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## The Increasing Frequency of Mania and Bipolar Disorder:

### Causes and Potential Negative Impacts

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### Abstract

The frequency of mania has not changed during the last century even with the development of new diagnostic criteria sets. More specifically, from the mid-1970s to 2000, the rate of mania (variably labeled major affective disorder–bipolar disorder and bipolar I disorder) was consistently identified in US and international studies as ranging from 0.4% to 1.6%. By the late 1990s to the 2000s, the prevalence reported by some researchers for bipolar disorders (I and II and others) was in the 5% to 7% and higher ranges. The purpose of this paper was to review explanations for this change and the potentially negative impacts on the field.

### Keywords

Mania; bipolar disorder(s); prevalence; diagnostic errors

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Since antiquity scholars have described the symptoms of mania and its associated illnesses: Hippocrates (460 to 377 BC) and the Hippocratic School are widely credited with the first description and classification of mania (Alexander and Selsnick, 1966). In the first or second century AD, Areteus of Cappadocia described the possible relationship between mania and depression (Alexander and Selsnick, 1966; Angst and Marneros, 2001). Falret in 1854 described manic-depressive disease in his *Memoir on Circular Insanity* (Sedler, 1983). In 1899, Kraepelin delineated mania from other psychoses and coined the term *manic-depressive insanity* (Angst and Marneros, 2001).

Conceptualization of mania and the associated disorder along with development of valid (and reliable) criteria was not accomplished until after the introduction of the *DSM-III* in 1980 (American Psychiatric Association, 1980). The forerunner of these criteria was a set of criteria identified as valid for mania by Feighner et al. in 1972 at the Washington University in St. Louis (Feighner et al., 1973). Validation was achieved through clinical description, follow-up, and family studies from research completed in the 1950s and 1960s. The

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### DISCLOSURE

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Feighner set formed the basis for the Research Diagnostic Criteria (RDC) published in 1975 (Spitzer et al., 1975, 1978). Validation for the RDC set was drawn through multiple research studies (Spitzer et al., 1978). The Feighner set and the RDC formed the bases for the *DSM-III* criteria for bipolar disorder and demonstrated exceptionally high concordance for mania (Singerman et al., 1981; Stoltzman et al., 1981). With the exception of bipolar II in *DSM-III-R*, subsequent iterations of the *DSM* series (*DSM-III-R*, *DSM-IV*, *DSM-IV-TR*) have not offered substantive changes to the bipolar section (American Psychiatric Association, 1987, 1994, 2000; Singerman et al., 1981). Researchers and clinicians in psychiatry and the field of medicine have overwhelmingly accepted the *DSM* criteria for bipolar I disorder.

The Epidemiological Catchment Area (ECA) study found a lifetime prevalence of 0.8% (bipolar II at 0.5%), and the National Comorbidity Study found a lifetime prevalence of 1.6% for manic episodes (Kessler et al., 1994; Regier et al., 1990). Comprehensive literature reviews beginning with the *DSM-III* in 1980 determined that the prevalence of bipolar I disorder ranged between 0.4% and 1.6%. The series also noted a rather remarkable stability of bipolar I (and bipolar II) disorder during the approximately 20-year (6 years for bipolar II disorder) reporting period. The *DSM* documented stability of the prevalence of bipolar disorder, with the highest ranges from 0.4% to 1.6% in *DSM-IV* and *DSM-IV-TR* (American Psychiatric Association, 1994, 2000). Gagrut and Spiro's (1980) review of 10 worldwide studies completed between 1938 and 1973 (before any valid criteria sets in the United States had been widely advanced) found prevalence rates for manic-depressive psychosis ranging between 0.07% and 1.88% with two outliers at 2% and 7%. It is also of particular interest that one of the earliest epidemiological studies of "admission prevalence" for mania dating back to 1875 to 1924 found mania to be rare at 3.6 admissions per 100,000 people per annum (Farquhar et al., 2007). Recent US and international studies have found lifetime prevalence rates for bipolar I using different methods ranging from 0.4% to 1.3% (Kessler et al., 1997; Merikangas et al., 2007; Pini et al., 2005; ten Have et al., 2002). Clearly and convincingly, the lifetime prevalence of mania/bipolar I ascertained using different methods during the lengthy reporting period is about 1%.

