghausen B. Course of illness and pattern of recurrences in patients with affective disorders during long-term lithium prophylaxis: A retrospective analysis over 15 years. Acta Psychiatrica Scandinavica 1996;93:349–354. [PubMed: 8792904]

Bidzinska EJ. Stress factors in affective diseases. British Journal of Psychiatry 1984;144:161–166. [PubMed: 6704602]

Black DW, Nasrallah A. Hallucinations and delusions in 1715 patients with unipolar and bipolar affective disorders. Psychopathology 1989;22(1):28–34. [PubMed: 2657835]

Blaney PH. Affect and memory: A review. Psychological Bulletin 1986;99(2):229–246. [PubMed: 3515383]

Borkowska A, Rybakowski J. Neuropsychological frontal lobe test indicate that bipolar depressed patients are more impaired than unipolar. Bipolar Disorders 2001;3:88–94. [PubMed: 11333068]

Bower GH. Mood and memory. American Psychologist 1981;36:129–148. [PubMed: 7224324]

Breslau N, Meltzer HY. Validity of subtyping psychotic depression: Examination of phenomenology and demographic characteristics. American Journal of Psychiatry 1998;145:35–40. [PubMed: 3337290]

Brockington IF, Altman E, Hillier V, Meltzer HY, Nand S. The clinical picture of bipolar affective disorder in its depressive phase: A report from London and Chicago. British Journal of Psychiatry 1982;141:558–562. [PubMed: 7159802]

Brown, GW.; Harris, TO. Social origins of depression: A study of psychiatric disorder in women. New York: the Free Press; 1978.

Brown GW, Harris TO. Fall-off in the reporting of life events. Social Psychiatry 1982;17:23–28.

Brown, GW.; Harris, TO. Life events and illness. New York, NY: Guilford Press; 1989.

Buchsbaum MS, Someya T, Wu JC, Tang CY, Bunney WE. Neuroimaging bipolar illness with positron emission tomography and magnetic resonance imaging. Psychiatric Annals 1997;27:489–495.

Butzlaff RL, Hooley JM. Expressed emotion and psychiatric relapse: A meta-analysis. Archives of General Psychiatry 1998;55:547–552. [PubMed: 9633674]

Chiaroni P, Azorin JM, Dassa D, Henry JM, Giudicelli S, Malthiery Y, et al. Possible involvement of the dopamine D3 receptor locus in subtypes of bipolar affective disorder. Psychiatric Genetics 2000;10:43–49. [PubMed: 10909128]

Clark L, Watson D, Mineka S. Temperament, personality, and the mood and anxiety disorders. Journal of Abnormal Psychology 1994;103:103–116. [PubMed: 8040472]

Coryell W, Andreasen NC, Endicott J, Keller M. The significance of past mania or hypomania in the course and outcome of major depression. American Journal of Psychiatry 1987;144:309–315. [PubMed: 3826429]

Coryell W, Keller M, Endicott J, Andreasen N, Clayton P, Hirschfeld R. Bipolar II illness: Course and outcome over a five-year period. Psychological Medicine 1989;19:129–141. [PubMed: 2727202]

Coyne, JC. Thinking interactionally about depression: A radical restatement. In: Joiner, T.; Coyne, JC., editors. The interactional nature of depression: Advances in interpersonal approaches. Washington, DC: American Psychological Association; 2000.

Coyne JC, Whiffen VE. Issues in personality as a diathesis for depression: The case of sociotropy-dependency and autonomy—self-criticism. Psychological Bulletin 1995;118:358–378. [PubMed: 7501741]

Davila, J.; Bradbury, TN. Psychopathology and the marital dyad. In: L'Abate, L., editor. Family psychopathology: The relational roots of dysfunctional behavior. New York, NY: The Guilford Press; 1998. p. 127-157.

Deicken RF, Fein G, Weiner MW. Abnormal frontal lobe phosphorous metabolism in bipolar disorder. American Journal of Psychiatry 1995;152:915–918. [PubMed: 7755123]

Delgado PL, Charney DS, Price LH, Aghajanian GK, Landis H, Heninger GR. Serotonin function and the mechanism of antidepressant action: Reversal of antidepressant-induced remission by rapid depletion of plasma tryptophan. Archives of General Psychiatry 1990;47:411–418. [PubMed: 2184795]

Demontis MG, Fadda P, Devoto P, Martellotta MD, Fratta W. SD increases dopamine D_1receptor antagonist binding in the rat limbic system. Neuroscience Letters 1990;117:224–227. [PubMed: 2149748]

Depue RA, Monroe SM. The unipolar–bipolar distinction in the depressive disorders. Psychological Bulletin 1978;85:1001–1029. [PubMed: 704718]

Depue, RA.; Zald, DH. Biological and environmental processes in nonpsychotic psychopathology: A neurobiological perspective. In: Costello, CG., editor. Basic issues in psychopathology. New York: Guilford Press; 1993. p. 127-237.

DeRubeis RJ, Crits-Christoph P. Empirically supported individual and group psychological treatments for adult mental disorders. Journal of Consulting and Clinical Psychology 1998;66:37–52. [PubMed: 9489261]

Donnelly EF, Murphy DL. Social desirability and bipolar affective disorder. Journal of Consulting and Clinical Psychology 1973;41:469. [PubMed: 4803282]

Donnelly EF, Murphy DL, Goodwin FK. Cross-sectional and longitudinal comparisons of bipolar and unipolar depressed groups on the MMPI. Journal of Consulting and Clinical Psychology 1976;44:233–237. [PubMed: 1254756]

Dorz S, Borgherini G, Conforti D, Scarso C, Magni G. Depression in inpatients: Bipolar vs. unipolar. Psychological Reports 2003;92:1031–1039. [PubMed: 12841481]

Drevets, WC. Prefrontal cortical–amygdalar metabolism in major depression. In: McGinty, JF., editor. Advancing from the ventral striatum to the extended amygdala: Implications for neuropsychiatry and drug use: In honor of Lennart Heimer. New York, NY: New York Academy of Sciences; 1999.

Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M, et al. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 1997;386:824–827. [PubMed: 9126739]

Drevets WC, Videen TO, Price JL, Preskorn SH, Carmichael ST, Raichle ME. A functional anatomical study of unipolar depression. Society for Neuroscience 1992;12:3628–3641.

Dunner DL. A review of the diagnostic status of "bipolar II" for the DSM-IV work group on mood disorders. Depression 1993;1:2–10.

Ebert D, Berger M. Neurobiological similarities in antidepressant sleep deprivation and psychostimulant use: A psychostimulant theory of antidepressant sleep deprivation. Psychopharmacology 1998;140:1–10. [PubMed: 9862396]

Ebert D, Feistel H, Barocks A, Kaschka WP, Pirner A. SPECT assessment of cerebral dopamine D_2receptor blockade in depression before and after sleep deprivation. Biological Psychiatry 1994;35:880–885. [PubMed: 8054411]

Eich E, Macaulay D, Lam RW. Mania, depression, and mood dependent memory. Cognition and Emotion 1997;11:607–618.

Ellicott A, Hammen C, Gitlin M, Brown G, Jamison K. Life events and the course of bipolar disorder. American Journal of Psychiatry 1990;147(9):1194–1198. [PubMed: 1974746]

Ellicott AG. A prospective study of life stress and bipolar illness. Doctoral dissertation, University of California, 1989. Dissertation Abstracts International 1989;49:2851–2852.

El-Mallakh RS, Li R, Worth CA, Peiper SC. Leukocyte transmembrane potential in bipolar illness. Journal of Affective Disorders 1996;41:33–37. [PubMed: 8938203]

Emamghoreishi M, Schlichter L, Li PP, Parikh S, Sen J, Kamble A, et al. High intracellular calcium concentrations in transformed lymphoblasts from subjects with bipolar I disorder. American Journal of Psychiatry 1997;154:976–982. [PubMed: 9210749]

Endicott J, Nee J, Andreasen N, Clayton P, Keller M, Coryell W. Bipolar II: Combine or keep separate? Journal of Affective Disorders 1985;8:17–28. [PubMed: 3156908]

Frank E, Grochocinski VJ, Spanier CA, Buysse DJ, Cherry CR, Houck PR, et al. Interpersonal psychotherapy and antidepressant medication: Evaluation of a sequential treatment strategy in women with recurrent major depression. Journal of Clinical Psychiatry 2000;61:51–57. [PubMed: 10695647]

Frank, E.; Kupfer, DJ.; Gibbons, R.; Houck, P.; Kostelnik, B.; Mallinger, A., et al. Interpersonal and social rhythm therapy prevents depressive symptoms in patients with bipolar I disorder. In: Miklowitz, D., editor. Is the course of manic–depressive illness influenced by psychosocial factors? Lessons from observational and treatment studies; Symposium conducted at the Fifteenth Annual Meeting of the Society for Research on Psychopathology; Boulder Colorado. 2000.

Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder: Remission, recovery, relapse, and recurrence. Archives of General Psychiatry 1991;48:851–855. [PubMed: 1929776]

Friedman E, Wang HY, Levinson D, Connel TA, Singh H. Altered platelet protein kinase C activity in bipolar affective disorder, manic episode. Biological Psychiatry 1993;33:520–525. [PubMed: 8513036]

Furukawa TA, Konno W, Morinobu S, Harai H, Kitamura T, Takahashi K. Course and outcome of depressive episodes: Comparison between bipolar, unipolar and subthreshold depression. Psychiatry Research 2000;96:211–220. [PubMed: 11084217]

Gessa, G.; Pani, L.; Serra, G.; Fratta, W. Animal models of mania. In: Gessa, G.; Fratta, W.; Pani, L.; Serra, G., editors. Depression and mania from neurobiology to treatment. New York: Raven Press; 1995. p. 43-66.

Giles DE, Rush AJ, Roffwarg HP. Sleep parameters in bipolar I, bipolar II, and unipolar depressions. Biological Psychiatry 1986;21:1340–1343. [PubMed: 3756280]

Goldberg, JF. The changing landscape of psychopharmacology. In: Johnson, SL.; Leahy, R., editors. Psychological treatments of bipolar disorder. New York, NY: Guilford Press; 2004.

Goodwin, FK.; Jamison, KR. Manic–depressive illness. Oxford, England: Oxford University Press; 1990.

Gottschalk A, Bauer MS, Whybrow PC. Low dimensional chaos in bipolar disorder?: Reply. Archives of General Psychiatry 1998;55:275–276. [PubMed: 9510223]

Gunderson, JG.; Triebwasser, J.; Phillips, KA.; Sullivan, CN. Personality and vulnerability to affective disorders. In: Cloninger, RC., editor. Personality and psychopathology. Washington, DC, USA: American Psychiatric Press; 1999. p. 3-32.

Gurpegui M, Casanova J, Cervera S. Clinical and neuroendocrine features of endogenous unipolar and bipolar depression. Acta Psychiatrica Scandinavica 1985;72(Suppl 320):30–37.

Guze SB, Woodruff RA, Clayton PJ. The significance of psychotic affective disorders. Archives of General Psychiatry 1975;32:1147–1150. [PubMed: 1180665]

Hall KS, Dunner DL, Zeller G, Fieve RR. A prospective study of life events. Comprehensive Psychiatry 1977;18:497–502. [PubMed: 891172]

Hammen C, Ellicott A, Gitlin M. Stressors and sociotropy/autonomy: A longitudinal study of their relationship to the course of bipolar disorder. Cognitive Therapy 1992;16:409–418.

