

Neuropsychology of Bipolar Disorder

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March 2006 "Manic-depressive illness, like other severe psychiatric disorders, has come out of the closet. Once relegated to the dark recesses of the family, it is now openly discussed as a brain disease – frequently a tragic disease, to be sure, but a disease nonetheless, like multiple sclerosis, Parkinson's disease, or Alzheimer's disease. The devils and demons once suspected of lurking in the brains of those afflicted have been permanently banished by the power of magnetic resonance imaging and molecular neuroscience. We are left with a brain disease whose precise cause is unknown, but for which effective treatment is, in most cases, available"

Torrey and Knable (2002, p. 1)

Introduction

People with bipolar disorder, known as manic-depressive illness until the early years of the twentieth century, were part of a large group sometimes labeled "insane." The word "insane" comes from the Latin derivative *insanus*, which means "unsound of mind". This term was widely used for four hundred years to identify people who experienced hallucinations, delusions, excess mood swings, bizarre behavior, disordered thinking, or a combination of these symptoms. "Madness" and "lunacy" were also used as descriptors of these misunderstood behaviors and synonymous with "insane" (Torrey and Knable, 2002).

The word "insanity" was replaced by "psychosis" in the early part of the twentieth century. At this time, "psychosis" became associated with an increasing number of mental disorders. Since some cases of psychosis were discovered to be related to medical problems such as vitamin deficiencies or syphilis, they were given names related to their cause. According to Torrey and Knable (2002), remaining cases involving psychosis were separated into dementia praecox (schizophrenia) and affective psychoses (including manic-depressive illness, psychotic depressive reactions, and involuntal melancholia).

Today, "psychosis" is defined as an altered mental condition that is characterized by hallucinations, loosened associations, illogical thinking, and delusions, and is considered to be the main feature of schizophrenia. Symptoms of psychosis may be associated with etiologies that are neurological, although the word "psychotic" is reserved typically for psychiatric symptoms that do not have an obvious neurologic etiology. When people develop neurologically-derived psychotic symptoms, they generally are described as "hallucinations," "paranoid delusions," and "delusions," and are related to the neurological condition that underlies them (Loring, 1999).

In the United States, "manic-depressive illness" was given a new label and definition in 1980. This definition required that a person experience at least one episode of mania that lasted for a minimum of a week. "Bipolar disorder" was the name given to replace "manic-depressive illness" by the American Psychiatric Association. Hence, "manic-depressive illness" was re-labeled and re-defined for the third edition of the Diagnostic and Statistical Manual of Mental Disorders, also known as the DSM-III (Torrey and Knable, 2002).

Prior to 1980, people in the United States with “manic-depression” included the following: people with depression only (manic-depressive illness, depressed type); mania only (manic-depressive illness, manic type); or both (manic-depressive illness, circular type). According to Torrey and Knable (2002), 80 percent of patients identified with manic-depressive illness before 1980 had symptoms of depression only. This issue has made it difficult to compare current studies regarding “bipolar disorder” with studies that were done prior to this time (1980) because people were included in past research with “depression” alone under the definition of manic-depressive illness, and in contemporary studies, such people are not counted as having manic-depressive illness (bipolar disorder) at all.

The same authors stated that “bipolar disorder” was an “unfortunate” choice as a name for “manic-depressive illness.” They added that the dictionary defines “bipolar” as “having two poles” and “involving both of the earth’s poles or polar regions,” which connotes an entity that is geographic. “Pole” is a word derived from a Latin term “polus” which means “pole of the heavens,” and the Greek “polos”, meaning “firmament.” According to Torrey and Knable (2002) “there is nothing heavenly about this disease” (preface p. xvi). To continue, “Polos” refers to two ends of a battery suggesting overtones of electricity. These authors assert that because of the inaccuracies in the definition of terms just described, the relatively new label “bipolar disorder” is unsatisfactory and “manic-depressive illness” remains a more accurate description of this disorder.

Be that as it may, the DSM-III definition of “bipolar disorder” required that people with depression alone no longer qualified for the diagnosis. This newer category included people with manic episodes alone and those with a combination of manic and depressive episodes. “Bipolar disorder” is considerably more restrictive than the older definition of “manic-depressive illness”. The definition of “bipolar” illness has continued to be tinkered with by American psychiatry and psychology since 1980, causing further confusion. Introduced in 1987 in the DSM-III-R (Revised), the requirement of a one-week minimum duration for a manic episode was eliminated. In its place it was stipulated that a correctly diagnosed individual had to be occupationally or socially impaired or in need of hospitalization, thus raising the threshold of dysfunction.

In 1994, however, the DSM-IV reinstated the stipulation that a manic episode had to last for at least one week’s duration. At this time, the category of bipolar disorder was subdivided into bipolar I (had a full manic episode) and bipolar II (had an episode of hypomania, i.e., does not exactly meet the criteria for mania).

Torrey and Knable (2002) stated that the concept of bipolar II had “previously been lurking in the diagnostic shadows under the heading ‘cyclothymic disorder’ in DSM-III and the heading ‘bipolar disorder, not otherwise specified’ in DSM-III-R. ‘Cyclothymic disorder’ and its DSM-III cousin ‘dysthymic disorder’ evolved into ‘cyclothymia’ and ‘dysthymia’ in DSM-III-R and back into ‘cyclothymic disorder’ and ‘dysthymic disorder’ in DSM-IV, but with continually modified definitions since that time. And if that did not sufficiently confuse everybody, DSM-IV added other caveats. For example, a manic episode precipitated by the taking of an antidepressant medication, which had qualified the person for a diagnosis of bipolar disorder under DSM-III and DSM-III-R, no longer did so under DSM-IV” (preface p.xvii).” In summary, attempts to define bipolar disorder / manic-depressive illness, is a work in progress.

It is also important to note that contemporary definitions of bipolar disorder identify Bipolar Disorder I as more likely than Bipolar II and Major Depressive Disorders, to have psychotic “features.” It is not necessary to have psychotic features to earn the diagnosis of Bipolar Disorder. However, with regard to differential diagnosis, Bipolar I is identified as the specific type

of Bipolar Disorder that may or may not have psychotic features. If psychotic features are present in Bipolar I, this diagnosis needs to be distinguished from other psychotic disorders: such as Schizoaffective Disorder, Delusional Disorder, and Schizophrenia.

Because many writers, musicians, and artists have suffered from the symptoms of bipolar disorder, there has been a tendency to romanticize it. In truth, however, without effective treatment, this condition is associated with enormous suffering, an increased risk of suicide; and many people's lives have been destroyed by this disease (NIMH, 2001-b). Bipolar disorder is a condition that causes extreme shifts in mental and physical energy, mood, and functioning, identifying it as a serious brain disease. Often disrupting school, work, social life, and family, symptoms including episodes, or cycles, of mania, depression, or a mixture of both, typically recur and may become more frequent over time (NIMH, 2001b).

Definition of the Disorder

The newest definition of bipolar disorder is of a mood disorder, characterized by long-term episodic, cyclical patterns involving extreme fluctuations of mood that cause significant disruptions in one's social, interpersonal, and occupational life (Reiser and Thompson, 2005).

Bipolar disorder falls within the diagnostic category of the broader mood disorders. These groupings are divided into bipolar and major depressive disorders. The World Health Organization's International Classification of Diseases (ICD-10) (Maier & Sandmann, 1993 paraphrased in Reiser & Thompson, 2005) and the Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition, Text Revision (DSM-IV-TR; American Psychiatric Association, 2000) emphasize the categorical nature of bipolar and unipolar disorders. There are also two main categorical groups for mood disorders identified in DSM-IV-TR: the bipolar disorders and the depressive disorders. These groups are primarily distinguished by the absence or presence of a history of manic episodes, mixed episodes, or hypomanic episodes (American Psychiatric Association, 2000).

Reiser and Thompson (2005) note that bipolar disorders, themselves, are currently placed into four categories. These mutually exclusive categories depend on the absence or presence of manic, mixed, and hypomanic episodes and use designated bipolar 1 disorder; bipolar II disorder; cyclothymic disorder; and bipolar disorder, not otherwise specified. Namely:

Bipolar I disorder consists of one or more manic or mixed episodes of sufficient severity to cause marked dysfunction in occupational and social functioning. These episodes most often result in hospitalization.

Bipolar II disorder consists of one or more major depressive episodes with at least one hypomanic episode. Client's functioning is not compromised severely enough to cause marked dysfunction in occupational or social functioning.

Cyclothymic disorder consists of mood instability over a two year period of time with depressed and hypomanic symptoms that do not meet full criteria for a major depressive episode or for a manic episode.

Bipolar disorder, not otherwise specified consists of bipolar disorder that does not meet full criteria described above due to failure to meet criteria for symptom clustering or duration, or due to a lack of information that is confirmatory for identifying a diagnosis.

According to Reiser and Thompson (2005), classification schema presented in DSM-IV-TR and ICD-10 have provided improvements in differential diagnosis, taking advantage of better levels of inter-observer reliability. This improvement was accomplished by deemphasizing the previously dichotomous view of disorders of mood.

According to Malhi, G.S., Ivanovski, B. Szekeres, V., and Olley, Amanda, (2004) episodes of hypomania or mania characteristically punctuate depressive symptoms in bipolar disorder. Because depressive episodes usually precede the occurrence of hypomania or manic episodes, diagnosis of bipolar disorder is frequently delayed for months or years.

The lacking of objective tests to determine whether a person has or does not have bipolar disorder makes diagnosis difficult. Despite recent advances in understanding the phenomenology and treatment of bipolar disorder, some researchers and clinicians hold that we are still left with basic and vital questions of what bipolar disorder actually is and what bipolar disorder actually is not (Maj, M, Akiskal, H.S., Lopez-Ibor, J.J., Sartorius, N., 2002).