Dunner et al. (1976) described a group of patients with hypomania and severe recurrent depression, which was captured in *DSM-III* by the label *atypical bipolar disorder* (American Psychiatric Association, 1980). The concept was later formalized in *DSM-III-R* as bipolar II disorder (American Psychiatric Association, 1987) and was later reviewed by Coryell (1996). The construct and criteria of bipolar II have not completed validation using the "gold standard" criteria to establish the validity and reliability of the major mental illnesses (Robins and Guze, 1970). Furthermore, bipolar II has neither been the subject of large-scale studies outside of the United States or France, nor has bipolar II been listed in the ICD-9 and ICD-10 (World Health Organization, 1977, 1992). Nonetheless, the lifetime prevalence of the bipolar II construct/criteria in the ECA and the *DSM* series was 0.5% (American Psychiatric Association, 1994, 2000; Regier et al., 1990).

The prevalence of bipolarity increased dramatically with a broadened definition of hypomania. In 1998, Angst (1998) reported a lifetime prevalence of 5.5% in a community sample of bipolar I and II disorder with an additional 2.8% using a reduced hypomania specifier from 4 days to 1 to 3 days. Akiskal (1996) reviewed the emerging literature in the 1990s and opined that "3% to 6% of the general population, possibly worldwide, seem to exhibit temperamental instability along hypomanic or cyclothymic lines." Studies of outpatient psychiatric samples of mood disorders subsequently reported bipolar II disorder rates from 10% to 45% (Benazzi, 1997; Hantouche et al., 1998; Manning et al., 1997). The increased prevalence rates also extended to primary care settings, with up to 30% of patients presenting with anxiety or depression having "bipolar spectrum disorders" (Piver et al., 2002). Bipolar spectrum disorders included bipolar type 1.5 (depression with protracted

hypomania), bipolar 2.5 (cyclothymic depressive episodes), bipolar type III (depressive episodes with antidepressant-induced hypomanic episodes), and bipolar type IV (depressive episodes with premonitory hyperthymic temperament) and cyclothymic disorder (Akiskal and Pinto, 1999; Manning et al., 1999; Piver et al., 2002). These increasing numbers have given more currency to a broader issue of whether there exists a group of bipolar disorders. Terms such as *soft bipolar*, *bipolar spectrum*, *subsyndromal*, and *subthreshold* have gradually crept into the lexicon during the last 30 years, with variable definitions and limited data (Akiskal and Mallya, 1987; Angst and Ernst, 1993; Keller et al., 1992a; Klerman, 1981). Review of the literature reveals an extraordinary number of recent articles encouraging the assessment and identification of patients with bipolar spectrum disorders. Below, we review the causes for this trend and then turn to the potentially negative impacts of overdiagnosis for patients, psychiatry, and society.

## CAUSES OF OVERDIAGNOSIS

### Underdiagnosis of Bipolar I Disorder

Bipolar I disorder is a serious major mental illness that is commonly chronic in nature and associated with significant interpersonal, social, and occupational dysfunction (Goodwin and Jamison, 2007). The illness carries a significantly elevated morbidity and mortality risk (Baldessarini et al., 2006; Goodwin and Jamison, 2007). Consequently, every mental health clinician should be aware of and seek to properly identify the disorder. Unfortunately, a significant amount of time often elapses between the onset of the illness and initiation of appropriate treatment (Baldessarini et al., 1999; Bowden, 2001; Hirschfeld et al., 2003; Lish et al., 1994). During the last 15 years, various types of reports have identified the error of assigning a diagnosis of depression when one of bipolar disorder would have been appropriate (Ghaemi et al., 2000, 2002; Hirschfeld, 2001; Hirschfeld and Vornik, 2004; Katzow et al., 2003; Perugi et al., 1998; Yatham, 2005). This error appears for several reasons but frequently results from lack of proper identification (exploration/knowledge) of earlier mood elevation or the presentation (at the time of the evaluation) of a “depressive symptom/depressive syndrome/major depression” before onset of the hypomanic/manic syndrome. No clinician wants to miss an underlying biological diathesis toward mania and inadvertently aggravate the true illness. Prescribing antidepressants places at least some patients at risk for mood dysregulation, if not hypomanic/ manic type behavior (Dunner, 2005; Ghaemi and Ko, 2002; Malhi et al., 2009). Concern for proper diagnosis of bipolar illness has been widely recognized by the insurance industry (Birnbaum et al., 2003; Shi et al., 2004), which has advocated in the medical literature for proper early identification and treatment. Comprehensive assessment of previous mood elevation (hypomania/mania), thorough family history focusing on mood/ elation/ suicide history, knowledge of the criteria, along with close and careful follow-up after initiation of antidepressant therapy in even remotely possible bipolar diathesis patients certainly seems warranted. Nonetheless, with the emphasis to identify “cases,” some clinicians will elect to err on the side of overdiagnosing bipolar spectrum disorders.