Hammen C, Ellicott A, Gitlin M, Jamison K. Sociotropy/autonomy and vulnerability to specific life events in patients with unipolar depression and bipolar disorders. Journal of Abnormal Psychology 1989;98:154–160. [PubMed: 2708658]

Heerlein A, Richter P, Gonzalez M, Santander J. Personality patterns and outcome in depressive and bipolar disorders. Psychopathology 1998;31:15–22. [PubMed: 9500682]

Hestenes, D. A neural network theory of manic–depressive illness. In: Levine, DS.; Leven, SJ., editors. Motivation, emotion, and goal direction in neural networks. Hillsdale, NJ: Lawrence Erlbaum Associates; 1992.

Hill CV, Oei TP, Hill MA. An empirical investigation of the specificity and sensitivity of the automatic thoughts questionnaire and dysfunctional attitudes scale. Journal of Psychopathology and Behavioral Assessment 1989;11:291–311.

Hirschfeld RMA, Cross CK. Epidemiology of affective categories. Archives of General Psychiatry 1982;39:35–46. [PubMed: 7055407]

Hlastala SA, Frank E, Mallinger A, Thase ME, Ritenour A, Kupfer DJ. Bipolar depression: An underestimated treatment challenge. Depression and Anxiety 1997;5:73–83. [PubMed: 9262937]

Hollon SD. Cognitive models of depression from a psychobiological perspective. Psychological Inquiry 1992;3:250–253.

Hollon SD, Kendall PC, Lumry A. Specificity of depressotypic cognitions in clinical depression. Journal of Abnormal Psychology 1986;95:52–59. [PubMed: 3700847]

Howland, RH.; Thase, ME. Affective disorders: Biological aspects. In: Millon, T.; Blaney, PH.; Davis, RD., editors. Oxford textbook of psychopathology. New York: Oxford University Press; 1999.

Hunt N, Bruce-Jones WD, Silverstone T. Life events and relapse in bipolar affective disorder. Journal of Affective Disorders 1992;25(1):13–20. [PubMed: 1624643]

Ingram RE, Bernet CZ, McLaughlin SC. Attentional allocation processes in individuals at risk for depression. Cognitive Therapy and Research 1994;18:317–332.

Isometsa E, Heikinen M, Henriksson M, Aro H, Lonnquist J. Recent life events and completed suicide in bipolar affective disorder: A comparison with major depressive suicides. Journal of Affective Disorders 1995;33:99–106. [PubMed: 7759667]

Jackson, SW. Melancholia and depression: From hippocrate times to modern times. New Haven: Yale University Press; 1986.

Joffe RT, Young LT, MacQueen GM. A two-illness model of bipolar disorder. Bipolar Disorders 1999;1:25–30. [PubMed: 11256651]

Johnson S, Meyer B, Winett C, Small J. Social support and self-esteem predict changes in bipolar depression but not mania. Journal of Affective Disorders 2000;58:79–86. [PubMed: 10760562]

Johnson SL. Treatment attitudes in bipolar disorder: Development and validation of a self-report measure. in preparation.

Johnson SL, Darcy K. Depression and mania: Two poles or two dimensions? in preparation.

Johnson SL, Fingerhut R. Negative cognitions predict the course of bipolar depression, not mania. Journal of Cognitive Psychotherapy 2004;18:149–162.

Johnson, SL.; Kizer, A. Bipolar and unipolar depression: A comparison of clinical phenomenology and psychosocial predictors. In: Gotlib, IH.; Hammen, CI., editors. Handbook of depression. New York: Guilford Press; 2002.

Johnson SL, Roberts JR. Life events and bipolar disorder: Implications from biological theories. Psychological Bulletin 1995;117:434–449. [PubMed: 7777648]

Johnson SL, Sandrow D, Meyer B, Winters R, Miller I, Keitner G, et al. Life events involving goal-attainment and the emergence of manic symptoms. Journal of Abnormal Psychology 2000;109:721–727. [PubMed: 11195996]

Johnson SL, Winett C, Meyer B, Greenhouse W, Miller I. Social support and the course of bipolar disorder. Journal of Abnormal Psychology 1999;108:558–566. [PubMed: 10609420]

Johnson, SL.; Winters, R.; Meyer, B. The role of the social environment in bipolar disorder: A polarity-specific model. In: Joiner, Thomas, editor. A Festschrift for J. Hokanson. Washington, DC: American Psychological Association; in press

Kaplan, HI.; Sadock, BJ. Synopsis of psychiatry: Behavioral sciences/clinical psychiatry. 8. Philadelphia: Lippencott Williams & Wilkins; 1998.

Karkowski LM, Kendler KS. An examination of the genetic relationship between bipolar and unipolar illness in an epidemiological sample. Psychiatric Genetics 1997;7:159–163. [PubMed: 9460800]

Kasper S, Sac DA, Wehr TA, Kick H, Voll G, Vieira A. Nocturnal TSH and prolactin secretion during sleep deprivation and prediction of antidepressant response in-patients with major depression. Biological Psychiatry 1988;6:631–641. [PubMed: 3167147]

Katz MM, Robins E, Croughan J, Secunda S, Swann A. Behavioural measurement and drug response characteristics of unipolar and bipolar depression. Psychological Medicine 1982;12:25–36. [PubMed: 7079431]

Kelsoe JR. Arguments for the genetic basis of the bipolar spectrum. Journal of Affective Disorders 2003;73:183–197. [PubMed: 12507751]

Kessing LV, Mortensen PB. Recovery from episodes during the course of affective disorder: A case-register study. Acta Psychiatrica Scandinavica 1999;100:279–287. [PubMed: 10510697]

Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. Psychological Medicine 1997;27:1079–1089. [PubMed: 9300513]

Klein DN, Lewinsohn PM, Rohde P, Seeley JR, Durbin CE. Clinical features of major depressive disorder in adolescents and their relatives: Impact on familial aggregation, implications for phenotype definition, and specificity of transmission. Journal of Abnormal Psychology 2002;111:98–106. [PubMed: 11866183]

Klein, M. Mourning and its relation to manic–depressive states. In: Frankiel, RV., editor. Essential papers on object loss. Essential papers in psychoanalysis. New York, NY: New York University Press; 1994. p. 95-122.