Many authors currently believe that the system of classification described above has compromised a more unitary view of mood disorders. The result of this compromise is thought to be that the entire spectrum of bipolar disorders, are not only under-diagnosed and under-recognized, but they are under-treated as well. According to Reiser and Thompson (2005), "This narrower definition of bipolar disorder establishes a number of arbitrary thresholds (e.g., bipolar I versus bipolar II) based on duration and clustering of symptoms that may not effectively identify individuals who are experiencing subsyndromal symptoms with significant functional impairments, and who may be at higher risk for dysthymic disorder, comorbid anxiety disorders, subsyndromal depression, and suicide" (p.4).

These same authors also cited a recent study (Post, Leverich, Altshuler, Frye, Suppes, Keck, 2003 paraphrased in Reiser and Thompson, 2005) that supplies extremely compelling empirical evidence that people often experience significant subsyndromal fluctuations of mood in functioning and significant levels of impairment outside of severe episodes. Findings such as these, and others as well, have led researchers to argue for a more unitary view of mood disorders that distributes all mood disorders along a bipolar spectrum. This less categorical perspective on disorders of mood more closely joins bipolar and unipolar depression as well as bipolar II and bipolar I disorders.

See appendix for specific criteria diagnosing Major Depressive Episode, Manic Episode, Mixed Episode, Hypomanic Episode taken directly from DSM-IV-TR.

Epidemiology of Bipolar Disorder

Determining the prevalence of bipolar disorder is not an easy task. Figures vary widely, in part, because of the various definitions that have been used over the years. According the NIMH (2001-b), bipolar disorder affects approximately 2.3 million American adults which is about 1.2 percent of the population. Reiser and Thompson (2005) more recently reported that a lifetime prevalence of bipolar disorder may actually range from 2.6% to 7.8%, when the full spectrum of this diagnostic category is considered. Rihmer and Angst (2005) stated that the lifetime prevalence alone for bipolar I and bipolar II ranged from 0.3% to 7.2%.

Refined diagnostic precision and greater attention to improved assessment practices are likely to result in an increased rate of bipolar disorder (Reiser and Thompson, 2005). Reiser and Thompson (2005) also note that more recent work on bipolar disorder has emphasized the

importance of briefer (< 4 days) episodes of hypomania that alternate with depression, in addition to other sub-syndromal symptoms that occur in between episodes.

Clinicians reporting on this diagnosis are cautioned that there will be additional formal changes to diagnostic criteria and classification schemes in the near future and these changes will be more in concert with recent conceptualizations of regarding bipolarity as a spectrum disorder ranging from predominant depression with intermittent hypomania to dominant mania (Akiskal, 2005; Judd, Akiskal, Schettler, Coryell, Maser, and Rice, 2003). The nosological distinctions that are currently outlined in the DSM-IV-TR are still considered useful in categorizing clients with bipolar disorder (Judd, et al., 2003). Bipolar disorder seems to be equally distributed among women and men as well as between black and white people. Mexican-Americans, Amish, and traditional Hutterites (descendants of a Central European Anabaptist sect that migrated to the United States in the 1870's and settled in the northern prairie states and Canadian prairie provinces), appear to have a lower-than-average prevalence. There seems to be regional differences in the prevalence of bipolar disorder, both in the United States and in other places in the world (Torrey and Knable, 2002).

Cultural factors may affect patterns of syndromes involving both depression and mania. It is suggested however through epidemiological studies in the United States, that differences in bipolar disorder observed between African Americans, Hispanic Americans, and Caucasians may be partially accounted for by socioeconomic differences. There appears to be a clear relationship between harsh conditions of environment and the frequency and intensity of bipolar episodes. However, it may be that the more severe episodes (especially manic episodes) lead to divorce, loss of instrumental and emotional support systems, less professional and educational opportunity, unemployment, and low income. Stressful environmental conditions and people with Bipolar I tend to lead to devastating reciprocal interactions between the patient and others. People with hypomanic episodes or bipolar II appear to be less disrupted and this appears to contribute to their higher socioeconomic status (Rihmer and Angst, 2005).

Typically bipolar disorder emerges in the teen years or early adulthood. In some cases, it appears in childhood (Geller and Luby, 1997). Approximately 50% of people have their first episode of bipolar disorder before the age of 20 (Reiser and Thompson, 2005). This onset of bipolar disorder is about 10 years younger than the onset of unipolar depression. It is seldom that the onset of this disease occurs above 60 years of age. In general, this was also thought to be the case for prepubertal and early adolescent bipolar disorder. People with a positive family history of disorders of mood frequently experience their first episode at an earlier time in their lives and episodes are precipitated by fewer stressors than in those people who have no history of family mood disorder (Rihmer and Angst, 2005).

It is interesting to note that that bipolar illness was less common prior to the nineteenth century and seems to be increasing in prevalence (Torrey and Knable, 2002). Bipolar disorder is currently a major cause of disability in the United States, although its prevalence rate is less than that for other disorders of mood (Thomas, 2004). The economic burden for industry, health care programs, and families is immense. Some authors suggest that bipolar disorder is the most expensive disorder in psychiatry in the United States today (Peele, Xu, and Kupfer, 2003). Also of major importance is the psychological toll on friends and families of bipolar patients. Frequently the emotional and economic stresses of dealing with problems associated to this disorder eventually become great enough that loved ones become overwhelmed. One-fourth to one-half of bipolar patients are estimated to make at least one serious suicide attempt and approximately 10 – 20 % are successful in their attempt (Post & Altshuler, 2005). In addition, forty-five billion dollars is the estimated total annual cost to society of bipolar disorder in the United States alone,

according to Torrey and Knable (2002).

Genetic Predisposition One of the most influential risk factors for the development of a mood disorder is family history, particularly for bipolar disorder (Merikangas and Low, 2004). According to these authors, the average risk ratio, which was calculated from values obtained in four well-controlled studies among relatives of people with bipolar disorder (10.3) is similar to the risk ratio for many disease that are known to have a basis for genetics. This ratio is nearly 3 times greater than the average risk ratio for major depressive disorder (3.6). These findings suggest a moderate genetic influence. Twin studies provide more compelling evidence that mood disorders have hereditary components. According to Reiser and Thompson (2005), bipolar disorder shows a much higher involvement of genetic influence in the etiology (.59) than unipolar disorder (.37). These authors also state that attempts to look at familial or genetic differences in subtypes along gender differences of the bipolar spectrum have shown inconsistencies. For this reason, few generalizations can be made about the genetic background of these subtypes at the present time.

Unipolar depression occurs about twice as often in women than in men yet the prevalence rate of bipolar depression is approximately the same in men and women when all subtypes are considered. However, if one looks more closely at subtypes within the spectrum of bipolar disorder, there are a greater number of women found in the depression category, whereas more men are found in the mania end of the continuum (Reiser and Thompson, 2005).

Comorbidity

Roth and Fonagy (2005) state that data from epidemiologic catchment areas indicate that about half of the people with bipolar disorder have co-morbid drug or alcohol abuse sometime during their lifetime. This is an important finding because substance abuse is associated with a significantly poorer prognosis. In addition, it was noted that a large subset of individuals with bipolar disorder also meet criteria for panic disorder, obsessive-compulsive disorder, borderline disorder, generalized anxiety disorder, and schizoaffective disorder.

Neuropsychological Models

Precise neuropsychological models of bipolar disorder are yet available (Reiser and Thompson, 2005). According to Reiser and Thompson (2005), there are several factors that contribute to the diagnosis of bipolar disorder; including biochemical, genetic, psychodynamic, and environmental elements. It is known that treatment for bipolar disorder is complex and difficult. In part, because so many different classes of medications have been used in attempts to control symptoms of this illness (including anti-psychotics, anticonvulsants, mood stabilizers, and antidepressants), it has been difficult to develop a model that is specific enough to shed light on critical anatomical and physiological factors that underlie this disorder.

Genetics

In the past three decades, there has been compelling evidence to implicate biological mechanisms in the development of bipolar disorder; for instance, genetic components that appear to interact with stressors found in the environment to precipitate the onset of cyclical mood swings characterizing bipolar disorder (Reiser and Thompson, 2005). Glahn, D.C., Bearden, C.E., Niendam, T.A., & Escamilla, M.A. (2004), concur, noting that epidemiologic studies have shown that bipolar disorder is substantially heritable. At the current time, it is not known which of many candidate genes for bipolar disorder are associated with the neurocognitive

endophenotypes for this illness.

Specifically, family, twin, and adoption studies strongly suggest that bipolar disorder has a genetic component. First-degree relatives of people with bipolar disorder are about 7 times more likely to develop this disorder than the rest of the population (Soroff and McInnes, 2004).

Bipolar I disorder is especially noted to have a genetic component. The role of genetics in bipolar disorder takes several forms. First-degree relatives of individuals with Bipolar I are about 7 times more likely to develop this disorder than is the population at large. In addition, evidence shows that offspring of a parent with bipolar disorder have a 50% chance of having some other kind of major psychiatric problem (Soroff and McInnes, 2004).

Twin studies evidence a concordance rate of 33 – 90% for Bipolar I disorder in identical twins. A common environment is not the only factor that makes this disorder occur in families. Adoption studies show that offspring whose biologic parents have a major depressive, Bipolar I or Bipolar II disorder remain at increased risk to develop an affective disorder, even if they are raised in the home of parents who adopted them and who are not affected by any of these conditions (Soroff and McInnes, 2004).

There are many genetic studies regarding Bipolar I disorder that suggest genetic loci, but definitive identification of genes has not occurred yet. This seems to be the case because there are no objective ways to identify a specific genetic subtype and it appears that many genes probably contribute. Studies are continuing and Soroff and McInnes (2004) optimistically state that statistical and technological advances may lead to major breakthroughs in the next decade.