### Woodruff Factor

Three years before the publication of *DSM-III*, Woodruff et al. (1977) published an influential article advancing several strategies dealing with uncertainty in the less-than-precise art of psychiatric diagnosis. One fundamental strategy when dealing with an inability to decide between two major disorders (*i.e.*, bipolar I versus schizophrenia) was to use the affective disorder label, which was more associated with amenability to treatment. Their position coincided with rise in the acceptance of the treatment efficacy of lithium in bipolarity and a careful re-examination of the differential manner US psychiatrists used in diagnosing schizophrenia and bipolarity (Baldessarini and Tondo, 2000). In particular, Pope

and Lipinski (1978) found that, in the late 1970s, US psychiatrists' identified schizophrenia versus bipolar disorder at a rate of 8 (to 12) to 1 as opposed to 1 to 1 in Western Europe.

During the ensuing 30 years, any need for strategic bias in application of diagnosis (bipolar I disorder versus schizophrenia) has been reduced because separate sets of criteria for each have been validated and allow adequate delimitation particularly if longitudinal follow-up is used. The principle, however, can still be applied. One of the common indicia of mania, mood swings, is a commonly seen complaint in many other disorders including personality disorders (affective instability is one of the criteria for borderline personality disorder) and substance use/misuse disorders (American Psychiatric Association, 2000). This "overlap" facilitates erring on the side of the affective disorder because from a purely pharmacological viewpoint, bipolar illness is more treatable. However, careful elicitation of longitudinal history and family history should confidently allow identification of early onset in adolescence or early adulthood of personality conflicts or alcohol/substance issues. Differentiation of these disorders from mania can also be completed during hospitalization (common in mania) because gross euphoria usually stands in stark contrast to the interpersonal conflicts of the personality disorders and the "worn-out" detoxified patient. Nonetheless, intentionally erring on the side of application of a diagnosis of bipolar disorder (I and II and others) in these more common disorders will increase the frequency of the bipolar label.

### Criteria

Major mental illnesses have long histories of description, many dating back to antiquity (North and Yutzy, 2010). Changing the definition of an identified disorder (*e.g.*, bipolar I) by redefining a key component or changing the necessary criteria can certainly change the frequency (prevalence and/or incidence) of the disorder. For potentially new disorders or variants such as bipolar II disorder, a proposed consideration of changing the definition of hypomania by reducing the number of days from 4 to 2 will certainly increase the frequency of the label (Akiskal et al., 2000). It seems rather unusual to these authors to change or reconceptualize a disorder (bipolar II) that has undergone substantial progress toward validation as evidenced by follow-up studies and large-scale studies in the United States and France. This is particularly true because any new definition or criteria will require careful consideration of caseness and, ultimately, validation by research and the field. Although psychiatrists may be conservative regarding using new diagnostic labels and intervening therapeutically, general medical providers who provide an increasing amount of psychopharmacological care may proceed with an algorithmic medical approach once the "criteria are met" or the label (valid or not) has reportedly been applied previously. Unfortunately, reports in psychiatric samples of bipolar II disorder rates of up to 45% and primary care samples of bipolar spectrum disorders of up to 30%, as noted previously, can be problematic (Benazzi, 1997; Cassano et al., 1992; Hantouche et al., 1998; Manning et al., 1997; Piver et al., 2002). Identification of increased prevalence gives the impression to other mental health evaluators that they may be missing substantial numbers of "bipolar" patients. This can cause a reduction in the applied threshold broadly contributing to overdiagnosis. In addition, according to the American Psychiatric Association, the upcoming *DSM-5* will embrace the concept of dimensionalism (Helzer et al., 2008). If broader definitions of bipolar disorder (bipolar II reduced specifier and bipolar not otherwise specified) are included in the continuum, the prevalence is likely to increase.