Klerman GL. The classification of bipolar disorders. Psychiatric Annals 1987;17(1):13–17.

Kolko DJ, Brent DA, Baugher M, Bridge J, Birmaher B. Cognitive and family therapies for adolescent depression: Treatment specificity, mediation, and moderation. Journal of Consulting and Clinical Psychology 2000;68:603–614. [PubMed: 10965636]

Koslow SH, Maas JW, Bowden CL, Davis JJ, Hanin I, Javaid J. CSF and urinary biogenic amines and metabolites in depression and mania. A controlled, univariate analysis. Archives of General Psychiatry 1983;49(9):999–1010. [PubMed: 6193764]

Kuhs H, Reschke D. Psychomotor activity in unipolar and bipolar depressive patients. Psychopathology 1992;25:109–116. [PubMed: 1502292]

Kupfer D, Weiss BL, Foster FG, Detre TP, Delgado J, McPartland R. Psychomotor activity in affective states. Archives of General Psychiatry 1974;30:765–768. [PubMed: 4832184]

Leahy RL. Decision-making and mania. Journal of Cognitive Psychotherapy 1999;13:83–105.

Leake A, Fairbairn AF, McKeith IG, Ferrier IN. Studies on the serotonin uptake binding site in major depressive disorder and control post-mortem brain: Neurochemical and clinical correlates. Psychiatry Research 1991;39:155–165. [PubMed: 1798816]

Leibenluft E. Women and bipolar disorder: An update. Bulletin of the Menninger Clinic 2000;64:5–17. [PubMed: 10695156]

Leonard, K. Aufteilung der endogen Psychosen. Berlin: Akademieverlag; 1957.

Lester D. Suicidal behavior in bipolar and unipolar affective disorders: A meta-analysis. Journal of Affective Disorders 1993;27:117–121. [PubMed: 8440807]

Lex, C. Unpublished master's thesis. University of Vienna; Vienna, Austria: 2000. Kognitive Verarbeitung bei Bipolarer Depression (Cognitive processing in bipolar depression).

Lozano B, Johnson SL. Personality traits on the NEO-V as predictors of depression and mania. Journal of Affective Disorders 2001;63:103–111. [PubMed: 11246086]

Lyon HM, Startup M, Bentall RP. Social cognition and the manic defense: Attributions, selective attention, and self-schema in bipolar affective disorder. Journal of Abnormal Psychology 1999;108:273–282. [PubMed: 10369037]

Maas JW. Biogenic amines and depression: Biochemical and pharmacological separation of two types of depression. Archives of General Psychiatry 1975;32:1357–1361. [PubMed: 1200759]

Maes, M.; Meltzer, HY. The serotonin hypothesis of major depression. In: Bloom, FE.; Kuper, DJ., editors. Psychopharmacology: The fourth generation of progress. New York: Raven Press; 1995. p. 933-944.

Malkoff-Schwartz S, Frank E, Anderson B, Sherrill JT, Siegal L, Patterson D, et al. Stressful life events and social rhythm disruption in the onset of manic and depressive bipolar episodes. Archives of General Psychiatry 1998;55:702–707. [PubMed: 9707380]

Manji HK, Chen G, Shimon H, Hsiao JK, Porrer WZ, Belmaker RH. Guanine nucleotide-binding proteins in bipolar affective disorder. Archives of General Psychiatry 1995;52:135–144. [PubMed: 7848049]

Manki H, Kanba S, Muramatsu T, Higuchi S, Suzuki E, Matsushita S, et al. Dopamine D2, D3, and D4 receptor and transport gene polymorphisms and mood disorders. Journal of Affective Disorders 1996;40:7–13. [PubMed: 8882909]

Markou A, Kosten TR, Koob GF. Neurobiological similarities in depression and drug dependence: A self-medication hypothesis. Neuropsychopharmacology 1998;18(3):135–174. [PubMed: 9471114]

Mathews R, Li PP, Young LT, Kish SJ, Warsh JJ. Increased $G\alpha_{q/11}$immunoreactivity in postmortem occipital cortex from patients with bipolar affective disorder. Biological Psychiatry 1997;41:649–656. [PubMed: 9066988]

McElroy SL, Keck PE, Pope HG, Hudson JI, Faedda GL, Swann AC. Clinical and research implications of the diagnosis of dysphoric or mixed mania or hypomania. American Journal of Psychiatry 1992;149(12):1633–1644. [PubMed: 1359799]

McGuffin P, Rijsdijk F, Andrew M, Sham P, Katz R, Cardno A. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Archives of General Psychiatry 2003;60:497–502. [PubMed: 12742871]

McPherson H, Herbison P, Romans S. Life events and relapse in established bipolar affective disorder. British Journal of Psychiatry 1993;163:381–385. [PubMed: 8401970]

Meehl, PE. Psychodiagnostics: Selected papers. Minneapolis: University of Minnesota Press; 1973.

Meehl PE. What's in a taxon? Journal of Abnormal Psychology 2004;113:39–43. [PubMed: 14992655]

Meehl PE, Yonce LJ. Taxometric analysis: II. Detecting taxonicity using covariance of two quantitative indicators in successive intervals of a third indicator (MAXCOV procedure). Psychological Reports 1996;78:1091–1227.