Research has recently shown that schizoaffective, schizophrenic, and mania share common risk factors and there is a shared genetic liability for schizoaffective disorder. This understanding suggests that there is an independent genetic liability for psychosis that is shared by both schizophrenia and mood disorders (Cardno, A.G., Rijdsdijk, F.V., Sham, P. C., et al., 2002, paraphrased in Soroff and McInnes, 2004). Soroff and McInnes (2004) state that relatively new discoveries regarding psychiatric genetics are likely to lead to future revisions of the DSM-IV-TR based on a foundation that is etiological rather than a descriptive.

Biochemistry

According to Sassi and Soares (2002), the etiology and pathophysiology of bipolar disorder have not been identified. Thus far, there are no objective biological markers existing to correspond with the illness definitively.

There are multiple biochemical pathways that are likely to contribute to bipolar disorder making the detection of one particular abnormality difficult. There have been a number of neurotransmitters linked to this disorder based primarily on people's responses to psychoactive substances. For example, the blood pressure drug reserpine, which slows the transmission of catecholaminergic agents, was identified incidentally to cause depressive symptoms. This led to the hypothesis that a decrease in epinephrine and norepinephrine causes depressive symptoms and an increase in epinephrine or norepinephrine causes mania. Acting on this neurotransmitter system, drugs such as cocaine have been found to exacerbate mania. L-dopa also exacerbates mania. These findings involve dopamine and serotonin-reuptake inhibitors, which in turn, implicates serotonin. Also, appearing to disrupt the calcium regulation in neurons, calcium channel blockers have been used to treat mania. This hypothesized disruption of the regulation of calcium may be caused by a variety of neurologic insults such as ischemia or excessive

glutamnergic transmission. It is interesting to note that valproate specifically up-regulates expression of a calcium chaperone protein, GRP 78, which may be one of its major mechanisms for protection of cells (Soreff and McInnes, 2004).

Findling, Kowatch and Post (2003) note that serotonin is one of many cellular neurotransmitters that aids in sending electrical messages from one cell to another cell. In other words, chemical transmitters like serotonin (5-HT) are released via an electrical impulse into the space between cells (synapse). Binding to a receptor site on the second cell, 5-HT is associated with the activation and subsequent firing on the second neuron. It has been postulated that a deficiency of serotonin is a vulnerability factor in the development of affective disorders as well as the increased impulsivity that is associated with suicide attempts and completed suicides.

These authors also described the Serotonin-permissive theory that holds that a relative deficiency of 5-HT results in depression and forms the basis for the mood over-swings found in mania. Supporting this theory has been experience with serotonin-selective re-uptake inhibitor (SSRI) antidepressants medications, which increase the concentration of serotonin in the synapse by inactivation of serotonin or prevention of re-uptake of the substance. This process, in turn, makes 5-HT available for a longer time to act on the post-synaptic receptors. A tryptophan depletion test has recently been used to implicate serotonergic mechanisms in unipolar depression. When adults are given a diet amino acid deficient in tryptophan (which is a precursor to serotonin), and then to an SSRI, their mood is worsened transiently for several hours. This finding suggests that if serotonin production is blocked because of transient brain tryptophan deficiency there is an associated lowering of mood (Kindling, Kowatch and Post, 2003).

Cells found in the brain stem and midbrain, responsible for producing catecholamines (transmitters dopamine and norepinephrine) are thought to be deficient in depressive symptom and excessive in mania. This theory has been supported from a biochemical perspective through mechanisms of action of drugs. For instance, the major tranquilizers or neuroleptics (antipsychotic drugs) that block the actions of dopamine at the receptor are the treatment of choice for the psychosis of schizophrenia and for mania. Furthermore, blocking the synthesis of norepinephrine and dopamine is associated antimanic effects. Also found directly in adult manic patients have been excesses in norepinephrine in the spinal fluid (Kindling, Kowatch, and Post, 2003).

Molecular genetic studies of the pathophysiology of bipolar disorder have demonstrated that two chemically unrelated drugs used to treat this disorder, valproate and lithium, both up-regulate the expression of the cytoprotective protein bcl-2 in the hippocampus and frontal cortex of rat brains. In addition, neuroimaging studies of people with mood disorders, including bipolar disorder, show evidence of a connection to the same brain regions. It is for this reason that researchers suggest a possible cause of this disorder to be abnormal programming of cell death, or apoptosis, in brain circuitry that is critical for regulating emotion. This hypothesis suggests that antidepressants and mood stabilizers may change mood by stimulating survival of cell patterns and increasing amounts of neurotrophic factors to improve the resiliency of cells (Soreff and McInnes, 2004).

Reiser and Thompson (2005) report that the most consistent information identified through summarizing bipolar disorder research supports the amine hypothesis, since that medications leading to excess of these neurotransmitters have been associated with savings to mania. Lack of these neurotransmitters is thought to lead to depression. However, this model alone has not been sufficient to establish a treatment regimen effective in preventing recurrence or relapse of bipolar disorder.

Symptom clusters associated with bipolar disorder, based on the wide-ranging psychopharmacological treatment pathways identified in studies of drug regimens, may eventually be found to be the final common pathway of a number of different etiological agents.

The biological approach to the treatment of bipolar disorder is important despite its complexity. Lack of knowledge highlights the challenges confronted by clinicians who need to find medication combinations that are most effective for each of their patients (Reiser and Thompson, 2005).

Various studies exploring psychopharmacological treatments, however, have shed some light on this confusion. Individual differences, not yet identified, may make the effects of different medications variable. Studies looking at these variable effects await further clarification. Reiser and Thompson (2005) state, "some pharmacological agents that influence different neurochemical systems seem to have similar effects, while others that may impact on one neuroendocrine system selectively in different ways (e.g., a reuptake blocker versus an enzyme inhibitor) may have totally different effects" (p. 21).

Findings that medications like antidepressants, physostigmine, and reserpine modulate emotion have contributed to speculation regarding how receptor signaling disturbance and neurotransmitters produce or ameliorate symptoms of mania or depression (Sassi and Soares, 2002). There appears to be no single class of medication that is effective in all cases of bipolar disorder. Even lithium has been effective in less than 50% of people receiving it as treatment (Reiser and Thompson, 2005).

Also noted by Sassi and Soares (2002), the receptor and neurotransmitter abnormalities identified over the years do not completely explain the complex clinical presentations of disorders of mood. More recently, research focus has shifted to the transcription factors and to the potential role of second, third, and fourth messengers in the pathophysiology of bipolar disorder, as well as action mechanisms of anti-mania treatments.

These authors (Sassi and Soares, 2002) explored mechanisms of cell signaling and a more detailed approach to intracellular abnormalities. The following areas of research are currently under investigation: levels of norepinephrine and its major metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG), in the urine, plasma and cerebrospinal fluid of people with bipolar disorder; activity of dopamine that originates from mesocorticolimbic neurons linked to motivational and reward behavior; serotonin and its relationship to mood abnormalities; GABA, which is used by at least one-third of all synapses in the human brain and mediates neurotransmission in key locations involved in affect regulation, such as the cerebral cortex, globus pallidus, and striatum through interneuronal synapses; G proteins and intracellular messengers*; and evidence of membrane dysfunction in peripheral tissues of people with bipolar disorder. This refers to the effectiveness of receptor-neurotransmission coupling in creating a unique cellular response, relying heavily on the ability of a transduction system to translate membrane signaling intercellularly.

While the complexity of this research is too detailed to explore adequately in this paper, suffice it to say that there are many hopeful leads developing in efforts to improve our understanding of bipolar disorder. For example, to name a few intriguing findings, postmortem studies of G protein levels in brains of patients with bipolar disorder have shown abnormalities such as increased amounts of specific subunits of G protein in the occipital, temporal, frontal lobes, caudate nucleus and hippocampus. There is compelling evidence suggesting abnormalities in G protein concentrations and function and in protein kinase in people with bipolar disorder as well. In addition, a hyperfunctional state in the phosphatidylinositol pathway is suggested during the

manic state, which could be reversed with lithium treatment or mood normalization. Several transcription factors have been identified thus far. They play crucial roles in the effectiveness of the long-term effects of mood stabilizers and antidepressants.

*Defining the limits of all cells and playing a critical role in neurotransmission is the phospholipid membrane bilayer of cells. G proteins, ion channels, receptors and transporters are found within this membrane.

Neuroendocrine / Hormones

Also contributing to the clinical understanding of bipolar disorder are findings of hormonal imbalances and disruptions of the hypothalamic-pituitary-adrenal axis involved in the stress response and homeostasis. It has been demonstrated that people who are depressed consistently secrete too much cortisol (the adrenal stress hormone) during episodes of depression. This over-secretion normalizes with recovery. Apparently if one gives dexamethasone (a synthetic steroid) to volunteers who are not depressed, cortisol production in the adrenal system will completely stop. This process occurs because the body sends feedback messages that circulating dexamethasone is at high levels. In contrast, 50% of people with severe depressive symptoms when given the same dose of dexamethasone, (that suppress cortisol in people without depressive symptoms) failed to suppress cortisol. This finding has become widely replicated in the clinical neuroscience of depression suggesting that there is an increased cortisol secretion in the hypo-thalamic-pituitary-adrenal axis (HPA) (Soreff and McInnes, 2004).

In some, but not all studies, it has been directly demonstrated that corticotrophin-releasing hormone (CRH) is hypersecreted in a subgroup of severely depressed patients, as measured indirectly in their spinal fluid. Therefore, an increased amount of CRH in the hypothalamus would also increase adrenocorticotrophic hormone (ACTH) secretion from the pituitary and release cortisol from the adrenal. When this occurs in Cushing's disease, the hypercortisolemia is associated with depression, cognitive impairment, and fatigue in a high percentage of patients (Soreff and McInnes, 2004).

Similarly, a disturbance of the functional endocrine system hypothesized to be related to hypercortisolemia is driven by increases in CRH. It is important to note that many effective antidepressants exert mechanisms that reverse this hypersecretion of cortisol. CRH hyperactivity or failure to normalize the dexamethasone suppression test is associated with an increased risk of relapse (Soreff and McInnes, 2004).

