2012

Can a Diagnosis Be Epidemic, with Therapeutic Efforts the Catastrophe?

Jill Littrell
Georgia State University, littrell@gsu.edu

Recommended Citation

Littrell, J. (2012). Can a diagnosis be epidemic, with therapeutic efforts the catastrophe? *Ethical Human Psychology and Psychiatry, 14*(2), 91-109. doi: 10.1891/1559-4343.14.2.91

Running Head: Bipolar

Can a Diagnosis Be Epidemic, with Therapeutic Efforts the Catastrophe?

Jill Littrell Ph.D.

Ph.D. in Clinical Psychology; Masters in Biology; MSSW

Associate Professor

School of Social Work

Georgia State University

Author Note

P.O. Box 3995

Atlanta, GA 30302-3995

404-413-1068

Fax: 404-413-1075

littrell@gsu.edu

Keywords: Bipolar I, Bipolar II, Pediatric Bipolar, Atypical Antipsychotics

Abstract

The diagnosis of Bipolar Spectrum Disorders (BSD) given for office visits has risen 40 fold for children and has risen dramatically for adults as well. Some of the growth may have been fueled by re-categorization of individuals who would previously have received diagnoses of major depression along with the widening of diagnostic criteria for BSD. Concomitant with the rise in BSD diagnoses, the number of adults and children receiving atypical antipsychotics has increased dramatically. Recent evidence finds that atypical antipsychotics cause considerable reduction in brain volume. It is thus imperative to ensure that those with diagnoses comprising BSD—Bipolar I, Bipolar II, and Bipolar Not Otherwise specified (NOS)—actually share a common etiology and are being appropriately treated. This paper reviews the history, evidentiary support, and implications associated with the expansion of the Bipolar Spectrum.

Can a Diagnosis Be Epidemic, with Therapeutic Efforts the Catastrophe?

In the years from 1999 to 2003, the diagnosis of bipolar given in office visits has increased 40 fold for children. Bipolar Disorder diagnoses have increased during the same time period for adults as well rising from 4.77% of office visits to 6.28% of office visits (Moreno et al., 2007).

Allen Frances (2009), the Chairperson of the DSM-IV, has suggested that the sharp rise in bipolar diagnoses is attributable to the manner in which criteria for the disorders were written—that it was an issue of taxonomy rather than epidemiology. Obviously, diagnostic criteria have profound implications for who is diagnosed, at what age, and whether they are treated with psychotropic medications. Because psychotropic medications carry substantial risks—if not guarantees—of side effects, those decisions must be judicious, and ever cognizant of Hippocrates' admonishment: First, do no harm. This review constitutes an audit of psychiatry's books, asking if they balance when the substantial risk of harm from such diagnoses and the regimen of medication they entail is taken fully into account.

Creation of the Bipolar Spectrum

Over the years, those behaviors categorized under the bipolar label have expanded greatly. In the DSM-II (Association, 1968), manic-depression, listed under the heading "affective psychoses", was the only bipolar type diagnosis. With subsequent editions of the DSM, new categories of affect perturbations were included in manuals. The DSM-III (Association, 1980) provided descriptions of the behaviors required to meet criteria for mixed and manic episodes. The DSM-III-R (Association, 1987) added criteria for hypomania (specified in the next paragraph). The literature recognized that some persons who had experienced an episode of depression did have periods when they were enthusiastic, energetic,

and animated to the extent that they met criteria for hypomania. Kupfer, Carpenter, and Frank (1988) had argued that such individuals, who were labeled Bipolar II, should be viewed as experiencing a variant of major depression. Dunner (1993) disagreed, arguing that since in family studies both probands with bipolar I and probands with bipolar II reported more family members with bipolar than did probands with major depression, bipolar II should be designated as a bipolar disorder. With the 1994 publication of the DSM-IV, the diagnosis of bipolar II was officially included in the manual under the heading of bipolar disorders.

The conventions for diagnosing bipolar spectrum disorders have basically been in effect since 1994. The diagnosis of bipolar I as defined in the DSM-IV-TR (Association, 2000) requires an episode of mania or a mixed episode. Mania criteria are comparatively restrictive, requiring one week of "elated, expansive, or irritable mood" with three or more of the following (or four or more of the following if irritable rather than expansive mood is present): inflated self-esteem, decreased need for sleep, pressured speech, flight of ideas/racing thoughts, distractibility, increased goal-directed activity, excessive involvement in risky but pleasurable activities. The episode must cause marked impairment in occupational activity or in interpersonal relationships. In contrast to bipolar I, bipolar II requires having experienced an episode of major depression and an episode of hypomania. Hypomania requires only four days of an elevated or irritable mood with the same number of symptoms from the above list, but with the caveat that none of the behaviors is severe enough to disrupt functioning. The need for hospitalization or psychotic features precludes a diagnosis of hypomania. Those persons exhibiting hypomania for less than four days can be diagnosed as bipolar not otherwise specified (NOS).

With the publication of the DSM-V soon approaching, arguments have been advanced for broadening the bipolar spectrum even further, adding recurrent depression without hypomania (Benazzi, 2002), irritability (Benazzi & Akiskal, 2005); agitated depression (Akiskal et al., 2000; Benazzi, Koukopoulos, & Akiskal, 2004) and borderline personality disorder (Mackinnon & Pies, 2006; Smith, Muir, & Blackwood, 2005). Even without a further loosening of diagnostic criteria, Akiskal et al. (2000) estimates that half of those now carrying diagnoses of major depression will be recast as bipolar. Studies tracking persons diagnosed with major depression over time are consistent with this estimate (Angst, Sellaro, Stassen, & Gamma, 2005; Goldberg, Harrow, & Whiteside, 2001). Zimmerman et al. (2009) in a study of a community sample of 2103 persons between the ages of 16 and 21 found that of the 23% of the sample meeting criteria for major depression, 41.4% displayed features of bipolar. In the recently published BRIDGE study (Angst et al., 2011), between 45.7 to 48.3% of those meeting criteria for major depression also exhibited "a bipolarity specifier criteria". If it can be assumed that half of persons who have experienced an episode of major depression can be more accurately diagnosed as bipolar, then the prevalence of bipolar in the population will be high indeed. Kessler et al. (Kessler et al., 2005) find that the prevalence of major depression is 23.3%, consistent with the estimate in the Zimmerman et al. study. If half of these individuals exhibit features of bipolar, potentially 11.6% of the population will be rebranded as bipolar.

The studies documenting a rise in the diagnosis of bipolar disorder in adults did not breakout which particular Bipolar Spectrum disorders were being counted. However, over the various DSM publications, the prevalence of bipolar I has remained relatively stable: both DSM-III (1980) and DSM-III-R (1987) indicate 0.4-1.2%; DSM-IV (1994) and DSM-IV-R (2000) indicate 0.4-1.6%. Although definitive conclusions cannot be drawn from the Moreno et al.

study, the expansion of individuals who are being labeled as exhibiting a bipolar spectrum disorder (BSD) may be attributable to the addition of hypomania as a diagnostic criterion. The addition of the new category is what has changed over editions of the manual. It is important to ask whether mania and hypomania reflect the same underlying etiology and therefore are appropriately treated in the same way. A related question concerns whether hypomania carries any predictive import for subsequent emergence of mania.

Evidence Suggesting Bipolar I and Bipolar II Share an Underlying Condition

A study by Shen et al. (2008) was interpreted as offering support for bipolar II being part of the same continuum as bipolar I. College students meeting criteria for bipolar not otherwise specified or bipolar II were tracked over a 33 month follow-up period. During this follow-up period, 9.4% of the 149 persons with BPII and 3.5% of the 57 Cyclothymic/BP-NOS group converted to mania while none of the normal controls experienced a manic episode.

The findings from this study deserve further scrutiny. Retrospective reports of adults with bipolar I disorder indicate that depressive symptoms are more often reported as precursors to the emergence of mania than are hypomanic symptoms (Calabrese et al., 2006). Moreover, if a young person meets criteria for major depression, the probability of a manic episode is even higher. When hospitalized young persons with depression (mean age of 23 in the study) were followed by Goldberg et al. (2001) for 15 years, an episode of mania occurred in 19% of the cases. All of the Shen et al. research participants with Bipolar Spectrum diagnoses had met criteria for major depression. Thus, depression, as opposed to hypomania, might have been the relevant risk factor driving the conversion to mania. Shen et al. did not include a sample of those who had experienced only an episode of major depression, so a comparison of whether major

depression or hypomania constituted a stronger predictor was not possible. Further, the authors did not analyze whether recurrent symptoms of depression or symptoms of hypomania were better predictors of subsequent mania.