Meyer B, Johnson SL, Carver CS. Exploring behavioral activation and inhibition sensitivities among college students at-risk for mood disorders. Journal of Psychopathology and Behavioral Assessment 1999;21:275–292.

Miklowitz DJ, Goldstein MJ, Nuechterlein KH, Snyder KS. Family factors and the course of bipolar affective disorder. Archives of General Psychiatry 1988;45:225–231. [PubMed: 3341878]

Miklowitz DJ, Simoneau TL, George EL, Richards JA, Kalbag A, Sachs-Ericsson N, et al. Family-focused treatment of bipolar disorder: 1-year effects of a psychoeducational program in conjunction with pharmacotherapy. Biological Psychiatry 2000;48:582–592. [PubMed: 11018229]

Mitchell P, Parker G, Jamieson K, Wilhelm K, Hickie I, Brodaty H, et al. Are there any differences between bipolar and unipolar melancholia? Journal of Affective Disorders 1992;25:97–106. [PubMed: 1644992]

Mitchell P, Wilhelm K, Parker G, Austin MP, Rutgers P, Malhi GS. The clinical features of bipolar depression: A comparison with matched major depressive disorder patients. Journal of Clinical Psychiatry 2001;62:212–216. [PubMed: 11305713]

Mitchell PB, Manji HK, Chen G. High levels of Gs Alpha I platelets of euthymic patients with bipolar affective disorder. American Journal of Psychiatry 1997;154:218–223. [PubMed: 9016271]

Naranjo CA, Tremblay LK, Busto UE. The role of the brain reward system in depression. Progress in Neuro-Psychopharmacology & Biological Psychiatry 2001;25:781–823. [PubMed: 11383978]

National Institute of Mental Health (NIMH). Genetics and mental disorders: Report of the NIMH genetics workgroup. Bethesda, MD: NIMH publication number NIH-98-4268; 1998.

Newman, C.; Leahy, RL.; Beck, AT.; Reilly-Harrington, N.; Gyulai, L. Bipolar disorder: A cognitive therapy approach. Washington, DC: American; 2002.

Norman RM, Malla AK. Stressful life events and schizophrenia: II. Conceptual and methodological issues. British Journal of Psychiatry 1993;162:166–174. [PubMed: 8435686]

Nunes GP Jr, Tufik S, Nobrega JN. Autoradiographic analysis of $D_1$and D_2dopaminergic receptors in rat brain after paradoxical sleep deprivation. Brain Research Bulletin 1994;34:453–460. [PubMed: 8082038]

Okamoto Y, Kagaya A, Shinno H, Motohashi N, Yamawaki S. Serotonin-induced platelet calcium mobilization is enhanced in mania. Life Sciences 1994;56:327–332. [PubMed: 7837932]

Pandey GN, Dwivedi Y, Sridhara Rao J, Ren X, Janicak PG, Sharma R. Protein kinase C and phospholipase C activity and expression of their specific isozymes is decreased and expression of MARCKS is increased in platelets of bipolar but not in unipolar patients. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 2002;26:216–228. [PubMed: 11790517]

Parker G, Roy K, Wilhelm K, Mitchell P, Hadzi-Pavlovic D. The nature of bipolar depression: Implications for the definition of melancholia. Journal of Affective Disorders 2000;59:217–224. [PubMed: 10854638]

Perez J, Zanardi R, Mori S, Gasperini M, Smeraldi E, Racagni G. Abnormalities of cAMP-dependent endogenous phosphorylation in platelets from patients with bipolar disorder. American Journal of Psychiatry 1995;152:1204–1206. [PubMed: 7625472]

Perris H. A study of bipolar and unipolar recurrent depressive psychoses. Acta Psychiatrica Scandinavica 1966;(Supplement):194.

Perris H. Life events and depression: Part 2. Results in diagnostic subgroups and in relation to the recurrence of depression. Journal of Affective Disorders 1984;7:25–36. [PubMed: 6236241]

Plomin, R.; DeFries, JC.; McClearn, GE.; Rutter, M. Behavioral genetics. 3. New York: W.H. Freeman and Company; 1997.

Prange AJ Jr, Wilson IC, Lynn CW, Alltop LB, Stikeleather RA. L-tryptophan in mania. Contribution to a permissive hypothesis of affective disorders. Archives of General Psychiatry 1974;30:56–62. [PubMed: 4587067]

Priebe S, Wildgrube C, Muller-Oerlinghausen B. Lithium prophylaxis and expressed emotion. British Journal of Psychiatry 1989;154:396–399. [PubMed: 2597843]

Reilly-Harrington NA, Alloy LB, Fresco DM, Whitehouse WG. Cognitive styles and life events as predictors of bipolar and unipolar symptomatology. Journal of Abnormal Psychology 1999;108:567–578. [PubMed: 10609421]

Roy A. Personality variables in depressed patients and normal controls. Neuropsychobiology 1991;23:119–123. [PubMed: 2098667]

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 Psychiatrica Scandinavica 1985;71 (Suppl 317):1–34. [PubMed: 3969837]

Schatzberg, AF.; Schildkraut, JJ. Recent studies on norepinephrine systems in mood disorders. In: Bloom, FE.; Kuper, DJ., editors. Psychopharmacology: The fourth generation of progress. New York: Raven Press; 1995. p. 911-920.

Schildkraut JJ. Biogenic amines and affective disorders. Annual Review of Medicine 1974;25:333–348.

Schreiber G, Avissar S, Danon A, Belmarker RH. Hyperfunction G proteins in mononuclear leukocytes of patients with mania. Biological Psychiatry 1991;29:273–280. [PubMed: 1901735]

Scott J. Cognitive therapy for clients with bipolar disorder: A case example. Cognitive and Behavioral Practice 1995;3:1–23.