In depressive disorders, in addition to CRH hypersecretion, evidence suggests that there is an increase in the secretion of thyrotropin-releasing hormone (TRH), another peptide that is localized in the hypothalamus and is associated with the increased secretion of thyroid-stimulating hormone (TSH) from the pituitary. This hormone allows the thyroid gland to release T4 as well as T3. People with depression tend to hypersecrete these thyroid hormones. This process normalizes with improvement in the depressive symptoms (Soreff and McInnes, 2004).

Neuroanatomy

Bearden, C. E., Hoffman, K. M., & Cannon, T. D. (2001) state that there is no doubt that mania and depression affect one's ability to concentrate, reason, remember, and think. The extent and nature of these changes is less clear. Poorly understood is their relationship to neuroanatomical abnormalities specifically underlying a mood disorder, the etiology of bipolar disorder, and the existence of these changes before the onset of symptoms.

Bearden, et al., (2001) further report that the etiology of structural brain abnormalities commonly seen in bipolar disorder and the functional deficits that correspond to them, remain basically unknown. They think it possible that neurodevelopmental anomalies may have a role. It also remains unclear whether there is some kind of a progression that is pathophysiological in nature that occurs with repeated episodes of this illness.

Bearden, et al., (2001) noted that it appears that structural abnormalities are quite common in bipolar disorder. White matter hyper-intensities are one example of these abnormalities. These appear to be more common to mood disorders than to schizophrenia and may also be more relevant to the pathophysiology of bipolar than unipolar mood disorders.

In addition, ventricular enlargement is another structural abnormality that appears to be common to both bipolar mood disorder and schizophrenia. However, structural volumetric reduction in brain tissue does not appear to be a consistent finding in bipolar disorder as it is in schizophrenia. A recent review comparing structural imaging and post mortem neurohistological studies of schizophrenia and mood disorder report that, despite the broad overlap in structural findings, the heteromodal association cortex, the mesiotemporal structures, and the limbic system appear to be especially affected in schizophrenia. However, subtle structural abnormalities in basal ganglia structures may actually be a primary site of anatomical change in mood disorders (Bearden, et al., 2001).

Bearden, et al., (2001), discusses early cognitive findings and the laterality hypotheses. Structural anatomical findings on MRI and CT scans, specifically showing right hemisphere abnormalities, conclude that there is little compelling evidence for abnormal asymmetry or specific right hemisphere abnormalities in people with bipolar disorder. However, there was an isolated report of a smaller right hippocampal structure, however. Neuroanatomical data do not support the hypothesis of a selective right hemisphere problem in bipolar disorder.

Findling, Kowatch and Post (2003) report that biochemical and structural abnormalities have been found in depression and are associated with decreased neural activity in the frontal cortex and alterations in the function of the limbic areas of the brain. These are regions of the brain which are thought to be most intimately involved in the regulation of affect. They speculate that deficient excitation or increased inhibition may be the cause of depressive episodes while the opposite might be true for mania.

Findling et al., (2003) state there is considerable evidence linking affective disorders to alterations in the activity and size of structures found in the medial part of the temporal lobe or limbic system, such as the amygdala, hippocampus, and parahippocampal gyrus. Again, these are areas thought to be intimately involved in modulation of cognition and affect. Modern brain imaging techniques are beginning to provide evidence of limbic dysfunction that has long been postulated based on laboratory animal studies of emotions and indirect data from humans.

In addition, these authors (Findling et al., 2003) point out that an increase in the size of the amygdala in bipolar disorder has been reported by a number of investigators. Decreases in the activity and number of glial cells have also been found in the frontal cortex and related areas of the brain (for example, anterior cingulate gyrus).

Another interesting finding noted by Findling et al., (2003) is that the enzyme calcium calmodulin kinase-IIa is necessary for long-term memory and responds to calcium signals. This enzyme is apparently decreased in the frontal cortex of people with bipolar disorder compared to people without bipolar disorder. These deficits in addition to other changes might account for some of

the problems in cognition experienced by people with bipolar disorder. Also reported is the largeness of the third ventricle (in proportion to the degree of cognitive deficit) these authors note alterations in the hippocampus and anterior cingulate that appear to occur in proportion to the duration of the illness.

Sassi and Soares (2002) discuss findings from current brain-imaging and postmortem studies suggesting that there may be a mood-regulating pathway involving a prefrontal cortex-striatum-pallidum-thalamus-limbic circuit. These areas of the brain are connected via fast-conductance neurotransmitters (glutamate and γ -aminobutyric acid [GABA] and are modulated by the action of catecholamines, serotonin (5-hydroxytryptamine [5-HT]), acetylcholine (ACh), neuropeptides, and hormones. Mood disorders seem to involve abnormalities in this theorized circuit. Huntington's, Parkinson's, Fahr's disease, stroke, and closed-head injuries are some of the diseases known to affect the brain regions included in this neuroanatomic model and are often thought to lead to secondary mania or depression.

Sassi and Soares (2002) point out that evidence supports the involvement of discrete circuits in mood regulation as well as particular brain locations. More specifically, interconnecting pathways including the striatum, thalamus, pallidum, limbic structures, and the prefrontal cortex are involved. There also are specific abnormalities unique to bipolar disorder found in signal transduction pathways that include protein kinase activity, G protein levels, intracellular messengers, and gene expression.

Disruptions in Circadian Rhythms

It is thought by several researchers (Frank, et al., 2000; Lam, Jones, Hayward, and Bright, 1999) that the main biological pathway to this disorder is through disruptions in the person's (with bipolar disorder) circadian rhythms. People with bipolar disorder are thought to be particularly sensitive to these kinds of disruptions. This concept claims that social routines such as eating, sleeping, and periods of activities aid to "entrain" circadian rhythms (Malhoff-Schartz et al., 1998, p. 702.). The greater the disruption in one's regular activities, the more likely that a person with bipolar disorder will become detached and dysregulated from their normal circadian rhythm. Frank, Hlastala, Ritenour, Houck, Tu, Monk, et al., paraphrased in Reiser and Thompson (2005) report that social routine disrupting events were associated strongly with the onset of mania. For people with this kind of vulnerability, instability in circadian rhythms is not self-correcting as it is for populations that are not vulnerable. Disruptions frequently lead to increasing disentrainment or desynchronization of the sleep/wake cycle, this then leads to somatic symptoms which eventually leads to the onset of a depressive or manic episode (Ehlers, Frank, and Kupfer, 1988; Frank et al., 1997; Frank, Swartz, Mallinger, Thase, Weaver, and Kupfer, 1999 paraphrased in Reiser and Thompson, 2005).

Psychodynamic

Psychodynamic clinicians commonly understand the dynamics of this disorder as follows: depression is seen as the manifestation of losses (sense of worthlessness and loss of self-esteem). Mania therefore serves as a defense against the feelings of depression. Melanie Klein was one of the major authors of this formulation (Soreff, et al., 2004).

Assessment Findings

In conjunction with brain imaging techniques, neuropsychological tests are increasingly being used as aids to improve our understanding of cognitive impairments as they may relate to

treatment and rehabilitation in psychiatric disorders. Neuropsychological assessment is particularly important for people with bipolar disorder (Bearden, et al., 2001).

Bearden, et al. (2001), noted that while there is little evidence to support right hemisphere dysfunction, significant cognitive impairment may be present in bipolar illness, particularly in the subgroups of multiple-episode, chronic or elderly people. A toxic disease process and the functional correlates of these problems may be white matter lesions based on “signal hyperintensities” in the basal ganglia and frontal lobes. These are the regions of the brain that are critical for learning and memory, executive function, attention, affect regulation, and speeded information-processing. This hypothesized neural correlate of cognitive dysfunction in bipolar disorder is speculative. However preliminary evidence from functional neuroimaging supports frontal and subcortical hypo-metabolism abnormalities in bipolar disorder.

According to Malhi, G.S., Ivanovski, B., Szekeres, V., and Olley, A. (2004), there have been relatively few studies that have attempted to uncover the neuropsychological profile of people with bipolar disorder. In addition, few studies have examined bipolar II issues specifically. Most researchers have looked at bipolar I, with some people exploring a mixture of bipolar I and bipolar II. Differentiating state-specific neuropsychological limitations that successfully partition hypomania, euthymia, bipolar depression, and mania is likely to be useful in understanding bipolar disorder II. Neuropsychological deficits found in hypomania, mania, bipolar depression, and euthymia are likely to provide important insights into the pathophysiology of bipolar disorder and may, eventually, distinguish more clinically meaningful subtypes (Malhi, et al., 2004).

In addition, it has been pointed out that there are too few neuropsychological studies that are longitudinal (conducting research designs across specific phases of bipolar disorder) and current neuropsychological tests are likely to have difficulty identifying the “real-world” subtle deficits in neurocognitive functioning experienced by people with bipolar disorder. For all of these reasons, these authors say that the clinical impact of the neurocognitive profile of bipolar disorder is hard to measure and is, as yet, basically unknown (Malhi et al., 2004).

Due to the paucity of studies as well as significant confounds, research on the neuropsychological profile of people with bipolar disorder is relative sparse. Malhi et al. (2004) discuss limitations and confounds of this neuropsychological research reporting that the most basic problem is that these studies have not assessed subsyndromal symptoms of people they define as euthymic. Also, effects of medication (patients are rarely medication-free even when symptomatic) are not considered, and sample sizes are too small. In addition, it appears likely that neuropsychological evaluations are not necessarily confined to periods of bipolar illness and coupling results with functional and neuroimaging assessments often not done are considered important to validate bipolar disorder research.

Malhi et al. (2004), note that bipolar and unipolar depression have been thought to have similar effects on learning and cognition. However, early studies apparently were unable to separate the cognitive correlates of other psychiatric diagnoses (like schizophrenia) from depression. In general, with regard to a comparative approach across phenotypes, studies have yielded few distinguishing neuropsychological markers. This may reflect the heterogeneity of psychiatric disorders and the poor specificity of many of the neuropsychological tests that were employed.