### The Depression Treatment Phenomenon

Shortly after the selective serotonin reuptake inhibitors (SSRIs) were introduced to the US market, fluoxetine (Prozac) became the most widely prescribed antidepressant medication in the world (Stokes and Holtz, 1997). The transition from the tricyclic era was clearly related

to ease of use (usually one tablet), treatment efficacy, significant reduction in adverse effects, and safety in overdose (Barbey and Roose, 1998; Papakostas, 2010; Peretti et al., 2000). Gone were increasing the antidepressant dose to toxicity and then backing off, blood levels, and special diets. By 2002, 93% of the surveyed prescribing psychiatrists listed SSRIs as their first choice for depression. In that same year, the American Psychiatric Association Practice Guidelines for the Treatment of Patients with Major Depressive Disorder listed SSRIs first in the list of available optimal antidepressants (American Psychiatric Association, 2002a). By 2004, US sales of SSRI/serotonin-norepinephrine reuptake inhibitors had reached \$11.2 billion (IMS Health National Sales Perspectives, 2011). In addition, primary care physicians have been encouraged to use the criteria less stringently (counting symptoms even if they may be associated with a medical illness) in assigning a diagnosis of major depressive disorder (Salazar, 1996). Broadly considered, what clinician of any type wanted to miss the opportunity of treating the potentially disabling mental illness of major depression?

The transmutation of this “revolution” from the identification (broadly defined) and treatment of depression to the identification (narrowly defined) and treatment of bipolar disorder I has been problematic for multiple reasons. In particular, here, the limited prevalence of bipolar I disorder (rare) and the substantial clinical therapeutic treatment index differential (between depression and bipolar; see “Informed Consent and Risk/Benefit Analysis” further below) have, so far, proved, to those with and without a beneficent agenda, to be almost insurmountable. Nonetheless, increasing the number of identified cases of depression would increase the number of evaluations to rule out history of mania, which will increase the frequency of the bipolar disorder (I and II and other) label (both true and false positives).

### Pharmaceutical Industry

In 1997, the Food and Drug Administration (FDA) relaxed broadcast restrictions, and Direct-To-Consumer-Advertising for prescription medications began to rise in prominence. The benefits and risks of this method of information dissemination continues to be debated (Block, 2007; Jureidini et al., 2008; Rosenthal et al., 2002). Standardized patients (actors) presenting with symptoms of depression and asking primary care doctors for an antidepressant by name increases the generation of an antidepressant prescription (Kravitz et al., 2005). Although this may be helpful in alerting providers to be aware of and to treat common illnesses (*e.g.*, depression), it may be unhelpful in uncommon or rare illnesses. More specifically, reporting “I have mood swings” or “I am bipolar” may simply be equated by some clinicians with bipolarity even when careful expert review would not reveal the illness. Of substantial concern also for many medical observers and physicians has been the number of the settlements with the government relating to “off-label” marketing/ advertising of medicines for “bipolarity” (see Table 1; US Department of Health and Human Service, 2011a, 2011b; US Department of Justice, 2011a, 2011b, 2011c, 2011d, 2011e).

The pharmaceutical industry seems to be directly and indirectly (possible associated symptoms of bipolarity: *i.e.*, anger, aggression, anger management, mood disorder, and sleep problems) targeting bipolar illness. Particularly concerning is the focus on primary care doctors for “symptomatic treatment” as opposed to the FDA-approved uses for the major mental illnesses of bipolar and schizophrenia. Even though the accepted frequencies of these major disorders have not increased, antipsychotics have become the top-selling drug class in the United States in 2008, a \$14.6-billion industry (IMS Health National Sales Perspectives, 2011). In 2010, major journals questioned the prescribing of antipsychotics despite serious risks (Kuehn, 2010).