Scott J, Pope M. Cognitive styles in individuals with bipolar disorders. Psychological Medicine 2003;33:1081–1088. [PubMed: 12946092]

Segal ZV, Gemar M, Williams S. Differential cognitive response to a mood challenge following successful cognitive therapy or pharmacotherapy for unipolar depression. Journal of Abnormal Psychology 1999;108:2–10.

Seligman MEP, Castellon C, Cacciola J, Schulman P, Luiborsky L, Ollove M, et al. Explanatory style change during cognitive therapy for unipolar depression. Journal of Abnormal Psychology 1988;97:13–18. [PubMed: 3351107]

Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: An fMRI study. Biological Psychiatry 2001;50:651–658. [PubMed: 11704071]

Shiah IS, Yatham LN, Baker GB. Divalproex sodium increases plasma GABA levels in healthy volunteers. International Clinical Psychopharmacology 2000;15:221–225. [PubMed: 10954062]

Solomon DA, Leon AC, Coryell W, Mueller TI, Posternak MA. Unipolar mania: A 20-year follow-up study. American Journal of Psychiatry 2003;160:2049–2050. [PubMed: 14594755]

Spoont M. Modulatory role of serotonin in neural information processing: Implications for human psychopathology. Psychological Bulletin 1992;112:330–350. [PubMed: 1454898]

Stoll AL, Renshaw PF, Yurgelun-Todd DA, Cohen BM. Neuroimaging in bipolar disorder: What have we learned? Biological Psychiatry 2000;48:505–517. [PubMed: 11018223]

Strakowski SM, Stoll AL, Tohen M, Faedda GL, Goodwin DC. The tridimensional personality questionnaire as a predictor of six-month outcome in first episode mania. Psychiatry Research 1993;48:1–8. [PubMed: 8416014]

Suzuki K, Kusumi I, Sasaki Y, Koyama T. Serotonin-induced platelet intracellular calcium mobilization I various psychiatric disorders: Is it specific to bipolar disorder? Journal of Affective Disorders 2001;64:291–296. [PubMed: 11313098]

Teasdale, JD.; Barnard, PJ. Affect, cognition, and change: Re-modelling depressive thought. Hillside, NJ: Lawrence Erlbaum Associates; 1994.

Teasdale JD, Fogarty SJ. Differential effects of induced mood on retrieval of pleasant and unpleasant events from episodic memory. Journal of Abnormal Psychology 1979;88:248–257. [PubMed: 500952]

Teasdale JD, Taylor R, Fogarty SJ. Effects of induced elation–depression on the accessibility of memories of happy and unhappy experiences. Behaviour Research and Therapy 1980;18:339–346. [PubMed: 7436981]

Thakore JH, O'Keane V, Dinan TG. D-fenfluramine-induced prolactin responses in mania: Evidence for serotonergic subsensitivity. American Journal of Psychiatry 1996;153:1460–1463. [PubMed: 8890681]

Tracy A, Bauwens F, Martin F, Pardoen D, Mendlowicz J. Attributional style and depression: A controlled comparison of remitted unipolar and bipolar patients. British Journal of Clinical Psychology 1992;31:83–84. [PubMed: 1559120]

Traskman L, Asberg M, Bertilsson L, Sjostrand L. Monoamine metabolites in CSF and suicidal behavior. Archives of General Psychiatry 1981;38(6):631–636. [PubMed: 6166274]

Veiel HO, Kuehner C, Brill G, Ihle W. Psychosocial correlates of clinical depression after psychiatric in-patient treatment: Methodological issues and baseline differences between recovered and non-recovered patients. Psychological Medicine 1992;22:415–427. [PubMed: 1615109]

Videbech P. PET measurements of brain glucose metabolism and blood flow in major depressive disorder: A critical review. Acta Psychiatrica Scandinavica 2000;101:11–20. [PubMed: 10674946]

von Zerssen, D. 'Melancholic' and 'manic' types of personality as premorbid structures in affective disorders. In: Mundt, C.; Goldstein, MJ.; Hahlweg, K.; Fiedler, P., editors. Interpersonal factors in the origin and course of affective disorders. London, England: Gaskell/Royal College of Psychiatrists; 1996. p. 65-85.

Wang HY, Markowitz P, Levinson D, Undie AS, Friedman E. Journal of Psychiatric Research 1999;33:171–179. [PubMed: 10221749]

Weingartner H, Cohen RM, Murphy DL, Martello J, Gerdt C. Cognitive processes in depression. Archives of General Psychiatry 1981;38:42–47. [PubMed: 7458568]

Weissman MM, Bland RC, Canino GJ, Fravelli C, Greenwald S, Hwu HG, et al. Cross-national epidemiology of major depression and bipolar disorder. JAMA: The Journal of the American Medical Association 1996;276:293–299. [PubMed: 8656541]

Weissman MM, Myers JK. Affective disorders in a US urban community: The use of research diagnostic criteria in an epidemiological survey. Archives of General Psychiatry 1978;35:1304–1311. [PubMed: 708194]

Williams, MG.; Watts, FN.; MacLeod, C.; Mathews, A. Cognitive psychology and emotional disorders. 2. England: John Wiley & Sons; 1997.

Winters KC, Neale J. Mania and low self-esteem. Journal of Abnormal Psychology 1985;94:282–290. [PubMed: 4031225]

Winters, R.; Scott, W.; Beevers, C. Affective distress as a central and organizing symptom in depression: Neurobiological mechanisms. In: Johnson, SL.; Hayes, AM.; Field, T.; Schneiderman, N.; McCabe, P., editors. Stress, coping and depression: Proceedings of the fifteenth annual stress and coping conference. Mahweh, NJ: Lawrence Erlbaum; 2000. p. 177-222.