It is also important to ask about the criteria used to identify manic attacks in the Shen et al. study. Do responses to a check list of symptoms, obtained in an interview, designate the same population as does more stringent criteria for manic episodes such as hospitalization or commitment to a state institution? The severity of the mania experienced by the college students in meeting criteria for mania was not reported; although Shen et al. indicated that 3.4% of the sample was hospitalized, which might have included hospitalization for depression. Moreover, the authors did not analyze whether antidepressants treatment was related to the experience of mania. Twenty of the 206 research participants in the Shen et al. study were receiving SSRIs, which can precipitate mania in as many as 44% of those who exhibit fluctuations in mood (Akiskal, Djenderedjian, Rosenthal, & Khani, 1977). In another publication, Alloy et al. (2009a, p. 468) acknowledged that their findings needed replication in samples with more severe Bipolar I. Findings from a study by Coryell et al. (1995), did examine whether bipolar II is a predictor of bipolar I and will be discussed in the next section.

Evidence Suggesting Bipolar I and Bipolar II Are Not Variants of the Same Underlying Condition

There is good reason to believe that bipolar I and bipolar II have distinct etiologies. First, in some genetic studies, candidate genes found to distinguish those with bipolar I fail to distinguish those with bipolar II and conversely those alleles distinguishing bipolar II are not identified for bipolar I. In reviewing studies, Vieta and Suppes (2008) conclude, “in summary, from the genetics perspective, most investigators tend to think that bipolar II breeds true (p.

166).” Second, in family association studies, probands with bipolar I tend to have relatives with bipolar I and probands with bipolar II tend to have relatives with bipolar II (Andreasen et al., 1987; Benazzi, 2004; Coryell, Endicott, Reich, Andreasen, & Keller, 1984; Coryell et al., 1989; Joyce et al., 2004). There have been a few exceptions to these findings. In the Joyce study (Joyce et al., 2004), having the same diagnoses in families as the probands was found only in relatives over 45. Both Heun and Maier (1993) and Gershon et al. (1982) found some elevation in bipolar I diagnoses in relatives of persons with bipolar II compared to persons without psychiatric diagnoses.

A third reason for believing that bipolar I and bipolar II are distinct is that people tend to stay in their diagnostic category over time. Coryell et al. (1995) tracked patients for 10 years. Few patients with bipolar II moved across categories. In fact, persons diagnosed with bipolar II were not any more likely to develop mania than were patients with diagnoses outside the bipolar spectrum. Coryell et al. concluded that bipolar II “is probably not simply a variant of bipolar I disorder or of nonbipolar disorder, but is a separate and autonomous disorder (p. 389).” The Shen et al. (2008) study of college students found evidence for conversion to mania in those with bipolar II. We have to compare the relative merits of a 10 year study with diagnosed clinical patients that did not find evidence of a crossover with a three year study with a non-clinical sample of college students responding to check-lists that did find supporting evidence. Questionnaires can be very helpful devices, and college students rewarding subjects, when, for example, personality variables are being explored. However, when asking about the natural history of disease processes, clinical samples offer more confidence that the observed phenomenon represents true pathology.

The final argument for bipolar I and bipolar II being distinct entities comes from longitudinal findings of persons with these diagnoses. In the 13 year follow-up study of persons with bipolar I and bipolar II by Judd et al. (2003), the data suggested that the disorders follow different courses. Persons with bipolar II followed a more chronic course, although the manic episodes of the persons with bipolar I were more severe. More of the persons with bipolar I (63.3%) returned to their previous level of functioning between episodes than did the persons in the bipolar II group (47.5%). The rate of anxiety disorder was higher than the general population in the bipolar II group which was not the case in the bipolar I group. Judd et al. (2003) did not take a position on whether their data supported bipolar I and bipolar II representing separate entities. They did suggest that the issue would be resolved when the alleles of genes mediating the disorder were identified. They agreed with the previously referenced position taken by Vieta and Suppes (2008),that at the present time, genetic studies favored the distinct entity point of view.

Hypomania is used as a criterion for a diagnosis of bipolar II. Unfortunately, the use of hypomania as a diagnostic criterion has also helped to obfuscate the diagnosis in children. It has fueled the explosion in the increase of children who are being diagnosed as pediatric bipolar. Its diagnostic use has been the linguistic bridge connecting bipolar I to bipolar II, the latter then being assumed to have an early form, pediatric bipolar. Without hypomania as a diagnostic criterion for bipolar II, pediatric bipolar would probably not be possible as a diagnostic category, because the natural history of classic bipolar suggests the disorder characteristically does not begin until late adolescence at the earliest.

Pediatric Bipolar

Prior to 1990, there was wide agreement that bipolar disorder did not manifest in young children (Anthony & Scott, 1960; Goodwin & Jamison, 2007; Loranger & Levine, 1978). An article by Carlson (1990) suggested that in some children bipolar disorder might emerge at a young age. Similar speculation followed in an article by Werry, McClellan and Chard (1991). Then in 1996, Biederman and colleagues published their findings that many children meet the behavioral criteria listed in the DSM for bipolar disorder. They noted the strong co-morbidity with attention deficit disorder hyperactivity and conduct disorder (Biederman et al., 1996). In 1996, bipolar disorder was the least frequent diagnosis for hospitalized children in the United States; by 2004, it was the most frequent diagnosis (Blader & Carlson, 2007). Issac (1995) claims that 50% of children receiving in-patient psychiatric treatment meet criteria for bipolar disorder.

What is surprising about the diagnosis of pediatric bipolar is the divergence from the previously assumed portrait of persons with bipolar I. Akiskal et al. (2000) describes the typical patient with bipolar as "warm, people-seeking or extroverted" and "articulate and eloquent" (p. s12). Children with pediatric bipolar exhibit poor social skills, often have few friends, are often teased (Geller et al., 2000) and achieve low scores on measures of social functioning and school achievement (Tillman et al., 2003). Adults with bipolar I disorder experience episodes of mania with the typical episodes lasting six weeks to six months (Biederman, Klein, Pine, & Klein, 1998; Goodwin & Jamison, 2007). Indeed for Kraepelin (1899, p. 269) the distinction between those with bipolar and those with schizophrenia was that between episodes those with bipolar were well functioning whereas the schizophrenics exhibited a deteriorating course. In contrast to adults with bipolar I, the children with pediatric bipolar studied by Geller's group experienced mania lasting on average 3.6 years (Craney & Geller, 2003; Tillman et al., 2003). Birmaher et

al. (2009a) report a mean duration of 123.7 weeks for the index episode. Finally, as previously mentioned, retrospective reports of well characterized persons with bipolar I concluded that their first episode of mood disorder was more often at the depressed pole and age of onset averaged 17 (Calabrese et al., 2006; Perlis et al., 2004). In children with pediatric bipolar, they are likely to display mania as preschoolers (Geller et al., 2000).

Youngstrom, Freeman, & Jenkins (2009) suggest that confidence in a childhood diagnosis of pediatric bipolar is increased if the parent also meets criteria for bipolar disorder. There is broad consensus that bipolar disorder is hereditary (Goodwin & Jamison, 2007, p. 41). Not surprisingly, the exponents of the legitimacy of the pediatric bipolar diagnosis have conducted studies examining the parents of children meeting criteria for bipolar disorder. They do find that a large number of parents meet criteria for bipolar disorder as well as meeting criteria for major depression, anxiety disorders, substance abuse and early onset of diverse symptomatology. Unfortunately, the studies do not specify whether the parents meet criteria for bipolar I or bipolar II; whether they exhibit any of the classic symptoms of bipolar I (spending sprees, grandiosity, hallucinations); or whether the parents' symptomatology ever became a focus of attention for others (Borchardt, Bernstein, & Crosby, 1995; Endrass et al., 2007; Faraone, Biederman, Mennin, Wozniak, & Spencer, 1997; Findling et al., 2005; Geller et al., 2006; Wozniak, Biederman, Mundy, Mennin, & Faraone, 1995). We can conclude from these studies that children share many behaviors with their parents. Whether the children or the parents share the same underlying etiology as classical bipolar I has not been established.

Many studies have been published examining the children of parents with bipolar diagnoses. The largest sample was studied by Birmaher et al. (2009b). Here again, the children were not divided according to type of bipolar disorder in the parent. Birmaher et al. found that

10.6% of the children met criteria for a bipolar spectrum disorder with 68% of these children reaching criteria for bipolar-not otherwise specified. The studies examining children of parents with bipolar disorder were recently reviewed (Littrell & Lyons, 2010). The findings from the studies varied according to whether they were published prior to 1990, or they were recently published, when the concept of bipolar II became more prominent. Early studies found relatively low rates (5%) of disruptive behavior and attention deficit hyperactivity disorder in children of parents with bipolar (Akiskal et al., 1985; Klein, Depue, & Slater, 1985; Laroche et al., 1987; Radke-Yarrow, Nottelmann, Martinez, Fox, & Belmont, 1992). Similarly, reviews from this period concluded that symptoms of depression were the most prominent finding (Goodwin & Jamison, 2007; Lapalme, Hodgins, & LaRoche, 1997). As studies began to include more children of parents with bipolar II, researchers noted a higher prevalence of ADHD, conduct disorder, and disruptive behavior (Chang, Blasey, Ketter, & Steiner, 2003; Hodgins, Faucher, Zarac, & Ellenbogen, 2002).