Previous investigators have also expressed concern about the pharmaceutical industry's use of the medical term *mood stabilizer* (Healy, 2006). Shou (1963) was the first to use the term *mood normalizer*. Other investigators later used the term in reference to the kindling phenomena (Post and Weiss, 1989). Years later, the debate continues with no widespread agreement on the definition of "mood stabilizer" (Bauer and Mitchner, 2004; Bowden, 1998; Ghaemi, 2001; Keck and McElroy, 2003; Sachs, 1996). Furthermore, each agent (lithium, valproic acid, carbamazepine, lamotrigine, and anti-psychotics) demonstrates a different pharmacological profile of activity during the various pathological phases of bipolarity without any direct evidence of "causing stabilization of mood" to normal. The FDA has not approved any medication as a mood stabilizer. Unfortunately, until a pathological paradigm is advanced, which draws the proverbial "bright line" between variability of mood based on the vicissitude of daily living (*i.e.*, normal) and "mood variability" in bipolarity, the statement, "the patient could benefit from a mood stabilizer" is bound to suggest a treatable and diagnosable "unstable emotional/affective state."

### Practical Realities: Time and Records

As the amount of time the psychiatrist spends with the patient is reduced overall through managed care and the common lack of availability of collateral information (including family as well as previous records), the question continues to arise whether it is better to err on the side of giving the patient the "benefit of the doubt." Although assigning a provisional diagnosis of major depression (unipolar) and instituting an antidepressant has limited downside potential, using a bipolar label and instituting treatment require a substantially different informed consent and benefit/risk analysis. Erring on the side of applying any bipolar label (I and II and other) will increase the prevalence (true and false positives).

### Fads

Fads are part of society, and psychiatry has made significant contributions over time. Particular labels have been introduced as "disorders," becoming the "diagnosis de jour" and, later, being used as vehicles to castigate psychiatry. Multiple personality disorder has been such a favorite (McHugh, 1995; Piper and Merskey, 2004a, 2004b). During the last 10 years, the public seems to have become particularly enamored with the self-description of "bipolarity." Very few active clinicians cannot identify one or more patients who presented with a complaint of "mood swings" or "I am bipolar" without other signs or symptoms. This strikes many clinicians as odd because the prognosis for bipolarity is significantly worse than that for depression. When asked the extreme but common symptoms of mania, the same patients usually deny all with a look of incredulity. Failure to inquire about the full diagnostic criteria and to not intentionally rule out the confounding issues of personality disorder (particularly borderline), drug use, and drug seeking will simply guide the mental health clinician toward an overuse of some label of "bipolarity."

## POTENTIAL IMPACTS OF OVERDIAGNOSIS

### Research

Investigators began to express their concern about the over-diagnosis of bipolarity in the late 1990s (Brim, 1998; Hutto, 2001). In a widely cited work, Baldessarini (2000) makes an open plea for uniformity of the bipolar diagnosis: "The main point of this communication is to encourage caution in premature and potentially misleading widening and dilution of the bipolar concept." Furthermore, he continues, "Widespread acceptance of increasingly broad definitions risk weakening or trivializing the core concept of bipolar disorder, much as occurred in the past with 'schizophrenia,' 'major depression,' and a growing number of other disorders." Because many would favor the principle that research should guide clinical

work, diffusion of the core concept can clearly lead to a multitude of easily identifiable as well as unforeseeable consequences.

### **Clinical: Erroneous Diagnosis, Prognosis, and Treatment**

Establishing the diagnosis is considered the cornerstone of medical practice. Once correctly identified, it facilitates identification of prognosis and treatment plan. Incorrect diagnosis creates false assumptions and beliefs about prognosis as well as course. Furthermore, it may subject patients to treatment, which may be unnecessary, contraindicated, or dangerous. Failing to establish the correct diagnosis also prevents initiating the proper state-of-the-art treatment.

Multiple pathways can lead to an erroneous diagnosis as noted above. One common to psychiatry is the provision of an erroneous diagnostic label to a new examiner. Often, no confirmation or refutation can be developed. Bipolarity has caught the public's eye, and there has been no shortage of anecdotes for the busy clinicians (*e.g.*, "the police showed up while I was having a bipolar moment, Doc!"). Some individuals want to simply use the label as a badge of nonresponsibility or the proverbial "get out of jail free card." Disability payments have been associated with overdiagnosis of bipolarity (established by patient report) but unconfirmed by formal assessment (Zimmerman et al., 2010a). A Structured Clinical Interview for *DSM* Disorders confirmed the diagnosis in less than 50% of patients with self-reported diagnosis of bipolar disorder (Zimmerman et al., 2008). Many of these overdiagnosed patients were subsequently diagnosed with borderline personality disorder (Zimmerman et al., 2010b). Other studies confirmed a much smaller percentage of bipolar patients in a substance abuse and dependence residential treatment center and inpatient setting in previously diagnosed samples of bipolar patients (Goldberg et al., 2008; Stewart and El-Mallakh, 2007).