In terms of patterns of neuropsychological impairment and severity, people with bipolar depression are not that different from people with unipolar depression. For example, executive functioning and memory are impaired similarly with both disorders and verbal learning is affected as well. Suggesting that depressed states may cause memory encoding deficits for people with

bipolar depression, are studies showing marginally more impairment on verbal recognition and recall. Verbal fluency impairment may be a measure of depression severity. Subtle differences reported suggest that bipolar depression is more likely to be associated with greater neuropsychological impairment than major depression. This is the case with immediate and delayed verbal recall, though recognition memory is largely intact in people with bipolar disorder with depression (Malhi et al., 2004).

Numerous studies have suggested that cognitive limitations in bipolar disorder primarily affect attention, memory, and executive functioning. Implicated in compromised executive domain functioning are the structures of the frontal lobe, especially the dorsolateral prefrontal cortex. This area of the brain is involved in attentional set-shifting, planning, working memory, problem solving, and temporal sequencing of information. Disrupted organization and execution of plans occurs when there is damage to this region. In addition, especially in mania, there is poor performance on measures of sustained attention associated with compromised parietal and frontal lobe functioning. Attention has been associated with many regions of the brain, including the prefrontal cortex, thalamus, anterior cingulate, and structures that are linked by "frontostriatal loops" that relate to the modulation and generation of affect (Malhi et al., 2004).

There are also deficits of learning and memory in people with bipolar disorder pointing to involvement of the temporal lobe, more specifically, the hippocampus and structures functionally related, like the thalamus. These regions of the brain as well as the ventromedial prefrontal cortex are implicated in tests of verbal fluency, self-monitoring, and inhibition. Cortical structures recruit subcortical assistance with task demand increases. The functioning of the orbitofrontal cortex is likely to be featured in the neuropsychological profile of someone with bipolar disorder. Risk-taking behavior and decision making are often affected. This is especially noticeable when decisions have an emotional component, suggesting that affective tasks influence executive functioning and producing neural interference that clinically manifests as a compromise to cognition (Malhi et al., 2004).

Bearden et al., (2002) report that while non-verbal memory, visuospatial, and abstraction skills appear to be more impaired in bipolar disorder than verbal skills (with the exception of memory and complex verbal learning), they are also more likely to be susceptible to the effects of symptoms of mood and require increased speed, attention, and speed. Verbal memory impairments are noted when people with bipolar disorder are in the midst of an affective episode and / or have longstanding illness. It also appears that the more reliable clinical decrements in performance occur in higher order cognitive functioning (flexibility, conceptual development, and abstraction), in memory functions, and in tasks requiring serial processing.

Thus far results of neuropsychological research, does not suggest a unique cognitive profile in people with bipolar disorder. The more consistent finding across studies seems to be that cognitive impairments are fewer and relatively less severe in euthymic and / or younger people, whereas studies of symptomatic, chronic elderly, or psychotic people tend to find impairments that are diffuse. Findings of persistent neuropsychological deficits in euthymic patients with longstanding illness, and the relationship of this impairment to length of illness, suggest that episodes of depression and mania may exact damage to learning and memory systems (Bearden et al., 2001).

Bearden et al. (2001), summarize that deficits of performance on neuropsychological tests seem to be more consistent with impairment of subcortical and frontal-temporal systems rather than with selective underlying right hemisphere impairment. Results vary across studies greatly due in part to the heterogeneity is same populations. People studied with bipolar disorder differ widely

also in medication status, mood state at time of testing, diagnostic category (e.g., bipolar-I versus bipolar-II, rapid-cycling, psychotic features), severity, chronicity of illness and age.

Future studies of bipolar disorder and cognitive function must carefully consider these methodological issues to clarify whether people with bipolar disorder show a significant decline in cognitive function over the course of illness, whether such impairments are limited to a subgroup of people, and whether there is a specific pattern of cognitive deficit (Bearden et al., 2001).

Differential Diagnoses

Swann (2002) noted that depression is responsible for much of the suffering that is associated with bipolar disorder and yet its role in the illness is not well enough understood. He feels that many of the unresolved problems with diagnosis involve depression. He identifies the concern that there are bipolar-disordered individuals who have experienced only the depressive episodes (but not yet the manic or hypomanic). This awareness has some larger practical diagnostic and treatment implications, since "antidepressant" medications may have effects that are deleterious in at least some people with bipolar disorder.

In addition, Swann (2002) suggest that the specificity of the relationship between temperament and other aspects of bipolar disorder is not yet understood. For example, temperament may be something which interacts with bipolar disorder, but is inherited independently. Alternatively, temperament may represent a useful indicator of genetic predisposition.

Summarizing the state of the knowledge about bipolar disorder, he believes that a number of features of bipolar disorder that are not fully appreciated, including the following (Akiskal, 1989, 2001, paraphrased in Swann, 2002):

- a. Many clients with bipolar disorder have never been manic.
- b. Bipolar I and bipolar II disorders appear to be basically different types of illness and can greatly differ in terms of their course. For instance, bipolar I is known to have more severe manias than bipolar II, and Bipolar II is known to have a more severe course. Also, depressive episodes associated with bipolar II disorder have psychotic features and can be very severe is not emphasized enough.
- c. Swann (2002) says that depression and mania can have mixed features. He adds that it is "absurd" that the DSM-IV-TR supports the notion that mixed states are a possibility only in bipolar I disorder (p. 63).
- d. Multiple interviews are needed in order to make a diagnosis of bipolar disorder rather than a structured single interview. In addition, evaluation and management should be measured longitudinally. In order to these a feature of research, it is required that changes be made in statistical design of studies and that assumptions regarding evaluation and treatment need revision.
- e. Contrary to the DSM and ICD systems, pharmacologic hypomania is "almost surely bipolar disorder" (p. 63).

Swann (2003) further summarizes his view in the following statement: "Perhaps a more pragmatic and descriptive system could be devised using a multi-axial approach, possibly based on a. temperament, b. cyclicity / course, c. intensity or type of episodes. We will ultimately need

a system that can be validated by objective physiological measures. Until that (probably distant) goal is achieved, better understanding of bipolar disorder will depend on rigorous clinical description and logic" (p. 63).

The following descriptions of differential diagnostic considerations are based on the work of Reiser and Thompson (2005) utilizing DSM-IV-TR categories:

Differential Diagnosis of Bipolar I and II Disorders versus Major Depressive Disorders: Reiser and Thompson (2005) note that major depressive disorder (MDD) is not readily identified or easily differentiated from bipolar I and II (BD I and II), despite the fact that it appears as if they should be easily distinguished. These authors add that this area of differential diagnosis is likely to account for the most significant and serious problems encountered in terms of improper treatment due to misdiagnosis. The implications for treatment with regard to these differential diagnostic problems are extremely significant because prescribing an antidepressant to a person with bipolar I or II, while in an episode of depression, without a mood stabilizing medication, increases the probability of actually inducing an episode of hypomania or mania.

Since a large number of clients with bipolar I or II present initially in the depressive phase and because the majority of people with bipolar I or II have significant periods of depression that occur between hypomanic, mixed or manic phases, misdiagnosis is common. Clients who are in a current depressed state frequently under-report past histories of both hypomania and mania. For this reason, very careful history-taking is in order. It is recommended that history be supplemented by family members and others' significant to the client, to make a proper and accurate diagnosis. In addition, because of the cyclical and chronic nature of disorders of mood, a cross-sectional approach for assessment is less valid than a longitudinal one.

Differential Diagnosis of Bipolar I Versus Bipolar II Disorder: When a person presents during a hypomanic or manic episode, it is relatively easy to make a correct diagnosis. This is so because of the likelihood that there will be psychotic features associated with mania or marked impairment. Frequently however, clients present in a state of depression and accurate information regarding hypomania or mania needs to be developed through history (from significant others, family, previous records of treatment).

Differential Diagnosis of Bipolar I Disorder Versus Psychotic Disorders (Schizoaffective Disorder, Schizophrenia, and Delusional Disorder)

Both psychotic disorder (PD) and bipolar I patients (BD I) have persecutory and/or grandiose delusions. They also can be extremely disorganized in their thinking, with loosened associations. Both diagnoses include high irritability, agitation and the possibility of symptoms of catatonia. Distinguishing features between these two diagnoses are the following: PD clients are less likely to have mood-related symptoms than BD I; between episodes, psychotic symptoms in the absence of a mood disturbance, are less likely with BD I; a higher premorbid level of functioning is more common with BD I clients; BD I clients more precipitously lapse into an episode than PD; and BD I clients are more likely to have relatives with BD I or II. It is important to take a careful history and evaluate symptom changes across time to distinguish between these two diagnoses when considering differential features (Reiser and Thompson, 2005).

Differential Diagnosis of Bipolar Disorder (Current Episode Manic or Mixed) Versus Substance-Induced Mood Disorder

Both of these diagnostic categories display symptoms of mania, but mood disorder exclusively is

associated with intoxication from alcohol or substances like inhalants, anxiolytics, hallucinogens, or amphetamines, or a mood disorder occurs within 1 month after withdrawal from the use of any of these substances.

Differential Diagnosis of Bipolar I and II Disorders Versus Borderline Personality Disorder

Clients with BD I and borderline personality disorder (BPD), share characteristics of impulsivity, significant periods of symptoms of depression, and primary difficulty with regulation of emotions. Misdiagnosis of clients with bipolar disorder with inappropriate and overdiagnosis of BPD, occurs commonly when there is rapid cycling (more than four mood episodes in a year). A differential diagnosis should be avoided during an acute episode because there is overlap between BPD and BD I and II in the following areas: intense anger (occurs mostly during manic phase); suicidal ideation (occurs mostly during depressed phase); and impulsivity and reactivity. BPD, like all other personality disorders, is characterized by a pattern of behavior that begins typically with an early onset (adolescence or young adulthood) and has a course that is long-standing.