Duffy, Alda, Hajek, and Grof (2009) recently published the findings of the children of parents with well characterized bipolar I. The children in Duffy et al.'s sample conform to the previously assumed portrait of persons with bipolar: the first mood episode occurred at a mean age of 17 with none of the children meeting criteria for a DSM disorder prior to 12; episodes of depression lasted an average of 6.1 months and episodes of mania lasted an average of 1.7 months; the first episode of mood disorder was most frequently major depression. Moreover, with regard to the characterization of the first episode, Duffy et al's findings were very similar to those of Akiskal et al.'s (Akiskal et al., 1985) earlier longitudinal study of children of parents with bipolar I, from which the authors concluded, "bipolar disorder often begins insidiously in

late childhood, adolescence, and early adulthood with relatively minor oscillations in mood, most characteristically depressive in nature (p.1002)".

In psychiatry, proposals of other ways to categorize children displaying affective symptoms are available. Leibenluft (2011) reviewed the literature following children exhibiting chronic irritability. She has been an exponent of labeling children with continual, non-episodic irritability and disruptive behavior as severe mood dysregulation, although recognizing that these children currently are frequently diagnosed as pediatric bipolar disorder. Studies by Brotman et al.(2006) and Stringaris, Cohen, Pine, and Leibenluft (2009) found that continuous irritability predicted adult depression and anxiety and not the bipolar pattern. Moreover, those children with chronic irritability do not respond to treatment with lithium (Dickstein et al., 2009). With an alternative diagnosis, the rates of pediatric bipolar may decline.

It is beyond the scope of this article to discuss the various possibilities for classifying children who exhibit dysregulation in mood being considered by the DSM-V Mood Disorders Work Group (Workgroup, 2011). However, it is noted that the DSM Childhood and Adolescent Disorder Work Group has proffered the terminology of temper dysregulation disorder with dysphoria as an alternative to severe mood dysregulation (Workgroup., 2011). The workgroup has noted that alternative terminology could reopen the question of appropriate treatment for children currently labeled bipolar as "current convention renders treatment with antidepressants or stimulants relatively contraindicated without concurrent mood stabilizers or antipsychotics (p. 6)".

Creating Confusion

The combining, in some research, of the various categories aggregated together under the bipolar spectrum has not been helpful. In particular, the sharing of the term bipolar, in bipolar I

and bipolar II, implies a closer association between the two diagnoses than has been justified by empirical evidence. Specific confusion has been created by sometimes aggregating data from both persons with bipolar I and bipolar II, or not even making a distinction between the two. This could explain many of the inconsistencies in the published data.

Prior to the liberal use of the concept of hypomania in association with bipolar II, the modal picture of manic illness was relatively well defined. It was episodic with major depression occurring first. It was rare for disorder to be diagnosed before age 17 (DSM-III-R, 1987; Calabrese et al., 2006) . With the advent of bipolar II and the elevation of energetic and enthused behavior to a medical label of hypomania, these historically received views have been challenged. When criteria are changed, beliefs about natural history get revised. The big issue is whether bipolar I and bipolar II share a common etiology. As the studies reviewed here suggest, there is little empirical support for a common etiology; in fact, the bulk of the evidence supports the opposite conclusion. Yet the assumption that they are manifestations of a common brain mechanism has probably contributed to the explosion of antipsychotic medications.

The Rise in the Use of Atypical Antipsychotics

Atypical antipsychotics include risperidone, olanzapine, quetiapine, ziprasidone, clozapine, aripiprazole, paliperidone, as well as others. They are referred to as second generation antipsychotics. The first of the class, clozapine, was approved by the FDA for the treatment of schizophrenia in 1989. Others followed. The use of atypicals has accelerated rapidly since their introduction into the market. Domino and Swartz (Domino & Swartz, 2008) compared the period of 1996-1997 to 2004-2005 among outpatients receiving psychiatric care. They reported that in the earlier period 0.72% of the non-institutionalized persons in the population were prescribed atypical whereas in 2004-2005, l.17% of the non-institutionalized person in the U.S.

received atypicals. The percentage of schizophrenics being treated with atypicals remained roughly the same across the two periods. The increase was accounted for by the increased use of atypical antipsychotics for treatment of mood disorders. Whereas in the earlier period, 18% of those with a mood disorder received atypicals, in the later period 35% of those with a mood disorder received an atypical. Moreover, more youth are being treated with the atypicals, rising from 0.2% to 0.7% of American youth. Consistent with these figures, Crystal, Olfson, Huang, Pincus, and Gerhard (2009) found that from 1996 to 2006, antipsychotic treatment rates escalated from 0.21% to 0.90% of privately insured children in the United States. The rates were even higher for children in state Medicaid programs, rising from 2.7% in 2001 to 4.2% in 2004. Mojtabai and Olfson (2010), looking at office-based psychiatry from 1996 to 1997, documented the increase in the practice of polypharmacy, e.g., prescribing an atypical antipsychotic with an antidepressant. Blanco, Laje, Olfson, Marcus, and Pincus (2002) documented the increase in the use of atypical antipsychotics and valproate and the decline in the use of lithium in the treatment of bipolar disorder from 1992 to 1999.

Cause for Concern

Ho et al. (Ho, Andreasen, Ziebell, Pierson, & Magnotta) followed first episode persons with psychosis for a mean of 7.2 years, obtaining multiple high-resolution magnetic resonance scans over time. They found that after controlling for severity of symptoms, higher use of antipsychotics (both atypicals and older neuroleptics) was associated with brain tissue loss. While they noted that causal inference is not possible without random assignment and a control group, their findings are consistent with the results of studies examining the impact of antipsychotic medication in macques. The animal studies did observe random assignment and did have a control group. Konopaske et al. (2008) found a 20.5 percent reduction in astrocyte

numbers and Konopaske et al. (2007) reported a 11.8-15.2% reduction in gray matter volume in the left parietal lobes. Moreover, antipsychotics do impair cognitive function in the short term in humans (Frangou, Donaldson, Hadjulis, Landau, & Goldstein, 2005). While Ho et al. did not speculate on the mechanism behind lack of dopamine signaling and brain volume, there is a voluminous literature on growth factors released from glial cells being critical to maintain the health of the brain (Schwartz & Schechter, 2011; Ziv & Schwartz, 2008). Dopamine can induce astrocyte cells to release growth factors (Miklic, Juric, & Carman-Krzan, 2004). Reflecting on the strong possibilities that dopamine antagonists reduce brain cortex, Ho et al. raised the issue of cost-benefit analysis in the use of antipsychotics for those with affective disorders.

Other side effects of atypical antipsychotics are not trivial. The Clinical Antipsychotic Trials of Intervention Effectiveness found that the atypicals are associated with movement disorders, although perhaps movement problems are less likely than with the older neuroleptics (Casey, 2006; Manschreck & Boshers, 2007; Miller et al., 2005). In children, reports of tardive dyskinesia with atypicals have been reported (Woods, Martin, Spector, & McGlashan, 2002) and, in children, extrapyramidal symptoms with atypicals are more pronounced (Sikich, Hamer, Bashford, Sheitman, & Lieberman, 2004; Tohen et al., 2007). The atypicals are, however, most notorious for inducing weight gain (which fails to plateau), dyslipidemia, and diabetes (Ghaemi, 2008; Goodwin & Jamison, 2007).

Other pharmacological interventions for bipolar include lithium and anticonvulsant drugs. Major concerns for lithium are the kidney damage and thyroid gland dysfunction (Bendz, Aurell, & Lanke, 2001; Goodwin & Jamison, 2007; Markowitz et al., 2000). For those treated for more than 12 years, 50% of patients exhibit impaired renal concentrating ability and 20% of patients exhibit frequent urination. In a sample of 74 patients on lithium for an average of 20 years, 12

reached End Stage Renal Disease (Presne et al., 2003). Even after lithium is discontinued, kidney destruction can continue (Markowitz et al., 2000). Lithium also impairs cognitive function (Ghaemi, 2008; Silva et al., 1992).

Anticonvulsant drugs include valproate, lamotrigine, and carbamazepine. Both valproate and carbamazepine can induce depression (Boylan, Devinsky, Barry, & Ketter, 2002), and the FDA has issued a warning regarding suicidal ideation with these drugs (Administration, 2007, 2008). All the anticonvulsants disrupt cognitive functioning. There are also specific effects on other organs with these drug (Goodwin & Jamison, 2007; Loring & Meador, 2004).