Wu J, Bunney WE. The biological basis of an antidepressant response to sleep deprivation and relapse: Review and hypothesis. American Journal of Psychiatry 1991;147:14–21. [PubMed: 2403471]

Yatham LN, Liddle PF, Shiah I, Scarrow G, Lam RW, Adam MJ, et al. Brain serotonin$_2$receptors in major depression: A positron emission tomography study. Archives of General Psychiatry 2000;57:850–858. [PubMed: 10986548]

Young LT, Bagby RM, Cooke RG, Parker JDA, Levitt AJ, Joffe RT. A comparison of Tridimensional Personality Questionnaire dimensions in bipolar disorder and unipolar depression. Psychiatry Research 1995;58:139–143. [PubMed: 8570765]

Young LT, Li PP, Kamble A, Siu KP, Warsh JJ. Mononuclear leukocyte levels of G proteins with bipolar disorder or major depressive disorder. American Journal of Psychiatry 1994;151:594–596. [PubMed: 8147460]

Yurgelun-Todd DA, Gruber SA, Kanayama G, Killgore WD, Baird AA, Young AD. fMRI during affect discrimination in bipolar affective disorder. Bipolar Disorders 2000;3:237–248. [PubMed: 11249801]

Clin Psychol Rev. Author manuscript; available in PMC 2010 April 7.

Table 1

Author	*N*	Sample	Diagnosis	Current or retrospective reports	How symptoms Measured	How Episode Status Determined	Control over Medication	Control over Potential Confounds	Findings in Comparing Unipolar (UP) with Bipolar (BP) Depression
No controls over confounds or medications									
Abrams and Taylor (1980)	40	inpatients with diagnosis of endogenous depression	psychiatric diagnosis using semi-structured interview	current	interviewer rated depressive, manic, and catatonic symptoms	all patients admitted during depressive episode	none	none	UP: greater weight loss and more sxs no difference on number of episodes per year, hx of xubstance or ETOH abuse, ADHD, seizures, or head trauma
Black and Nasrallah (1989)	1715	inpatient BP and primary UP	psychiatric	retrospective	chart review	chart review of admission diagnosis using DSM-III criteria	none	none	no difference in frequency of psychosis
Brockington et al. (1982)	154 (London) 102 (Chicago)	inpatient schizoaffective-depressed, MDD, & minor depressive disorder in UP group; BP=hx of definite or probable mania	chart review	current	Present State Examination (PSE)	all patients admitted during depressive episode	none	none	London UP: depression less severe in AM, less derealization, greater suicidality, more ideas of reference, more auditory hallucinations, greater loss of insight, greater observed anxiety; Chicago UP: less mood lability, fewer somatic complaints, less haughty attitude, more unvarying depression, more initial insomnia, more muddled thoughts
Guze et al. (1975)	253	inpatient UP or BP with either primary or secondary affective disorder	structured interview	retrospective	interviewer	no distinctions between episodes	none	separate comparisons between primary and secondary disorders	UP: fewer hospitalizations, more psychosis
Lester (1993)	meta-analysis of 23 studies	studies comparing suicidal behavior in patients with bipolar and unipolar disorder	varied	varied	varied	no distinction between manic and depressive episodes in most studies	varied	none-age and sex often not reported	no significant difference in completed suicides, although result is due to one large deviant study; BP had significantly more subsequent suicide attempts; studies split on differences in previous suicide attempts; single studies found significantly greater combined previous and

Author	*N*	Sample	Diagnosis	Current or retrospective reports	How symptoms Measured	How Episode Status Determined	Control over Medication	Control over Potential Confounds	Findings in Comparing Unipolar (UP) with Bipolar (BP) Depression
									subsequent suicide attempts and ideation in UP; studies comparing BP I and II disorders split on difference in previous and subsequent suicide attempts
Statistical control over confounds									
Breslau and Meltzer (1998)	111	voluntary-admission inpatients with psychotic depression	PSE, psychiatric and family history schedule, and Hamilton Rating Scale for Depression (HRSD) for diagnosis of schizoaffective, unipolar, or bipolar disorder or per RDC criteria at discharge	current	Schedule for Affective Disorders and Schizophrenia-C (SADS)	all patients admitted during depressive episode	none	no significant differences in sex, ethnicity, age at admission, or age at onset	in UP and BP depressions, no significant differences on any particular symptom among comparisons of individual SADS-C psychotic symptoms; only significant difference was greater hypomania in BP on comparison on nonpsychotic SADS-C symptoms
Coryell et al. (1989)	559	inpatient and outpatient BP I, BP II, and UP	SADS using RDC criteria	prospective over 5 years	Longitudinal Interval Follow-up Evaluation (LIFE)	all patients entered study during depressive episode	medications converted into drug equivalency scores	no significant differences in age or sex	no difference in GAS scores, suicide, symptoms of RDC syndromes, or endogenous subtype
Statistical control over confounds									
Parker et al. (2000)	987	inpatient and outpatient BP and UP	chart review	retrospective	DSM-III, Clinical, CORE	DSM-III defined major depressive disorder	none	no significant differences in age or sex	UP: less psychotic depression or melancholia, to have appetite loss, slowed thinking, indecisiveness, psychomotor retardation, loss of interest, anticipatory anhedonia, non-reactivity of mood, pathological guilt, delusions, or hallucinations; more likely to be diagnosed with reactive depression and to have non-variable mood
Matched on potential confounding variables									
Endicott et al. (1985)	292	inpatient recurrent unipolar, BP I, and BP II	SADS using RDC criteria	current and retrospective	observation, chart review, family interviews	all patients admitted during depressive episode	none	all data analyzed between groups matched on sex;	UP: less lifetime psychotic major depression, less frequent moderate suicidal intent; less primary depression,