Differential Diagnosis of Bipolar I and II Disorders Versus Attention Deficit Disorders

There appears to be a significant overlap between attention deficit with hyperactivity disorder (ADHD) and BD criteria, involving distractibility, impulsivity, and hyperactivity (Kend and Craddock (2003) in both the ICD-10 and the DSM-IV-TR. According to Reiser and Thompson (2005), items that are non-overlapping and are typically used to discriminate between these two disorders are often associated with symptoms that are mood-related and associated with inattention. Clients with BD I or II frequently have ideas of grandiosity and inflated self-esteem. They also frequently experience rapid flight-of-ideas trivializing requirements for attention to daily routines and a decreased need for sleep. On the other hand, clients with ADHD have problems with sustaining attention even with high priority tasks and they are often inattentive without expansiveness.

Differential Diagnosis of Bipolar I and II Disorders Versus Antisocial Personality Disorder

During mania, a client may behave in ways that are foolish, reckless, and cause family members and/or significant others to be upset. He/she may become involved excessively in pleasure-seeking behaviors such as sexual indiscretions, gambling, etc. Antisocial personality disorder should not be diagnosed when the antisocial behavior occurs exclusively during the course of a manic episode. The indifference or lack of remorse that characterizes antisocial personality disorder can be contrasted with the extreme guilt, regret, and remorse that people with BD I or II typically feel at the end of a manic episode.

According to Findling, Kowatch, and Post (2003), there are several general medical conditions that can mimic symptoms of psychosis, depression, and mania. These conditions include infectious diseases, neurological conditions, metabolic disorders (most particularly those diseases that involve the adrenal, parathyroid, and thyroid glands), and medications (especially antidepressants and stimulants). Because of the possibility of a medication-related or general medical disorder, these conditions should always be considered when symptoms of bipolar disorder are identified.

* See Appendix 2 for differential diagnosis of bipolar disorder versus other diagnoses.

Neurodiagnostic Findings

Advances in cognitive neuropsychology and brain imaging techniques have created new possibilities for the in vivo study of the pathophysiology of neuropsychiatric disorders, including bipolar disorder. Recently, these studies have been extended to pediatrics (Caetano, Olvera, Glahn, Fonseca, Pliszka, and Soares, 2005).

Sassi and Soares (2002) noted that alterations in the temporal lobe, basal ganglia, and cerebellum were found in the first studies performed with computed tomography (CT) in bipolar patients. MRI studies found abnormalities in specific sub-areas of the frontal lobe (decreased prefrontal cortex in manic subjects and decreased gray matter content in the subgenual prefrontal cortex) in people experiencing depressed unipolar and bipolar disorders with a family history of affective disorders.

Conclusive evidence of generalized brain atrophy has not been demonstrated in most studies of mood disorders. Evidence was found for increased ventricular enlargement in people with mood disorders in a meta-analysis of the literature. The effect size was small in magnitude but statistically significant. This postulated difference in cerebral volume healthy people and between people with mood disorders has not been confirmed in most controlled studies conducted to date (Sassi and Soares, 2002).

Haldane, M. and Frangou, S. (2004) report that with the development of Magnetic Resonance Imaging (MRI) neuroimaging methods are allowing exploration of the neurocircuitry involved in bipolar disorder. This ability has encouraged further neuropathological investigation of the brain. Magnetic Resonance Spectroscopy and structural MRI studies suggest that abnormalities of the brain found in bipolar disorder are mostly regional, as cerebral white and gray matter and ventricular volumes do not seem to be affected in the majority of people with this disorder. The amygdala and prefrontal and anterior cingulate cortices are implicated consistently in bipolar disorder. Evidence for hippocampal involvement is not as convincing. It has been shown through functional studies that activity of the anterior cingulate and dorsal prefrontal cortex are associated closely with symptoms involving mood. Activity in the ventral and orbital prefrontal cortex appears to be reduced both during episodes and in remission. Amygdala activity shows a persistent increase, in contrast. These authors suggest that there is an abnormal interaction between the ventral/orbitofrontal cortex that may be a central feature of the pathophysiology of bipolar disorder.

Findling, et al. (2003) report that a large number of studies have shown that people who are experiencing depression, have decrements in either metabolism or blood flow in the frontal cortex. This decrement is often in proportion to the severity of depression as it is rated on the Hamilton depression scale. This deficit is reported to normalize in many instances on recovery from depression.

Caetano, Olvera, Glahn, Fonseca, Pliszka, and Soares (2005) state that magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI) studies suggest that there are abnormalities in the frontolimbic structures in pediatric bipolar disorder. This is similar to adults, with the notable exception that in pediatric cases, there are smaller amygdala volumes compared to controls of healthy individuals. This finding is contrary to what has been reported in most studies of adults. Future research assessing adolescents and children is suggested to study normal neurodevelopmental processes and to answer questions regarding when and how this illness developmental pattern results in bipolar disorder and exert their effects on the developing brain.

Sassi and Soares (2002) note that glucose metabolism and brain blood flow studies in people with mood disorders have found similar patterns of abnormalities in bipolar and unipolar mood disorders. These primarily involve the limbic, subcortical and the prefrontal cortical structures (Soares and Innis 2000). Hypofrontality is shown in most PET cerebral blood flow and glucose metabolism and single photon emission computed tomography (SPECT) studies of people with bipolar disorder. This has been similarly reported in people with unipolar disorders. People with bipolar disorder frequently have abnormalities in the areas of the temporal lobe blood flow. Similar findings have occurred in reports of unipolar disorders. A recent study on unipolar and bipolar depressed people found that there was a positive correlation between severity of depressive symptoms and blood flow in the amygdala. There was a subsequent decrease in blood flow noted after treatment with antidepressants. In unipolar depression, decreases in glucose utilization and blood flow have been observed in the basal ganglia, primarily in the caudate.

Bearden et al. (2001) stated that some lateralized abnormalities in brain function that appear to fluctuate with mood state and to be highly state-dependent are shown on functional neuroimaging data (PET). This finding is consistent with earlier studies of lateralization of function in bipolar disorder and suggests that the lateralization abnormalities may be state-dependent and highly variable. It is possible that findings of laterality, while speculative, may reflect a state-dependent neurotransmitter imbalance that fluctuates with mood state, whereas reflected in disruptions in frontal-subcortical systems (possibly mediated by white matter hyperintensities) are other more enduring cognitive deficits.

According to Malhi, G.S., Ivanovski, B., Szekeres, V., & Olley, A. (2004) structural neuroimaging studies of people with bipolar disorder reveal enlarged lateral and third ventricles and increased white matter hyperintensities in periventricular basal ganglia, frontal lobes, and white matter. These results occur more commonly in bipolar disorder than in schizophrenia and major depression. In addition, subgenual cingulate and prefrontal volumes are decreased in bipolar disorder; however, medial temporal and subcortical, including the amygdala and basal ganglia, are actually enlarged, whereas in major depression, these structures are reduced in size. These findings suggest that subcortical structure changes are likely to be of more assistance in defining phenotypes of bipolar disorder.

Functional neuroimaging studies of bipolar disorder have basically identified the same regions of the brain thought to be strategic in the modulation and generation of mood in major depression and healthy populations. Several studies have begun to identify state- and trait- specific abnormalities as well as to implicate greater involvement of subcortical processes in both bipolar depression and mania. Of note is a study of functional magnetic resonance imaging that has examined the three phases of bipolar disorder and found state-related changes in the caudal ventral prefrontal cortex in both mania and depression, as well as trait-related abnormalities in the rostral ventral prefrontal cortex across all phases of illness. Further, the observed deficits in attentive and affective processing in bipolar disorder could be the result of frontocortical functioning that is reduced, as evidenced by increased activation of the amygdala during affect discrimination in euthymic bipolar disorder and reduced activation of the prefrontal cortex. Disruption of the cortical-subcortical neural circuits in bipolar disorder may translate into a disturbance that is affective in which people are not able identify the emotional salience of affective stimuli or regulate behavior that is emotional (Malhi, et al., 2004) .

Prognostic Factors

Bipolar disorder is a long-term illness that can be treated effectively (NIMH, 2001). Despite the fact that episodes of depression and mania come and go naturally, one must understand that

bipolar disorder is a long-term condition that has no cure at this time. Even during well time, it is recommended that people stay on their medication regimen to reduce the chance of having worsening, recurrent episodes and to keep the illness under control.

According to the National Institute of Mental Health ((2002), healthy and productive lives can be lead by people with bipolar disorder if they get effective treatment. The natural course of this disorder, without treatment, however, tends to worsen over the lifespan. A person may suffer from more frequent (rapidcycling) and more severe depressive and manic episodes over time. In most cases, the severity and frequency of episodes can be reduced with proper treatment helping people with bipolar disorder maintain a good quality of life. The course of bipolar disorder includes episodes of depression and mania that typically recur across the life span. Between episodes, NIMH says that most people with bipolar disorder are free of symptoms, but one-third of people may have some residual symptoms. They add that a small percentage of people experience unremitting, chronic symptoms despite treatment.

Reiser and Thompson (2005) state that there is " substantial evidence that psychosocial interventions when added to standard medication management can improve outcomes for patients with bipolar disorder by reducing relapses and rehospitalization, reducing both the frequency and intensity of manic and depressed episodes, increasing symptom-free survival time, and improving social skills and overall functioning and quality of life. The value of adjunctive psychotherapies is recognized in the field. These adjunctive psychotherapeutic approaches have now been demonstrated as efficacious in multiple randomized trials, and should be considered as a fundamental phase of treatment" (p. 1672). Reiser and Thompson (2004) pointe out that positive outcomes include improved social functioning, increased medication adherence, improved marital relationships, decreased number and length of hospitalizations, improved attitudes towards and knowledge about treatments, fewer relapses over extended symptom-free periods, increased work productivity, and improved sense of well-being improved family functioning.