Treatment of depression observed in persons carrying bipolar diagnoses has long been controversial. Antidepressant drugs are believed to induce rapid cycling, although exact prevalence may only be 20% (Benazzi, 2007; Ghaemi, Hsu, Soldani, & Goodwin, 2003). Of greater concern is the FDA warning of induction of suicidality in those with bipolarity when treated with antidepressants (Administration, 2007).

Case for early treatment. Kiki Chang and others (Chang, Howe, Gallelli, & Miklowitz, 2006; Chang & Kowatch, 2007; Chang, 2010) have been advocates of early medication of pediatric bipolar in order to prevent the emergence of full blown bipolar disorder. Their assumption is that experiencing extremes of affect operates as a kindling mechanism. The kindling hypothesis is based on the observation that giving a small amount of electrical stimulation to an animal over time will eventually elicit a seizure at a dose which would not provoke a seizure in a naïve animal. Post (2007) suggested that the course of bipolar disorder is analogous to the process of kindling in producing seizures. The experience of affective episodes changes the brain in a way that would make the occurrence of subsequent episodes more likely.

The hypothesis that more episodes of affective disorder will cause more extreme or more frequent later episodes has been criticized. It is true that duration of wellness intervals between episodes is inversely correlated with total number of episodes during the life-time (Goodwin & Jamison, 2007, p. 128). However, these findings do not necessarily imply that episodes cause a greater degree of subsequent illness. Slater (1938) as translated by Oepen et al. (Oepen, Baldessarini, Salvatore, & Slater, 2004) cautioned that persons with short cycles will have more episodes whereas those with long cycles will have fewer episodes. Aggregating across individuals will yield an inverse relationship between number of episodes and duration of wellness intervals. One must examine whether the duration of wellness shortens with the ordinal value (first, second, third) for the individual to discover whether an episode will increase the length of a subsequent episode. Goodwin and Jamison (2007, p. 152) concluded there is no consistent evidence that periods of wellness decrease as a function of the ordinal value of the episode. Moreover, Goodwin and Jamison (2007, p. 129) concluded that after the first three episodes, the frequency of subsequent episodes is fairly constant. This was consistent with the Duffy et al. (2009) observations in those children of well characterized parents with bipolar I who developed their own bipolar disorder. There was no evidence of shortening of wellness periods across the first three observed episodes.

With regard to early pharmacological treatment changing the course of the disorder, the evidence is against early treatment altering the course. Baldessarini et al. (2007) in a study of 764 adults, found that whether latency of treatment was measured as number of prior episodes or time to seek treatment after initial emergence of symptoms, latency did not relate to percentage of time spent ill during treatment or the need for hospitalization. Baldessarini et al.'s findings

were consistent with an earlier meta-analysis of 11 published studies involving over 1458 individuals (Baethge et al., 2003).

Outcomes before psychotropics compared to current outcomes: The difference a drug makes. Studies evaluating the efficacy of psychotropic medications tend to be short term (Oldham, 2011). For example, Geddes, Burgess, Hawton, Jamison, & Goodwin (2004) review of "long-term" lithium therapy examined studies with follow-up of two years. Winokur et al. (1994) conducted a naturalistic study with an unusually long follow-up period of ten years. Interestingly, in the Winokur et al. study, the authors concluded "treatment intensity was not related to decreasing episodes or to changes in cycle length". Nevertheless, for addressing questions regarding long term efficacy of pharmacotherapy, current outcomes with medications can only be contrasted with the pre-drug treatment outcomes.

Perhaps the most surprising contrast in the literature on treating persons with Bipolar Disorder is the contrast in the outcome statistics for those treated before the emergence of modern psychiatry. According to Kraepelin (1899, p. 115-116) there are patients who suffered only one episode of mania requiring hospitalization. Rennie's report (1942) on 208 patients treated between 1913 and 1916 is similarly optimistic though different in details. Ninety percent of patients recovered from their initial episode, while 21% never relapsed. Of the cases experiencing relapse, 30% remained in remission for between 10 to 20 years. Thus, 51% exhibited long term recovery. Winokur, Clayton, and Reich (1969) reviewed early studies and concluded there "was no basis to consider manic depressive psychosis permanently affected those who suffered from it (p.21)".

Outcomes from earlier studies stand in sharp contrast to the findings reported for adult bipolar patients in later years. Harrow, Goldberg, Grossman & Meltzer (1990) found that 80%

of those who recovered from an episode relapse within 1.7 years; 23% are continuously unemployed and another 35% are erratically employed. Post et al. (2003) found that 62.8% of persons experienced 4 or more mood episodes per year. Judd et al. (2002) followed persons with bipolar I for 12.8 years assessing their status on a weekly basis. They found that adult patients with bipolar I were symptomatic on average for 47.3% of the follow-up interval with only 2.1% of the sample exhibiting low levels of symptoms. Some patients (9.6%) were symptomatic during all of the weeks. Depressive symptoms occurred during an average of 31.9% of weeks; manic symptoms occurred during an average of 8.9% of weeks; and mixed states occurred during an average of 5.9% of weeks.

Scant data are available regarding the outcome of bipolar II disorder prior to the advent of psychotropic medications because the diagnosis did not exist before the drug era. Persons with bipolar II would probably be classified as depressed. Questions have been raised regarding whether antidepressant treatment contributes to chronicity in depression (Fava, 2003; Fava & Offidani, 2010).

The previously cited study by Judd et al. (2003) suggested a more chronic course for those with bipolar II than those with bipolar I. This outcome is particularly surprising given the findings on the personality characteristics of those individuals who meet criteria for bipolar II. Alloy et al. (2009a) found that college students with bipolar II are more likely to exhibit elevated scores on the Carver and White measure of the behavioral activation system (BAS) (Carver & White, 1994). Moreover, if students are selected for extreme scores on the BAS and compared to those with moderate scores, the former more often meet criteria for bipolar II (Alloy et al. 2006). There is an extensive literature on the behavioral activation system. Contrary to dysfuction, the general literature on the BAS (as measured by EEG asymmetry or scores on self-

report measures), suggests that having a strong behavioral activation system confers resilience in the face of stress (Davidson, 1998). Those who exhibit stronger left frontal brain activity, another measure of a strong behavioral activation system, are less responsive to negative events, and more responsive to positive stimuli (Davidson, 1998; Harmon-Jones & Allen, 1997; Jackson et al., 2003; Sutton & Davidson, 2000). Those who exhibit stronger left brain activity are less prone to depression (Davidson, 1998). If they do become depressed, high BAS sub-scale scores predict shorter duration of the depressive episode (Kasch, Rottenberg, Arnow, & Gotlib, 2002). Tomarken and Davidson (1994) found that repressors are high on BAS measures and repressors cope better with bereavement (Coifman, Bonanno, Ray, & Gross, 2007). In the Alloy et al. studies, although high scores on the BAS predicted hypomania, BAS scores were unrelated to subsequent depressive symptoms (Alloy, Abramson, Urosevic, Bender, & Wagner, 2009b; Alloy et al., 2008). Thus, hypomania, perhaps through its correlation with stronger BAS, may indeed reflect resilience rather than a cause for concern.

Extending the bipolar label to those meeting criteria for bipolar II implies that hypomania is an abnormal state, suggestive of illness. Benazzi (2007) acknowledges that hypomanic episodes can be productive. Johnson (2005) reviewed the many studies suggesting that those who experience hypomania are more successful in terms of occupational status than the general population. But, according to Benazzi (2007), hypomania is often rapidly followed by depressive episodes. Empirical support for this statement was based on a study by Benazzi and Akiskal (2006) of the retrospective reports of 206 patients, 80% of whom had switched poles rapidly, although the authors failed to analyze whether hypomania was quickly followed by depression or the depression was followed by hypomania. Other researchers have examined whether depression reliably follows extremes in positive mood (mania). Haag et al. (1987) failed

to find a reliable pattern in whether depressive episodes followed manic episodes within a short window of time or whether mania followed depression within a short window of time. Vieta et al. (2009) found that a switch from mania into depression within in a 12 week period in a sample of 2390 patients was a rare event (5.0%). Moreover, across studies, 25-33% of persons who have experienced a manic episode never have an episode of major depression (Karkowski & Kendler, 1997; Kessler, Rubinow, Holmes, Abelson, & Zhao, 1997). Studies examining whether depressive symptoms follow shortly after hypomania are sparse. However, the finding that periods of hypomania are common in non-clinical samples argues against hypomania operating as a precipitant to depression (Udachina & Mansell, 2007; Wicki & Angst, 1991).