Author	*N*	Sample	Diagnosis	Current or retrospective reports	How symptoms Measured	How Episode Status Determined	Control over Medication	Control over Potential Confounds	Findings in Comparing Unipolar (UP) with Bipolar (BP) Depression
								no significant difference in age	intake episode more likely to include major depressive period; no significant difference in endogenous depression
Mitchell et al. (1992)	54	inpatients and outpatients	diagnosis of BP or UP depression that meets DSM-III, RDC, and CORE criteria for melancholy or endogenous depression; BP meet RDC criteria for past manic or hypomanic episodes	current	semi-structured interview to evaluate present episode & mental state signs; previous medical records	all patients in depressive episode	none	BP and UP matched on age, sex, and endogenous depression; no difference in psychosis or depression severity	in comparisons of 31 mental state signs and 37 symptoms, no significant difference on index of psychomotor change; unipolars significantly more likely to have slowed movements; bipolars significantly more likely to be nihilistic; nonsignificant trends for bipolars to be less retarded and more agitated
Mitchell et al. (2001)	78	inpatient and outpatient BP and UP	DSM-IV criteria for major depressive disorder or bipolar disorder	current	HRSD, Newcastle Endogenous Depression Diagnostic Index, CORE	current diagnosis meets DSM-IV criteria for major depressive disorder	none	matched on age, sex, and melancholic subtype	UP: less likely to have psychomotor-retarded atypical and melancholic symptoms, less likely to have had psychotic depresion; no difference in depression severity
Control over medication and some control over confounds									
Beigel and Murphy (1971)	50	inpatient BP and UP in psychotic depressive episodes	psychiatric, interviews with family, and chart review; BP had to have documented manic episode on research ward	retrospective	Bunney-Hamburg 15-point nurse rating scale	all patients admitted during depressive episode; all patients had at least 2 weeks clinical ratable depression and at least 3 days without manic symptoms before and after rating period	14 day drug washout	matched on age, sex, and depression severity	UP: greater pacing, overt anger, and somatic symptoms; no significant differences in anxiety or psychosis (although trend for UP to have greater anxiety)
Borkowska and Rybakowski (2001)	45	inpatient BP and UP	psychiatric using ICD-10 or DSM-IV criteria	current	HRSD	all patients admitted during depressive episode; excluded if psychotic or manic symptoms present	no ECT within 1 year prior to study; mood stabilizers washed out 1 month prior to study; all drugs washed out 7 to 10 days prior	no significant differences in education, severity of depression, or duration of illness	BP showed greater frontal lobe cognitive dysfunction, particularly in strategy shifting, visiospatial working memory, and executive functioning on administration of various neuropsychological tests

Author	*N*	Sample	Diagnosis	Current or retrospective reports	How symptoms Measured	How Episode Status Determined	Control over Medication	Control over Potential Confounds	Findings in Comparing Unipolar (UP) with Bipolar (BP) Depression
Giles et al. (1986)	44	BP I, BP II, and endogenous unipolars	SADS-L using RDC criteria	current	HRSD	interview with HRSD (no cut-off published)	drug washout for 14 days prior to study entry	matched on age, sex, and depression severity	BPII: greater REM latency and total sleep time compared to UP (total non-REM sleep explained greater sleep total), no significant differences in % time in each stage of sleep; no significant differences between BP I and BP II or BP I and UP
Gurpegui et al. (1985)	27	consecutively-admitted inpatients diagnosed with endogenous UP depression or BP depression	psychiatric per ICD-9 criteria	current	Comprehensive Psychopathological Rating Scale, HRSD	all patients admitted during depressive episode	one-week drug washout; exclusion criteria included the use of lithium within 6 months prior to admission	no significant differences in sex, age at admission, or age at first depressive episode	subsequent to dexamethason suppression test and thyrotropin releasing hormone stimulation test, unipolars had significantly more frequent and higher scores for weight loss, reduced appetite, muscular tension, and autonomic disturbances; hostile feelings was the only elevated symptom in the bipolar depressed patients
Katz et al. (1982)	74	inpatient UP and BP I	psychiatric	current	HRSD, SADS-C, interviewer ratings, self-reports, psychomotor performance	all patients admitted during depressive episode	all patients administered tricyclics (either amitryptiline or imipramine)	none	baseline: UP: greater anxiety, agitation, somatization, and depression; after 2–3 weeks of tricyclic treatment: UP: less anxiety, agitation, and psychoticism than BP
Kuhs and Reschke (1992)	37	patients who met criteria of both major depressive episode according to DSM-III and endogenous depression per ICD-9	psychiatric diagnosis of either UP or BP depression	current	HRSD	all patients in depressive episode	22 out of 25 UP patients and 9 out of 12 BP patients receiving antidepressant medication; 10 out of 25 UP and 6 out of 12 BP patients receiving benzodiazepines	no significant difference in depressive inhibition or HRSD score at baseline	no significant difference in actometrically-registered or subjectively-rated psychomotor activity/restlessness and sleep time once unipolars and bipolars matched for age and gender
Kupfer et al. (1974)	11	psychiatric, mental status exams, self reports	current	interviews, staff ratings, self reports, activity measured telemetrically	all patients admitted during depressive episode	baseline measures after 14 day drug washout; 2nd time period 3 weeks after drug treatment (150 mg amitryptyline for	norelationshipbetween telemetric activity and depression scores		UP: greater psychomotor activity at baseline (differences explained by greater anxeity in UP group); at 2nd measurement no

Author	*N*	Sample	Diagnosis	Current or retrospective reports	How symptoms Measured	How Episode Status Determined	Control over Medication	Control over Potential Confounds	Findings in Comparing Unipolar (UP) with Bipolar (BP) Depression
						UP; lithium level 0.9–1.2 mEq/liter for BP			significant difference; as UP improved activity decreased; as BP improved activity increased