Maj, et al. (2002), report that prognosis will be formulated usually to reflect a clinician's expectation that the course of illness will be modulated by treatment. The truth of this expectation depends on several patient factors, such as comorbid substance abuse and compliance as well as genetic factors that predict treatment response. External factors to the person with bipolar disorder have received less attention in research on outcome of treatment and course of illness. These factors might include any of the following: access to and quality of care; pharmacological treatment requiring vigilance, persistence, and empiricism (persistence in trying new approaches to treatment planning, vigilance in treating and detecting the earliest signs and symptoms of episodes, and empiricism in finding the combinations of treatments that are effective for each unique person and avoiding those medications that are deleterious); the person with bipolar disorder learns the strategic role of collaborator with the treating person; and the clinician's ability and willingness to provide vital information and create the type of relationship that is conducive to collaboration. With this clarification, prognosis in not only connected to the illness, but it is also a function of the quality of care provided.

Indicators of a better prognosis according to Soreff and McInnes (2004) include the following: late age onset, manic phases that are short in duration, few psychotic symptoms, few medical problems, and few thoughts of suicide. These authors said that patients with major depression fare better than patients with bipolar disorder and that around 50% of people with bipolar disorder will experience another manic attack within the first 2 years of the initial episode. In addition only 50 – 60% of people with bipolar I disorder and who are on lithium, gain control of their symptoms. Symptoms do not recur in 7% of these patients. 40% of people with bipolar

disorder go on to have a persistent disorder while 45% experience more episodes. Cycling between depression and mania often accelerates with age. Factors that suggest a worse prognosis include alcohol abuse, poor job history, depressive features between periods of depression and mania, male sex, evidence of depression, and psychotic features.

Treatment

Fountoulakis, Vieta, Sanchez-Moreno, Kaprinis, Goikolea, and Kaprinis (2005) stated that bipolar disorder has a complex clinical picture and treatments that are even more complex. They cite a traditional difference between academic authorities in the United States versus those authorities in Europe. In the United States, at the present time, mood stabilizing medications are favored while in Europe, the use of antipsychotic and antidepressant medications are favored.

Roth and Fonagy (2005), note that psychological interventions for people with bipolar disorder will almost definitely be adjunctive to medication treatments. Medication has a primary role for ameliorating symptoms. These authors report that prophylactic response is provided with lithium salts in about two-thirds of people with bipolar disorder. There are, however, newer mood stabilizers that may have an equivalent efficacy to lithium. Valproate and seem to prevent relapse as monotherapy, even though there is still little data from placebo-controlled randomized trials. Preventing or delaying the recurrence of depressive episodes especially, is the mood stabilizer, Lamotrigine. Other mood stabilizers, such as Carbamazepine, all of which are also anti-epileptic drugs, typically have at least some efficacy in the regulation of mood. However, divalproex sodium and lithium still remain the first-line treatment medications.

Antipsychotic drugs, especially the safer "atypical antipsychotics" such as Olzapine and especially Aripipizole clearly also have their place in regulating and treating bipolar swings. More research is needed, however, for all these pharmacological treatments (Norcross et al 2006*). Traditional antipsychotics, mainly the phenothiazines are effective, but carry a much greater risk for tardative dyskinesia than the newer antipsychotics. Note, with the possible exception of clozapine, which has its own risks, all the antipsychotics medications may sooner or later may lead to the development of tardative dyskinesia. Important to remember is that standard antidepressant medications show efficacy during depressive phases of bipolar disorder, however their use is complicated potentially by the risk of accelerating cycling or provoking a manic episode.

Roth and Fonagy (2005) report that even if a person with bipolar disorder is maintained on appropriate medication, despite its efficacy, it is estimated that between 41 – 60% of people with bipolar disorder will experience a depressive relapse or a manic episode over a 2-year follow-up period. In addition, it is estimated that between 25 and 50% of people with bipolar disorder will not adhere to their medication regimen thus reducing its clinical effectiveness. However, even with optimal treatment response and adequate adherence, the effect of medication on social functioning is frequently limited.

The efficacy of psychological interventions for people with bipolar disorder lags behind pharmacological measures. Historically psychotherapy for people with bipolar disorder was linked to therapies for a schizophrenia and, at least in part assumed to be the result of noxious developmental influences. This linkage, in part, is because both of these groups of people seem to be uniquely vulnerable to similar kinds of psychosocial stressors. Family stress increases a person with bipolar disorder's vulnerability to relapse. In addition, family members experience considerable stress related to this disorder, further complicating the stress factor for the person with bipolar disorder. Miklowitz, D., Goldstein, M., Nuechterline, K., Snyder, K and Mintz, J.

(1988) followed patients and their families post discharge from the hospital after an acute episode of bipolar illness for 9 months. These researchers used measures assessing the family's affective-style combined with a measure that estimated expressed emotion in the family. Families with high ratings on both measures showed a relapse rate of 94% while families with low ratings on both measures had a relapse rate of only 17%.

These types of findings have resulted in the place of psychoeducation and reduction of family and marital stress in the treatment of bipolar disorder. Developed also are techniques geared to help people with this disorder stabilize their lifestyle, react more appropriately to prodromal signs and cope better with specific stressors (Roth and Fonagy, 2005).

A critical areas of research with direct application to the development of effective treatments include identifying the signs and relevance of early indications of relapse. Inaccurate assumptions about exposure to stress may encourage people with bipolar disorder to take more risks with their behaviors than they can safely tolerate. Finally, there is mounting evidence of the importance of patterns of social rhythm and the sometimes devastating effect of their disruption. Regarding evidence of efficacy, the following treatment strategies are currently considered to be the most effective: psychoeducation; cognitive-behavioral therapy aimed at relapse prevention and the management of depressive symptomatology and usually combined with cognitive techniques aimed at stabilizing the person's lifestyle; interpersonal and social rhythm therapy, and family intervention, particularly for families with higher levels of expressed emotion. More specifically, treatment strategies include group therapy, psychodynamic therapy, psychoeducation, cognitive therapies, interpersonal and social rhythm therapy*, couple therapy, family-based interventions, interventions for comorbid substance abuse, and interventions for different phases of the disorder. All of these interventions show promise, however at this stage, evidence is limited by a lack of replication, small sample sizes, and poor design. Enabling more conclusive statements about the efficacy of these approaches will presumably be possible as the results of several large-scale trials already in progress in the United States and the United Kingdom become available (Roth and Fonagy, 2005).

Therapeutic cautions noted by Roth and Fonagy (2005), include the following: holding and engaging people with bipolar disorder within psychotherapy is difficult, partly due to mood lability and partly due to unstable lifestyles; sufficient therapeutic expertise is important not only to apply the therapies competently but also to create a collaborative relationship that holds a person with bipolar disorder in therapy. Attrition rates are very high for this population of people.

In summarizing treatment strategies in more depth, Roth and Fonagy (2005) state that many research trials have been small, and while there are larger trials in progress, the field needs to further develop before conclusive statements about treatment are possible. With this awareness in mind, there is evidence that psychoeducation* focusing on identifying prodromal signs is at least somewhat effective in delaying manic (not so obviously depressive) relapse. In addition, research on cognitive-behavioral techniques that use a number of approaches for preventing relapse and for managing symptoms of depression, (with both smaller and larger trials) have demonstrated that this approach yields outcomes that are superior to simple clinical management of depressive symptoms and sometimes in the reduction of bipolar episodes. Interpersonal and Social Rhythm Therapy (IPSRT) explicitly focus on stabilizing the lifestyles of people with bipolar disorder. IPSRT employs interpersonal psychotherapy (IPT) techniques to manage symptoms of depression. A single but large-scale trail showed initial results that boost positive outcomes in terms of speed of remission from an episode (bipolar) compared to clinical management. (*citation needed!!!!) Long-term efficacy is not yet known. In addition, there is some evidence of reduced rates of relapse with family interventions occurring most obviously in families who

have higher levels of expressed emotion.

Roth and Fonagy (2005) report that relapse-rate reduction appears to impact differentially on depressive or manic relapses. It is not yet clear whether this pattern is meaningful. There are only a few studies showing that significant improvement in one form of relapse can be mirrored by a trend toward improvement in the other. Differential rates of improvement for manic relapse makes sense, according to Roth and Fonagy (2005), since manic prodromes are likely to be more obvious to people with bipolar disorder and thus are acted upon more readily by significant others or themselves. Clinicians, however, are generally more familiar with the psychosocial management of depression than they are with mania. Patients are more likely to be available for the aid of interventions while in a depressed state compared to a manic one. Before drawing any conclusions regarding this issue, further trials are needed.

Special attention needs to be drawn to the notion that all therapeutic approaches to bipolar disorder require carefully constructed collaborative relationship between therapist and patient. Of particular challenge however in working with this clinical population is that at different times in a patients' clinical presentation, different clinical and pharmacological approaches to treatment are required, most especially because people are often psychologically unavailable while in a manic state. Consistency of approach may be as important as technique to outcome according to Roth and Fonagy (2005). In their view this awareness suggests the "importance of establishing a sense of shared purpose and expectation between patient and therapist that can 'bridge' necessary shifts in approach as the therapist responds to the needs of the patient (p. 149)." For these reasons it is suggested that therapies for people with bipolar disorder are better conceived as "specialist treatments" rather than as accommodating a generic approach.

*Patient education includes: an explanation of the biology of bipolar disorder hopefully promoting compliance of medication while lessening guilt feelings; information about how to monitor bipolar disorder specifically around appreciating early warning signs, reemergence, and symptoms (recognition of changes can be a powerful preventive measure); strong collaborative therapeutic alliance with therapist; dangers of stressors (identify and work with stressors for both patient and family); inform the person about relapses within the total context of this disorder; individual stories may help families and patients (Soreff, et al., 2004). See Appendix IV.