Questions are Being Raised

Presently, the American Psychiatric Association is deliberating those diagnostic categories that will appear in the DSM-V. Allen Frances (2009), the Chair of the DSM-IV, has publicly raised concerns about the "unintended consequences" of the DSM-IV which resulted in an explosion of new cases of Autism, Bipolar, and ADHD. Frances is quoted by Gary Greenberg (2010), in explaining why he was moved to become a crusader, as saying ,"kids getting unneeded antipsychotics that would make them gain 12 pounds in 12 weeks hit me in the gut." Whereas Frances refers to unintended consequences of how criteria for various diagnoses were written, others suggest that the rise in the numbers being diagnosed and being treated with antipsychotics may have been intended. Senator Charles Grassley's Committee has been investigating the links between academic psychiatry and the pharmaceutical industry. Joseph Biederman, the initiating force behind the pediatric bipolar diagnosis, was found to have failed to report the extent of financial remuneration from the pharmaceutical industry(Harris & Carey, 2008). In a two part article followed by replies to letters in the *New York Review of Books*

(2011), Marcia Angell, former editor of the New England Journal of Medicine, voiced concern over the subjective nature of psychiatric diagnosis, the lack of studies on long term efficacy of pharmacotherapy, and the influence of the pharmaceutical houses on academic medicine.

Robert Whitaker (2010), a journalist, has documented the rise in the numbers of persons receiving disability on the basis of psychiatric diagnoses over the last several decades. Whitaker contrasts outcomes for various psychiatric disorders prior to drugs for the various conditions to the outcomes reported in the medication era. He accepts the arguments raised by others (Fava & Offidani, 2010) that although drugs might provide temporary amelioration, in the long run they may create a chronic course. In psychotropic drug studies, evaluation of efficacy occurs after 6-8 weeks (Jackson, 2005; Khan, Kolts, Thase, Krishnan, & Brown, 2004). Rarely are long-term outcomes of the never medicated contrasted with the outcomes of those who receive long-term treatment. Most of the drugs used to treat Bipolar Disorder impair cognitive function. In studies evaluating the efficacy of particular drugs for various disorders, the impact on target symptoms are evaluated. Rarely, are more general areas of functioning tested such as the ability to concentrate, calculate, or follow a complex argument. As important as a tranquil mood can be to daily function, these other capacities can be seen as equally integral to a person's successful functioning. Cognitive capacity is particularly important in small children who must master a great deal of material in school if they are to become productive citizens. Given the complexity of modern society and the demands to maintain a competitive workforce in the world, perhaps we need to question whether through irresponsible over-diagnosis and automatic medicating, we are in danger of producing an impaired generation.

References

Akiskal, H. S., Bourgeois, M. L., Angst, J., Post, R., Möller, H., & Hirschfeld, R. (2000). Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. *Journal of Affective Disorders, 59* (Suppl. 1), 5-30.

Akiskal, H. S., Downs, J., Jordan, P., Watson, S., Daugherty, D., & Pruitt, D. B. (1985). Affective disorders in referred children and younger siblings of manic-depressives. *Archives of General Psychiatry, 42* (10), 996-1003.

Alloy, L.B., Abramson, L.Y., Urosevic, S., Bender, R. E., & Wagner, C. A. (2009b). Longitudinal predictors of bipolar spectrum disorders: A behavioral approach system perspective. *Clinical Psychology: Science and Practice, 16,* 206-226.

Alloy, L. B., Abramson, L. Y., Walshaw, P. D., Cogswell, A., Grandin, L.D., Hughes, M. E., Iacoviello, B. M., Whitehouse, W. G., Urosevic, S., Nusslock, R., & Hogan, M. E. (2008). Behavioral Approach System and Behavioral Inhibition System sensitivities and bipolar spectrum disorders: prospective prediction of bipolar mood episodes. *Bipolar Disorders, 10*, 310-322.

Alloy, L. B., Abramson, L. Y., Walshaw, P. D., Cogswell, A., Smith, J. M., Neeren, A. M., Hughes, M. E., Iacoviello, B. M., Gerstein, R. K., Keyser, J., Urosevic, S., & Nusslock, R. (2006). Behavioral Approach System (BAS) sensitivity and bipolar spectrum disorders: a retrospective and concurrent behavioral high-risk design. *Motivation and Emotion, 30*, 143-155.

Alloy, L. B., Abramson, L. YT., Walshaw, P. D., Gerstein, R. K., Keyser, J. D., Urosevic, S., Nusslock, R., Hogan, M. E., & Harmon-Jones, E. (2009a). Behavioral approach system

(BAS)-relevant cognitive styles and bipolar spectrum disorders: concurrent and prospective associations. *Journal of Abnormal Psychology, 118,* 459-471.

American Psychiatric Association. (1980). *Diagnostic and Statistical Manual of Mental Disorders, third edition*. Washington DC: Author.

American Psychiatric Association. (1987). *Diagnostic and Statistical Manual of Mental Disorders, third edition-revised*. Washington DC: Author.

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders, fourth edition*. Washington DC: Author.

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders, fourth edition-TR*. Washington DC: Author.

American Psychiatric Association, Mood disorders workgroup. (2011). Issues pertinent to a developmental approach to Bipolar Disorder in DSM-5. 1-6. http://www.dsm5.org

American Psychiatric Association, Childhood and Adolescent Disorders Work Group. (2011). Justification for temper dysregulation disorder with dysphoria. http://www.dsm5.org

Andreasen, N. C., Rice, J., Endicott, J., Coryell, W., Gorve, W. M., & Reich, T. (1987). Familial rates of affective disorder. *Archives of General Psychiatry, 44,* 461-469.

Angell, M. (2011, June 23). Why there is an epidemic of mental illness. *New York Review of Books, LVIII* (11), 20-22.

Angell, M. (2011, July 14). The illusion of psychiatry. *New York Review of Books, LVIII* (12), 20-22.

Angell, M. (2011, August 18). The illusion of psychiatry': An exchange. *New York Review of Books, LVIII* (13), 82-84.

Angst, J., Azorin, J. M., Bowden, C. L., Perugi, G., Vieta, E., Gamma, A., & Young, A. H. (2011). Prevalence and Characteristics of Undiagnosed Bipolar Disorders in Patients With a Major Depressive Episode: The BRIDGE Study. *Arch Gen Psychiatry, 68*(8), 791-798.

Angst, J., Sellaro, R., Stassen, H. H., & Gamma, A. (2005). Diagnostic conversion from depression to bipolar disordres: results of a long-term prospective study of hospital admissions. *Journal of Affective Disorders, 84*, 149-157.

Anthony, J., & Scott, P. (1960). Manic-depressive psychosis in childhood. *Journal of Child Psychology and Psychiatry, 4*, 53-72.

Baethge, C., Tondo, L., Bratti, I. M., Bschor, T., Bauer, M., Viguera, A. C., & Baldessarini, R. J. (2003). Prophylaxis latency and outcome in bipolar disorders. *Canadian Journal of Psychiatry, 48* (7), 449-457.

Baldessarini, R. J., Tondo, L., Baethge, C. L., & Bratti, I. M. (2007). Effect of treatment latency on response to maintenance treatment in manic-depressive disorders. *Bipolar Disorder, 9*, 386-393.

Benazzi, R. (2002). Highly recurrent unipolar may be related to Bipolar II. *Comprehensive Psychiatry, 43* (4), 263-268.

Benazzi, F. (2004). Bipolar II disorder family history using the family history screen: Findings and clinical implications. *Comprehensive Psychiatry, 45*(2), 77-82.

Benazzi, F. (2007). Bipolar II Disorder: Epidemiology, diagnosis, and management. *CNS Drugs, 21* (9), 727-740.

Benazzi, F., & Akiskal, H. (2005). Irritable-hostile depression: further validation as a bipolar depressive mixed state. *Journal of Affective Disorders, 84*, 197-207.

Benazzi, F., & Akiskal, H. S. (2006). Biphasic course in bipolar II outpatients: Prevalence and clinical correlates of a cyclic pattern described by Baillarger and Falret in hospitalized patients in 1854. *Journal of Affective Disorders, 96,* 183-187.

Benazzi, F., Koukopoulos, A., & Akiskal, H. S. (2004). Toward a validation of a new definition of agitated depression as a bipolar mixed state (mixed depression). *European Psychiatry, 19,* 85-90.

Bendz, H., Aurell, M., & Lanke, J. (2001). A historical cohort study of kidney damage in long-term lithium patients: continued surveillance needed. *European Psychiatry, 16,* 199-206.

Biederman, J., Faraone, S., Mick, E., Wozniak, J., Chen, L., Ouellette, C., Marrs, A., Moore, P., Garcia, J., Mennin, D., & Lelon, E. (1996). Attention-deficit hyperactivity disorder and juvenile mania: A overlooked co-morbidity? *Journal of the American Academy of Child and Adolescent Psychiatry, 35,* 997-1008.

Biederman, J., Klein, K. R., Pine, D.S., & Klein, D. F. (1998). Resolved: mania is mistaken for ADHD in prepubertal children. *Journal of the American Academy of Child and Adolescent Psychiatry, 37* (10), 1091-1096.