The prognosis and treatment of these other disorders (*e.g.*, borderline personality, alcohol/substance abuse/dependence) are arguably not as hopeful as those of the affective disorder(s). However, proper recognition is still considered to be the first step toward treatment and recovery. Any delay clearly impedes that process. Although comorbidity (mania as the primary and borderline personality disorder or alcohol/substance as the secondary) may initially be a diagnostic confounder, it is rarely the case after hospitalization or sobriety that true mania cannot be identified.

The public has been regaled with retrospective application of the bipolar label to famous dignitaries (Brim, 1998; Paris, 2008). A thorough review tells a very different story for many people with this illness (Goodwin and Jamison, 2007). Comparing the prognoses of bipolar I and depression, those with bipolar disorder can expect an earlier onset of symptoms, more mood episodes, comorbid substance use disorders, possibly less response to antidepressants, and fewer treatment options (Goodwin and Jamison, 2007). Although long-term studies of bipolar disorder have proven difficult, it seems that less than one third of bipolar patients reach symptom remission, whereas only 10% to 15% of those diagnosed with major depression have not recovered after 5 years (Keller et al., 1992b). Even more worrisome, approximately 30% of bipolar patients will continue to struggle with symptoms precluding them from social function (Goodwin and Jamison, 2007). The remaining 30% fall between these outcomes. Recent research also highlights ongoing cognitive difficulties and multiple domains of dysfunction (Burdick et al., 2007; Gutierrez-Rojas et al., 2011). Rates of morbidity, mortality, and suicide are increased in those with bipolar I disorder (Goodwin and Jamison, 2007).

The somatic treatment of bipolar disorder is neither simple nor without significant risks. Pharmacological treatment advanced substantially after the discovery of lithium in 1949 by

Cade (Cade, 1949). Lithium eventually became and remains to be a first-line choice for bipolar I disorder (American Psychiatric Association, 2002b; Baldessarini and Tondo, 2000; Goodwin, 2009; Yatham et al., 2009). Lithium has a narrow therapeutic index, significant nonadherence rates, and substantial lethality in overdose (Bronstein et al., 2009; Johnson and McFarland, 1996; Ketter et al., 1999). These and other issues prompted psychiatry to search for alternative pharmacological interventions such as carbamazepine, valproic acid, and lamotrigine. Carbamazepine also has a narrow therapeutic index, multiple problematic drug-drug interactions, and significant nonadherence rates and is lethal in overdose (Keck et al., 1997; Ketter et al., 1999; Litovitz et al., 2001). Valproic acid has a “somewhat more favorable” therapeutic index but also has significant nonadherence rates and is lethal in overdose (Keck et al., 1997; Litovitz et al., 2001). Lamotrigine is efficacious in prophylaxis against recurrence of depression in bipolar I disorder (Bowden et al., 2003). Lamotrigine has a wide therapeutic index, slow/complex dosing schedule, and good adherence but can be lethal in overdose (Anderson et al., 1996; Baldessarini et al., 2008; Hirsch et al., 2004; Ketter et al., 2005; Levine et al., 2000).