*Reiser and Thompson (2005) described Interpersonal and Social Rhythm Therapy (IPSRT), as a treatment with goals to help people with bipolar disorder stabilize their interpersonal and social routines and to minimize or avoid potentially disruptive circumstances or events that are likely to impact their stability. See Appendix IV.

Other Relevant Issues

Approximately half of the people with bipolar disorder have comorbid drug or alcohol abuse at some time in their lives. Substance abuse is associated with a significantly poorer prognosis. In addition, a large subgroup of people with this disorder also meet criteria for generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, borderline personality disorder, and schizoaffective disorder (Roth and Fonagy, 2005). Most studies of this population exclude people with substance abuse disorders with the exception of Weiss, Griffin, Greenfield, Najavits, Wyner, Sotor, et al (2000). These researchers used cognitive behavioral therapy techniques to improve relapse prevention as it related to both substance abuse and bipolar disorder. Results showed some reduction in substance abuse over a 6-month period of monitoring with improvement in symptoms of mania (not depression) occurred.

Conclusion

It would be comforting to think that one could write a conclusion to this paper. Sadly, if we ever achieve that state, it will be in the far distant future.

Bipolar illness is obviously an affliction that takes an unspeakable toll on its victims and their families. It destroys hope and assaults self-esteem. Knowledge that it can strike at any time, and can only be controlled not cured is usually progressively devastating to those who suffer from it.

And, yet, we are making progress. Its genetic, neurological, biochemical, and psychological structure, as well as its various forms and manifestations, are progressively being unraveled. Its expression, especially toward the manic pole, is distinctly more manageable than it was even ten years ago.

Clearly, if the patient can remain committed to both pharmacological and psychosocial treatment, its individual course can often be altered, at times dramatically. Complicating successful management, however, is the frequency with which its victims resort to the illusion that they have recovered and no longer require medication or psychotherapy. This illusion is assisted by the glorification of personal reality that generally accompanies mania. This commonplace clinical observation underscores the place of education and psychotherapy in any treatment regime.

To the extent that this report is dense and complex it reflects the state of the field. This is a field of medical research that is in its infancy and clearly is growing at a breakneck pace.

Engelman: Neuropsychology of Bipolar Disorder

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Appendix I: Taken Directly from DSM-IV-TR

I. Criteria for a Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood.
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms do not meet criteria for a mixed episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

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

E. The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

II. Criteria for Manic Episode

A. A distinct period during which there is an abnormally and persistently elevated, expansive or irritable mood lasting at least 1 week (or less if hospitalization is necessary).

B. During the period of mood disturbance, three or more of the following have persisted (four, if mood is only irritable) and have been present to a significant degree:

1. Inflated self-esteem or grandiosity.
2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Distractibility (attention too easily drawn to unimportant or irrelevant external stimuli).
6. Increased involvement in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.
7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The symptoms do not meet the criteria for a mixed episode.

D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm self or others, or there are psychotic features.

E. The symptoms are not due to the direct physiological effects of a substance (e.g., drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

III. Criteria for the Diagnosis of a Mixed Episode

A. The criteria are met for both a manic episode and for a major depressive episode (except for duration) nearly every day during at least a 1-week period.

B. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

C. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

IV. Criteria for the Diagnosis of a Hypomanic Episode

A. A distinct period of persistently elevated, expansive or irritable mood lasting throughout at least 4 days that is clearly different from the usual non-depressed mood.

B. During the period of mood disturbance, three(or more) of the following have persisted (fourif mood is only irritable) and have been present to a significant degree:

1. Inflated self-esteem or grandiosity.
2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Distractibility (attention too easily drawn to unimportant or irrelevant external stimuli).
6. Increased involvement in goal-directed activity (either socially, at work or school, or

- sexually) or psychomotor agitation.
7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
- C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic.
- D. The disturbance in mood and change in functioning are observable by others.
- E. The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.
- F. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Appendix II: (taken directly from Reiser & Thompson, 2005, p. 10 - 13).

Differential Diagnosis of Bipolar Disorder (BD I and II) Versus Major Depressive Disorder (MDD)

Characteristics that differ between the disorders

- Earlier age of onset (BD>MDD)
- More acute onset (BD>MDD)
- More frequent episodes (BD>MDD)
- Greater likelihood of psychotic features (BD>MDD)
- Greater likelihood of atypical features including psychomotor retardation, agitation, and hypersomnia (BD>MDD)
- Greater likelihood of history of attempted suicide (BD>MDD)
- Higher rates of family members with manic episodes (BD>MDD)
- Higher rates of other psychiatric disorders in the family (BD>MDD)
- Higher rates of co-morbid substance disorders (BD>MDD)

Differential Diagnosis of Bipolar (BD I) Versus Bipolar II disorder (BD II)

A. Common signs and symptoms

- see DSM-IV-TR tables above

B. Characteristics that distinguish bipolar I and bipolar II disorders

- Duration of current and past episodes (4 days for BD II versus 7 days for BD I)
- Severity of current and past episodes especially as indicated by hospitalization or psychotic features (BD I > BD II)
- Marked impairment during episode (BD I > BD II)
- More likely to return to baseline functioning between episodes (BD II > BD I)
- Cyclothymic temperament (BD II > BD I)
- Greater chronicity of major and minor depressive episodes (BD II > BD I)
- Higher level of co-morbid anxiety disorders (BD II > BD I)

- Longer duration of less severe episodes (BD II > BD I)
- Higher risk for suicide (BD II > BD I)
- Higher rates of psychomotor retardation, hypersomnia and weight gain during depressive episodes (BD II > BD I)

Differential Diagnosis of Bipolar I Disorder (BD I) Versus Psychotic Disorders (PD)
(Schizoaffective Disorder, Schizophrenia, and Delusional Disorder)

A. Common signs and symptoms --Grandiose or persecutory delusions and hallucinations -- Disorganized thinking – thought disorder (the accelerated thinking characteristic of mania can lead to loosening of associations and appear to be disorganized) --Irritability --Agitation -- Catatonic symptoms.

B. Characteristics that distinguish bipolar I and psychotic disorders --During the episode, prominent affective, mood-related symptoms (BD > PD) --Between episodes, continued presence of psychotic symptoms in the absence of prominent mood symptoms (PD >BD)

- Family history, first degree relative with bipolar disorder (BD > PD)
- Higher pre-morbid functioning (BD > PD)
- More likely to return to pre-morbid baseline functioning between episodes (BD > PD)
- Grossly disorganized behaviors (PD > BD)
- Insidious onset more likely (PD > BD)

Differential Diagnosis of Bipolar Disorder (Current Episode Manic or Mixed) Versus Substance-Induced Mood Disorder

A. Common signs and symptoms

These disorders may share many symptoms listed under DSM-IV-TR Criterion B for **mania**, including elevated, irritable or expansive mood; or, for **mixed episodes**, a combination of symptoms characteristic of **major depressive episodes** and **manic episodes** may be present including depressed mood, and markedly diminished interest or pleasure in all or most activities.

B. Characteristics that distinguish bipolar I and substance-induced mood disorders

Onset during substance intoxication: Mood disorder occurs exclusively in association with intoxication from alcohol, amphetamines, cocaine, hallucinogens, inhalants, phencyclidine, sedatives, hypnotics, other anxiolytics; or unknown substances.

Onset during substance withdrawal: Mood disorder occurs within 1 month of withdrawal from alcohol, amphetamines, cocaine, hallucinogens, inhalants, phencyclidine, sedatives, hypnotics, other anxiolytics; or unknown substances.

Appendix III: Summary of Neuropsychological Assessment Findings -(one source)

Quraishi and Frangou (2002) Intellectual function: largely preserved in bipolar disorder; impairments were limited to acute episodes and to performance scores.

Attention/Concentration: abnormalities in attention were noted in people who were symptomatic and persisted in remission in measures of inhibitory control and sustained attention.

Learning and Memory: even in people described as euthymic verbal memory was impaired.

Visuo-spatial memory: depending on task used deficits were variable.

Executive Function: all aspects of executive function (set shifting, planning, and abstract) were impaired in people with symptoms of bipolar disorder -- performance on executive function tests was sensitive to the presence of residual symptoms but it may be normal in fully recovered patients with uncomplicated bipolar disorder.

Comparison to other groups: no major differences in cognitive profile between bipolar and unipolar depression were found; stable schizophrenics out-performed remitted people with bipolar disorder on most measures of cognition but this advantage disappeared when they became acutely symptomatic.

Conclusions: People with bipolar disorder have cognitive abnormalities that are widespread. Trait related deficits appear to be present in sustained attention and verbal memory. Visual memory and executive function may be affected at least in some people who have recovered from their disorder.

Appendix IV:

Key Elements of Effective Psychoeducational Programs (taken directly from Reiser and Thompson, 2005).

- Recognize the “readiness” of the patient/family to accept treatment and modify your approach accordingly, e.g., tailor information as specifically as possible to the patient's and family's concerns.
- Emphasize a collaborative approach, helping patients and family members become actively engaged in treatment.
- Enhance medication compliance by focusing on identifying specific beliefs and concerns that might interfere with treatment and developing concrete, specific behavioral strategies for daily compliance.
- Help patients monitor their activity and sleep levels and encourage a regular schedule.
- Help patients develop effective self-management skills, including:
 - managing stressors effectively
 - identifying warning signs of new episodes
 - developing specific coping skills
 - formulating a relapse plan

Key Objectives of Interpersonal and Social Rhythm Therapy (Adapted from Frank et al, 1999 by Reiser and Thompson, 2005).

- Helping patients recognize the relationship between mood and life events
- Helping patients manage stressful life events
- Assisting patients in stabilizing disrupted social rhythms
- Addressing medication noncompliance
- Focusing on the impact of the illness in terms of loss, grief over lost roles, and role transitions
- Addressing interpersonal difficulties and deficits in social skills

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