Birmaher, B., Axelson, D., Goldstein, B., Strober, M., Gill, M. K., Hunt, J., Houck, P., Ha, W. Iyengar, S., Kim, E., Yen, S., Hower, H., Esposito-Smythers, C., Goldstein, T., Ryan, N., & Keller, M. (2009a). Four-year longitudinal course of children and adolescent with bipolar spectrum disorders: The course and outcome of Bipolar youth (COBY) study. *American Journal of Psychiatry, 166,* 795-804.

Birmaher, B., Axelson, D., Monk, K., Kalas, C., Goldstein, B., Hickey, M. B., Obreja, M., Ehmann, M. A., Iyengar, S., Shamseddeen, W., Kupfer, D., & Brent, D. (2009b).

Lifetime psychiatric disorders in school-aged offspring of parents with bipolar disorder. *Archives of General Psychiatry, 66*(3), 287-296.

Blader, J. C., & Carlson, G. A. (2007). Increased rates of bipolar disorder diagnoses among U.S. child, adolescent, and adult inpatients, 1996-2004. *Biological Psychiatry, 62* (2), 107-114.

Blanco, C., Laje, G., Olfson, M., Marcus, S. C. & Pincus H. A. (2002). Trends in the treatment of bipolar disorder by outpatient psychiatrists. *American Journal of Psychiatry, 159* (6), 1005-1010.

Borchardt, C. M., Bernstein, G. A., & Crosby, R. D. (1995). Psychopathology in the families of inpatient affective disordered adolescents. *Child Psychiatry and Human Development, 26* (2), 71-84.

Boylan, L. S., Devinsky, O., Barry, J. J., & Ketter, T. A. (2002). Psychiatric uses of antiepileptic treatments. *Epilepsy & Behavior, 3*(Suppl. 5), 54-59.

Brotman, M. A., Schmajuk, M., Rich, B. A., Dickstein, D. P., Guyer, A. E., Costello, E. J., Egger, H. L., Angold, A., Pine, D. S., & Leibenluft, E. (2006). Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. *Biological Psychiatry, 60*, 991-997.

Calabrese, J. R., Muzina, D. J., Kemp, D. E., Sachs, G. S., Frye, M. A., Thompson, T. R., Klingman, D., Reed, M. L., & Hirschfeld, R. M. A. (2006). Predictors of bipolar disorder risk among patients currently treated for major depression. *MedGenMED 8 (*3), published on line, retrieved 8/14/2008.

Carlson, G. (1990). Child and adolescent mania: Diagnostic considerations. *Journal of Child Psychology and Psychiatry, 31*, 331-341.

Carver, C. S. & White, T. L. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS scales. *Journal of Personality and Social Psychology, 67*, 319-333.

Casey, D. E. (2006). Implications of the CATIE trial on treatment: extrapyramidal symptoms. *CNS Spectrum, 11* (Suppl. 7), 25-31.

Chang, K. D. (2010). Course and impact of bipolar disorder in young patients. *Journal of Clinical Psychiatry, 71* (2), doi:10.488/JCP.8125tx7c

Chang, K. D., Blasey, C. M., Ketter, T. A., & Steiner, H. (2003). Temperament characteristics of child and adolescent bipolar offspring. *Journal of Affective Disorders, 77*, 11-19.

Chang, K., Howe, M., Gallelli, K., & Miklowitz, D. (2006). Prevention of pediatric bipolar disorder: Integration of neurobiological and psychosocial processes. *Annals of the New York Academy of Sciences, 1094*, 235-247.

Chang, K., & Kowatch, R. A. (2007). Is this child bipolar? What's needed to improve diagnosis? *Current Psychiatry, 6* (10) 23-33.

Coifman, K. G., Bonanno, G. A., Ray, R. D., & Gross, J. J. (2007). Does repressive coping promote resilience? Affective-autonomic response discrepancy during bereavement. *Journal of Personality and Social Psychology, 92*, 745-758.

Coryell, W., Coryell, J., Endicott, T., Reich, N., Andreasen, N., & Keller, M. (1984). A family study of bipolar II disorder. *British Journal of Psychiatry, 145*, 49-54.

Coryell, W., Endicott, J., Maser, J. D., Keller, M. B., Leon, A. C., & Akiskal, H. S. (1995). Long-term stability of polarity distinctions in the affective disorders. *American Journal of Psychiatry, 152* (3), 385-390.

Coryell, W., Keller, M., Endicott, J., Andreasen, N., Clayton, P., & Hirschfeld, R. (1989). Bipolar II illness: course and outcome over a five-year period. *Psychological Medicine, 19*, 129-141.

Craney, J. L., & Geller, B. (2003). A prepubertal and early adolescent bipolar disorder-I phenotype: Review of phenomenology and longitudinal course. *Bipolar Disorders, 3*, 243-256.

Crystal, S., Olfson, M., Huang, C., Pincus, & Gerhard, T. (2009). Broadened use of atypical antipsychotics: Safety, effectiveness, and policy challenges. *Health Affairs, 28*(5) 770-781.

Davidson, R. J. (1998). Affective style and affective disorders: perspective from affective neuroscience. *Cognition and Emotion, 12* (3), 307-330.

Dickstein, D. P., Towbin, K. E., Van Der Veen, J. W., Rich, B. A., Brotman, M. A., Knopf, L., Onello, L., Pine, D. S., Leibenfult, E. (2009). Randomized double-blind placebo-controlled trial of lithium in youth with severe mood dysregulation. *Journal of Child and Adolescent Psychopharmacology, 19*, 61-73.

Domino, M. E., & Swartz, M. S. (2008). Who are the new users of antipsychotic medications? *Psychiatric Services, 59* (5), 507-514.

Duffy, A., Alda, M., Hajek, T., & Grof, P. (2009). Early course of bipolar disorder in high-risk offspring: Prospective study. *British Journal of Psychiatry, 195*, 457-458.

Dunner, D. L. (1993). A review of the diagnostic status of "bipolar II" for the DSM-IV work group on mood disorders. *Depression, 1*, 2-10.

Endrass, J., Vetter, S., Gamma, A., Gallo, W. T., Rossegger, A., Urbaniok, F., & Angst, J. (2007). Are behavioral problems in childhood and adolescence associated with bipolar

disorder in early adulthood? *European Archives and Clinical Neuroscience, 257*, 217-221.

Faraone, S. V., Biederman, J., Mennin, D., Woizniak, J., & Spencer, T. (1997). Attention-deficit hyperactivity disorder with bipolar disorder. A familial subtype? *Journal of the American Academy of Child and Adolescent Psychiatry, 36*, 1378-1390.

Fava, G. A. (2003). Can long-term treatment with antidepressant drugs worsen the course of depression? *Journal of Clinical Psychiatry, 64*(2), 123-133.

Fava, G. A., & Offidani, E. (2011). The mechanisms of tolerance in antidepressant action. *Progress in Neuropsychopharmacology and Biological Psychiatry*, 35 (7), 1593-1602.

Findling, R. L., Youngstrom, E. A., McNamara, N. K., Stansbrey, R. J., Demeter, C. A., Bedoya, D., Kahana, S. Y., & Calabrese, J. R. (2005). Early symptoms of mania and the role of parental risk. *Bipolar Disorders, 7* (6), 623-634.

Frances, A. (2009, June 26). A warning sign on the road to the DSM-V: beware of its unintended consequences. *Psychiatric Times, 26* (8).

Frangou, S., Donaldson, S., Hadjulis, M., Landau, S., & Goldstein, L. H. (2005). The Maudsley Bipolar Disorder Project: Executive dysfunction in bipolar disorder I and its clinical correlates. *Biological Psychiatry, 58,* 859-864.

Geddes, J. R., Burgess, S., Hawton, K., Jamison, K., & Goodwin, G. M. (2004). Long-term lithium therapy for bipolar disorder: systemic review and meta-analysis of randomized controlled trials. *American Journal of Psychiatry, 161* (2), 217-222.

Geller, B., Bolhofner, K., Craney, J. L., Williams, M., DelBello, M. P., & Gundersen, K. (2000). Psychosocial functioning in a prepubertal and early adolescent bipolar disorder phenotype. *Journal of the American Academy of Child and Adolescent Psychiatry, 39,* 1543-1548.

Geller, B., Tillman, R., Bolhofner, K., Zimerman, B., Strauss, N. A., & Kaufmann, P. (2006). Controlled, blindly rated, direct-interview family study of a prepubertal and early-adolescent bipolar I disorder phenotype: morbid risk, age at onset, and comorbidity. *Archives of General Psychiatry, 63,* 1130-1138.

Gershon, E. S., Hamovit, J., Guroff, J. J., Dibble, E., Leckman, J. F., Sceery, W., Targum, S. D., Nurnberger, J. Jr. Goldin, L. R., & Bunney, W. E. Jr. (1982) A family study of schizoaffective, bipolar I, bipolar II, and normal control probands. *Archives of General Psychiatry, 39* (10), 1157-1167.