The first-generation antipsychotics for acute mania have a wide therapeutic index, improved adherence (in hospital), and lower lethality in overdose but also have significant adverse-effect profiles (Bronstein et al., 2009; Miyamoto et al., 2003; Umbricht and Kane, 1996). For bipolar maintenance, the first-generation depot antipsychotics have assured adherence and significant adverse-effect profiles (particularly acute and chronic movement disorders) and can possibly “precipitate” depression (Bond et al., 2007; Taylor, 2009). The second-generation antipsychotics were introduced in the early 1990s with much fanfare and anticipation. Although all are FDA-approved for acute mania (Dunner, 2005), olanzapine and aripiprazole have also received FDA approval for single agent “bipolar maintenance” (Baldessarini and Tarazi, 2005). Maintenance is considered as prophylaxis against future manic episode. In comparison with haloperidol (first generation), both agents have an improved adverse-effect profile in the short term—extrapyramidal adverse effects (Balestrieri et al., 2000; Swainston Harrison and Perry, 2004)—and longer term—tardive dyskinesia (Correll et al., 2004; Stip and Tourjman, 2010); they have also not been found to “precipitate” depression (Narasimhan et al., 2007; McIntyre, 2010). Unfortunately, in comparison with the first-generation antipsychotics, several second-generation agents are associated with weight gain (in particular, olanzapine [Sachs and Guille, 1999; McIntyre et al., 2010] but not aripiprazole [Stip and Tourjman, 2010]). Obesity is associated with a worse outcome in bipolarity (Fagiolini et al., 2003). The FDA has also approved ziprasidone and quetiapine for adjuvant therapy (with lithium or valproic acid) in bipolar maintenance. Combining agents adds to the not-insubstantial risk sets. Bipolar illness often requires polypharmacy, and many of the psychiatric medications cause potentiation of the effects of common medicines (*e.g.*, analgesics). These effects can be additive or synergistic and precipitate serious events (*e.g.*, falls, auto accidents, respiratory depression, death).

### **Informed Consent and Risk/Benefit Analysis**

Obtaining informed consent for initiation of appropriate treatment of affective disorders requires a lengthy psychoeducational interaction with the patient (Applebaum and Gutheil, 2007). Usually included in this interaction would be imparting of the diagnosis, prognosis, and probable course. Careful weighing of the clinical presentation with discussion of the appropriate options for treatment would be part of the sequence. If pharmacology is considered an option, a review of the potential agents requires disclosure of the common and uncommon adverse effects. When considering initiating unipolar depression pharmacology (SSRIs), the common and uncommon adverse effects are generally considered benign and manageable (Papakostas, 2010; Peretti et al., 2000). In bipolar illness, this is obviously far from the case as outlined above.



When considering a particular patient with a history of true mania (bipolar I) or clear hypomania (bipolar II), most clinicians can confidently make the argument for initiating pharmacological treatments demonstrated as efficacious because the benefits clearly outweigh the associated potential risks. However, the analysis becomes much less clear, in these authors' opinion, when the illness is described solely as a possible history of hypomania or "bipolar spectrum" or "a bipolar label" or "momentary bipolar" or "some mood instability." More specifically, as certitude of a bipolar I or II diagnosis declines and the clinical evidence for pharmacological efficaciousness relies on bipolar I or II treatment studies and the attendant pharmacological risks remain the same, the scales begin to tip in favor of avoiding risk. Alternatively, the clinician can ensure that the patient is fully informed of the potentially limited benefit of pharmacological intervention with clear delineation of the risks. Unfortunately, in erroneous treatment, the informed consent process for bipolarity (I and II and other) is the same, but any potential benefit is fortuitous, and the risk is substantial, unnecessary, and for some, deleterious.

### Permanence

Any label of bipolarity is highly likely to be carried through medical records because it is considered a chronic illness commonly associated with unusual, bizarre, or frankly dangerous behavior. Some would consider not continuing it in the records as depriving future examiners of significant information (risks of using antidepressant(s)/ dangerousness to self/others). Unfortunately, the permanent mislabel may also lead to bias or prejudice against the individual by uninformed providers (patients are inherently unreliable), potential employers (cost burden), and insurance entities (avoidance of higher cost risk; Ozminkowski et al., 1999; Peele et al., 2003). Merely receiving a label of "mental illness" (correct or erroneous) continues to be associated with a public perception that such individuals are erratic, untrustworthy and dangerous (Struening et al., 2001). Even in hypothetical patient scenarios with no overt dangerousness, the public's perception of "dangerousness" is often out of proportion with reality (Link et al., 1999).

### SUMMARY

The authors have reviewed together a multitude of causes, which seem to be playing major roles in the increasing frequency of identification of the label of "bipolarity." The influences driving overdiagnosis in particular, in our opinion, must be considered within the context of the fundamental advocacy principles of medical training and practice in the United States, including the fiduciary duty to "advocate for the best interest of the patient" (Cassel, 1996) and the Hippocratic Principle of *primum non nocere* (above all [or first], do no harm; Smith, 2005).