Ghaemi, S. N. (2008). *Practical guides in psychiatry: mood disorders, 2nd ed.* New York: Lippincott, Williams, & Wilkins.

Ghaemi, S. N., Hsu, D. J., Soldani, F., & Goodwin, F. K. (2003). Antidepressants in bipolar disorder: The case for caution. *Bipolar Disorders, 5,* 421-433.

Goldberg, J. F., Harrow, M., & Whiteside, J. E. (2001). Risk for bipolar illness in patients initially hospitalized for unipolar depression. *American Journal of Psychiatry, 15,* 1265-1270.

Goodwin F. K., & Jamison, K. R. (2007). *Manic-depressive illness: bipolar disorders and recurrent depression, 2nd ed.* New York: Oxford Press.

Greenberg, G. (2010, December 10). Inside the battle to define mental illness [Web log post]. Retrieved from www.wired.com /magazine/2010/12/ff_dsmv/all/1 on 3/1/11

Haag, H., Heidorn, A., Haag, M., & Greil, W. (1987). Sequence of affective polarity and lithium response: preliminary report on Munich sample. *Progress in Neuropsychopharmacology and Biological Psychiatry, 11* (2-3), 205-208.

Harmon-Jones, E. & Allen, J. J. B. (1997). Behavioral Activation Sensitivity and resting frontal EEG asymmetry: Covariation of putative indicators related to risk for mood disorders. *Journal of Abnormal Psychology, 106*(1), 159-163.

Harris, G., & Carey, B. (2008b, July 12). Psychiatric Association faces Senate scrutiny over drug industry ties. *New York Times*, A 13.

Harrow, M., Goldberg, J. F., Grossman, L. S., & Meltzer, H. Y. (1990). Outcome in manic disorders. *Archives of General Psychiatry, 47* (7), 665-671.

Heun, R., & Maier, W. (1993). The distinction of bipolar II disorder from bipolar I and recurrent unipolar depression: results of a controlled family study. *Acta Psychiatrica Scandinavica, 87,* 279-284.

Ho, B-C., Andreasen, N. C., Ziebell, S., Pierson, R., & Magnotta, V. (2011). Long-term antipsychotic treatment and brain volume. *Archives of General Psychiatry, 68* (2), 128-137.

Hodgins, S., Faucher, B., Zarac, A., & Ellenbogen, M. (2002). Children of parents with bipolar disorder: A population at high risk for major affective disorders. *Child and Adolescent Psychiatric Clinics of North America, 11*, 533-553.

Isaac, G. (1995). Is bipolar disorder the most common diagnostic entity in hospitalized adolescents and children? *Adolescence, 30,* 273-276.

Jackson, D. C., Mueller, C. J., Dolski, I., Dalton, K. M., Nitschke, J. B., Urry, H. L., Rosenkranz, M. A., Ryff, C. D., Singer, B. H., & Davidson, R. J. (2003). Now you feel it, now you don't: Frontal brain electrical asymmetry and individual differences in emotion regulation. *Psychological Science, 14* (6) 612-617.

Jackson, G. E. (2005). *Rethinking psychiatric drugs: a guide for informed consent.* Bloomington, IN: Authorhouse.

Johnson, S. L. (2005). Mania and dysregulation in goal pursuit: A review. *Clinical Psychology Review, 25*, 241-262.

Jones, S. H., Tai, S., Evershed, K., Knowles, R., & Bentall, R. (2006). Early detection of bipolar disorder: a pilot familial high-risk study of parents with bipolar disorder and their adolescent children. *Bipolar Disorders, 8*, 362-372.

Joyce, P. R., Doughty, C. J., Wells, J. E., Walsh, A.E. S., Admiraal, A., Lill, M., & Olds, R. J. (2004). Affective disorders in the first-degree relatives of bipolar probands: Results from the South Island Bipolar Study. *Comprehensive Psychiatry, 45* (3), 168-174.

Judd, L. L., Akiskal, H. S., Schettler, P. J., Coryell, W., Maser, J., Rice, J. A., Solomon, D. A., & Keller, M. B. (2003). The comparative clinical phenotype and long term longitudinal episode course of bipolar I and II: a prospective, comparative, longitudinal study. *Journal of Affective Disorders, 73*, 19-32.

Judd, L. L., Akiskal, H. S., Schettler, P. J., Endicott, J., Maser, J., Solomon, D. A., Leon, A. C., Rice, J. A., & Keller, M. B. (2002). The long-term natural history of the weekly symptomatic status of Bipolar I Disorder. *Archives of General Psychiatry, 59*, 530-537.

Karkowski, L M., & Kendler, K. S. (1997). An examination of the genetic relationship between bipolar and unipolar illness in an epidemiological sample. *Psychiatric Genetics, 7*, 159-163.

Kasch, K. L., Rottenberg, J., Arnow, B. A., & Gotlib, I. H. (2002). Behavioral activation and inhibition systems in the severity and course of depression. *Journal of Abnormal Psychology, 111* (4), 589-597.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity survey replication. *Archives of General Psychiatry, 62,* 593-602.

Kessler, R. C., Rubinow, D. R., Holmes, C., Abelson, J. M., & Zhao, S. (1997). The epidemiology of DSM-III-R bipolar I disorder in a general population survey. *Psychological Medicine, 27,* 1079-1089.

Khan, A., Kolt, R. L., Thase, M. E., Krishnan, K. R. R., & Brown, W. (2004). Research design features and patient characteristics associated with the outcome of antidepressant clinical trials. *American Journal of Psychiatry, 161*, 2045-2049.

Klein, D. N., Depue, R. A., & Slater, J. F. (1985). Cyclothymia in the adolescent offspring of parents with bipolar affective disorder. *Journal of Abnormal Psychology, 94,* 115-127.

Konopaske, G. T., Dorph-Petersen, K-A., Pierri, J. N., Wu, Q., Sampson, A. R., & Lewis, D. A. (2007). Effect of chronic exposure to antipsychotic medication on cell numbers in the parietal cortex of the macaque monkeys. *Neuropsychopharmacology, 32,* 1216-1223.

Konopaske, G. T., Dorph-Petersen, K-A., Sweet, R. A., Pierri, J. N., Zhang, W., Sampson, A. R., & Lewis, D. A. (2008). Effect of chronic antipsychotic exposure on astrocyte and oligodendrocyte numbers in macaque monkeys. *Biological Psychiatry, 63*, 759-765.

Kraepelin, E. (1899). *Manic-depressive insanity and paranoia*. Transalated by R. M. Barclay. Edinburgh: E.& S. Livingstone. www.archive.org/details/manicdepressivei00kraeuoft

Kupfer, D. J., Carpenter, L. L., & Frank, E. (1988). Is bipolar II a unique disorder? *Comprehensive Psychiatry, 29,* 228-236.

Lapalme, M., Hodgins, S., & LaRoche, C. (1997). Children of parents with bipolar disorder: A meta-analysis of risk for mental disorders. *Canadian Journal of Psychiatry, 42*, 623-631.

LaRoche, C., Sheiner, R., Lester, E., Benirakis, C., Marrache, M., Engelsmann, F., & Cheifetz, P. (1987). Children of parents with manic-depressive illness: A follow-up study. *Canadian Journal of Psychiatry, 32,* 563-569.

Leibenluft, E. (2011). Severe mood dysregulation, irritability, and the diagnostic boundaries of Bipolar Disorder in youths. *American Journal of Psychiatry, 168,* 129-142.

Littrell, J. & Lyons, P. (2010). Pediatric Bipolar Disorder: Part I—Is it related to classical Bipolar? *Children and Youth Services Review, 32*(7), 945-964.

Loranger, A., & Levine, P. (1978). Age at onset of bipolar affective illness. *Archives of General Psychiatry, 35,* 1345-1348.

Loring, D. W., & Meador, K. J. (2004). Cognitive side effects of antiepileptic drugs in children. *Neurology, 62,* 872-877.

MacKinnon, D. F., & Pies, R. (2006). Affective instability as rapid cycling: theoretical and clinical implications for borderline personality and bipolar spectrum disorders. *Bipolar Disorders, 8,* 1-14.

Manschreck, T. C., & Boshers, R. A. (2007). The CATIE schizophrenia trial: results, impact, controversy. *Harvard Review of Psychiatry, 15* (5), 245-258.

Markowitz, G. S., Radhakrishnan, J., Kambham, N., Valeri, A. M., Hines, W. H., & D'Agati, V. D. (2000). Lithium nephrotoxicity: A progressive combined glomerular and tubulointerstitial nephropathy. *Journal of the American Society of Nephrology, 11,* 1439-1448.

Miklic, S., Juric, D. M., & Carman-Krzan, M. (2004). Differences in the regulation of bdnf and ngf synthesis in cultured neonatal rat astrocytes. *International Journal of Developmental Neuroscience, 22,* 119-130.

Miller, D. D., EcVoy, J. P., Davis, S. M., Caroff, S. N., Saltz, B. L., Chakos, M. H., Swartz, M. S., Keefe, R. S., Rosenheck, R. A., Stroup, T. S., & Lieberman, J. A. (2005). Clinical correlates of tardive dyskinesia in schizophrenia: baseline data from the CATIE schizophrenia trial. *Schizophrenia Research, 80 (*1), 33-43.

Mojtabai, R., & Olfson, M. (2010). National trends in psychotropic medication polypharmacy in office-based psychiatry. *Archives of General Psychiatry, 67* (1), 26-36.

Moreno, C., Laje, G., Blanco, C., Jiang, H., Schmidt, A. B., & Olfson, M. (2007). National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Archives of General Psychiatry, 64* (9), 1032-1039.

Oepen, G., Baldessarini, R. J., & Salvatore, P. (2004). On the periodicity of manic-depressive insanity by Eliot Slater (1938): translated excerpts and commentary. *Journal of Affective Disorders, 78* (1) 1-9.

Oldham, J., Carlat, D., Friedman, R. A., Nierenberg, A. A., & Angell, A. (2011). The illusions of psychiatry: An exchange. *New York Review of Books, LVIII*, 82-84.

Perlis, R. H., Miyahara, S., Marangell, L. B., Wisniewski, S. R., Ostacher, M., DelBello, M., Bowden, C. L., Sachs, G. S., & Nierenberg, A. A. (2004). Long-term implications of early onset in bipolar disorder: Data from the first 1000 participants in the systematic treatment enhancement program for Bipolar Disorder (STEP-BD). *Biological Psychiatry, 55*, 875-881.

Post, R. M. (2007). Kindling and sensitization as models for affective episode recurrence, cyclicity, and tolerance phenomena. *Neuroscience and Biobehavioral Reviews, 31*, 858-873.

Post, R. M., Denicoff, K. D., Leverich, G. S., Altschuler, L. L., Frye, M. A., Suppes, T. M., Rush, A. J., Keck, P. E., McElroy, S. L., Luckenbaugh, D. A., Pollio, C., Kupka, R., & Nolen, W. A. (2003). Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. *Journal of Clinical Psychiatry, 64* (6), 680-690.

Presne, C., Fakhouri, F., Noël, L-H., Stengel, B., Even, C., Kreis, H., Mignon, F., & Grünfeld, J-P. (2003). Lithium-induced nephropathy: Rate of progression and prognostic factors. *Kidney International, 64,* 585-592.

Radke-Yarrow, M., Nottelmann, E., Martinez, P., Fox, M. B.,& Belmont, B. (1992). Young children of affectively ill parents: A longitudinal study of psychosocial development. *Journal of the American Academy of Child and Clinical Psychiatry, 31*(1), 68-77.

Rennie, T. A. C. (1942). Prognosis in manic-depressive psychosis. *American Journal of Psychiatry, 98,* 801-814.

Schwartz, M., & Schechter, R. (2011). Systemic inflammatory cells fight off neurodegenerative disease. *Nature Reviews: Neurology, 6,* 405-410.

Shen, G. H. C., Alloy, L. B., Abramson, L. Y., & Sylvia, L. G. (2008). Social rhythm regularity and the onset of affective episodes in bipolar spectrum individuals. *Bipolar Disorders, 10,* 520-529.

Sikich, L., Hamer, R. M., Bashford, R. A., Sheitman, B. B., & Lieberman, J. A. (2004). A pilot study of risperidone, olanzapine and haloperidol in psychotic youth: A double-blind, randomized, 8-week trial. *Neuropsychopharmacology, 29,* 133-145.

Silva, R. R., Campbell, M., Golden, R. R., Small, A. M., Pataki, C. S., & Rosenberg, C. R. (1992). Side effects associated with lithium and placebo administration in aggressive children. *Psychopharmacology Bulletin, 28* (3), 319-326.

Smith, D. J., Muir, W. J., & Blackwood, D. H. R. (2005). Borderline personality disorder characteristics in young adults with recurrent mood disorders: A comparison of bipolar and unipolar depression. *Journal of Affective Disorders, 87,* 17-23.

Stringaris, A., Cohen, P., Pine, D. S., Leibenluft, E. (2009). Adult outcomes of youth instability: a 20-year prospective community-based study. *American Journal of Psychiatry, 166*, 1048-1054.

Sutton, S. K., & Davidson, R. J. (2000). Prefrontal brain electrical asymmetry predicts the evaluation of affective stimuli. *Neuropsychologia, 38*, 1723-1733.

Tillman, R., Geller, B., Nickelsburg, M. J., Bolhofner, K., Craney, J. L., DelBello, M., & Wigh, W. (2003). Live events in a prepubertal and early adolescent bipolar disorder phenotype compared to attention-deficit hyperactivity and normal controls. *Journal of Child and Adolescent Psychopharmacology, 13,* 243-251.

Tohen, M., Kryzhanovskaya, L, Carlson, G., DelBello, M., Wozniak, J., Kowatch, R., Wagner, K., Findling, R., Lin, D., Robertson-Plouch, C., Xu, W., Dittmann, R. W., & Biederman, J. (2007). Olanzapine versus placebo in the treatment of adolescents with bipolar mania. *American Journal of Psychiatry, 164,* 1547-1556.

Tomarken, A. J. & Davidson, R. J. (1994). Frontal brain activation in repressors and nonrepressors. *Journal of Abnormal Psychology, 103* (2), 339-349.

Udachina, A., & Mansell, W. (2007). Cross-validation of the mood disorders questionnaire, the internal state, and the hypomanic personality scale. *Personality and Individual Differences, 42*, 1539-1549.

U.S. Food and Drug Administration (2007). Antidepressant use in children and adults: Revisions to medication guide. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096273.htm retrieved on 3/1/11

U.S. Food and Drug Administration (2008, January 31). Information on carbamazepine (marketed as carbatrol, equetro, tegretol, and generics) with FDA alerts. http:www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm10784.htm retrieved on 3/1/11

Vieta, E., Angst, J., Reed, C., Bertsch, J., Haro, J. M., & the EMBLEM advisory board. (2009). Predictors of switching from mania to depression in a large observational study across Europe (EMBLEM). *Journal of Affective Disorders, 118*, 118-123.

Vieta, E., & Suppes, T. (2008). Bipolar II disorder: Arguments for and against a distinct diagnostic entity. *Bipolar Disorders, 10*, 163-178.

Werry, J. S., McClellan, J. M., & Chard, L. (1991). Childhood and adolescent schizophrenic, bipolar and schizoaffective disorders: A clinical and outcome study. *Journal of the American Academy of Child and Adolescent Psychiatry, 30*, 457-465.

Whitaker, R. (2010). *Anatomy of an epidemic.* New York: Crown Publishers.

Wicki, W., & Angst, J. (1991). The Zurich study: X. Hypomania in a 28-30 year-old cohort. *European Archives of Psychiatry and Clinical Neuroscience, 240*, 339-348.

Winokur, G., Clayton, P. J., & Reich, T. (1969). *Manic Depressive Illness*. St. Louis: C.V. Mosby Company.

Winocur, G., Coryell, W., Akiskal, H.S., Endicott, J., Keller, M., & Mueller, T. (1994). Manic-depressive (bipolar) disorder: the course in light of a prospective ten-year follow-up of 131 patients. Acta Psychiatrica Scandanavia, 89 (2), 102-110.

Woods, S. W., Martin, A., Spector, S. G., & McGlashan, T. H. (2002). Effects of development on olanzapine-associated adverse events. *Journal of the American Academy of Child and Adolescent Psychiatry, 41* (12), 1439-1446.

Wozniak, J., Biederman, J., Mundy, E., Mennin, D., & Faraone, S. V. (1995). A pilot family study of childhood-onset mania. *Journal of the American Academy of Child and Adolescent Psychiatry, 34,* 1577-1583.

Youngstrom, E. A., Freeman, A. J., & Jenkins, M. M. (2009). The assessment of children and adolescents with bipolar disorder. *Child and Adolescent Psychiatric Clinics of North America, 18* (2), 353-390.

Zimmermann, P., Brückl, T., Nocon, A., Pfister, H., Lieb, R., Wittchen, H-U., Holsboer, F., & Angst, J. (2009). Heterogeneity of DSM-IV Major Depressive Disorder as a consequence of subthreshold bipolarity. *Archives of General Psychiatry, 66* (12), 1341-1352.

Ziv, Y., & Schwartz, M. (2008). Immune-based regulation of adult neurogenesis: Implications for learning and memory. *Brain, Behavior, and Immunity, 22,* 167-176.