Contemporary medical ethics outlined by Beauchamp and Childress (2008) advances four principles (autonomy, beneficence, nonmaleficence, and justice) for analysis of medical issues such as overdiagnosis and treatment. Beneficence (fiduciary obligation to advocate for best interest) and nonmaleficence (Hippocratic Principle) are the components that can be balanced when consideration of diagnosis/treatment is raised (Body and Foex, 2009). Using them as distinct polar opposites, it is readily apparent that overdiagnosing possible major depression would barely move off the beneficence pole because of the limited adverse-effect profile. However, over-diagnosing bipolarity immediately raises the issue of inserting substantial risk. Sharpe (1997) has argued to add another element to the obligation of nonmaleficence, which should be to "...not impose unnecessary or unreasonable risk of harm" (p. 167). Whether over-diagnosis falls under this newly offered element would be based on three principle factors. These factors are clinical confidence in diagnosis of the illness, amenability to treatment of the illness, and a realistic appraisal of any potential

benefit (weighed against risk). These three factors could determine how far from the beneficence pole (toward nonmaleficence) the analysis would move.

The authors are of the firm opinion that all clinicians using the diagnosis should be thoroughly knowledgeable about the state of the art of bipolarity: the valid and reliable criteria (long established) for the diagnosis of bipolar I (as well as efforts toward bipolar II); the pharmacological efficacy treatment studies for bipolar I (and II); the current factors directly bearing on clinicians' judgment driving the application of the bipolar labels; and a clear understanding of the attendant risks associated with erroneous diagnosis, prognosis, and treatment.

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TABLE 1

## Settlements

Company	Year	Medication	Settlement	Error
1. Warner-Lambert	2004	Gabapentin	420 million	False marketing/promotion—off-label marketing for bipolar mental disorder when it had been shown in a scientific study that placebo was equally effective or better
2. Bristol-Myers Squibb	2007	Aripiprazole	25 million (of 515 million)	False promotion—off-label marketing targeting children/adolescents and geriatrics (dementia-related psychosis) when medication was unapproved in pediatric population; it was the subject of a black box warning for dementia-related psychosis.
3. Lilly	2009	Olanzapine	1.4 billion	Misbranding—promoting Zyprexa in the treatment of dementia, including Alzheimer disease Criminal court filing in the Eastern District of Pennsylvania alleged that Lilly tried to convince doctors that Zyprexa can be used in the treatment of "...depression, anxiety, and sleep problems." It also alleged, in October 2000, that Lilly began off-label marketing to primary care physicians even though there were no approved uses for Zyprexa in the primary care market. Furthermore, it also alleged that sales representatives promoted Zyprexa focusing on symptoms rather than on Food and Drug Administration-approved indications.
4. Pfizer	2009	Ziprasidone	301 million; 2.3 billion multiple medications (combined settlement)	False claims act—off-label marketing targeting multiple unapproved psychiatric uses including "bipolar maintenance," anxiety, depression, attention deficit hyperactivity disorder, obsessive-compulsive disorder, and posttraumatic stress disorder
5. Astra Zeneca	2010	Quetiapine	520 million	False claims act—off-label marketing targeting multiple unapproved psychiatric uses including "bipolar maintenance," aggression, anger management, mood disorder, anxiety, attention deficit hyperactivity, Alzheimer disease, posttraumatic stress disorder, and sleeplessness. Targeted Seroquel not toward physicians who treat schizophrenia or bipolar affective disorder but toward doctors who treat older patients and are in primary care, pediatrics, and corrections. Recruited physicians to serve as authors on articles ghost written by medical literature companies.
6. Ortho-McNeil Pharmaceutical and Ortho-McNeil Janssen Pharmaceutical	2010	Topiramate	81+ million	Misbranding—off-label marketing when no psychiatric uses had been approved Use of "Doctor-for-a-Day" program, wherein outside physicians were hired to go with sales representatives to physicians' offices to promote off-label uses
7. Novartis	2010	Oxycarbamazepine	185+ million	Off-label marketing for nonapproved psychiatric uses—bipolar disease False Claims Act—Additional 237.5 million paid for multiple medications including oxycarbamazepine

This is not a comprehensive list.

See text for References.