# Magellan's Update of its Introduction to the American Psychiatric Association's Clinical Practice Guideline for the Treatment of Patients with Bipolar Disorder

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## Purpose of This Document

This document is an introduction and update to Magellan Health's adopted clinical practice guideline (CPG) for the treatment of patients with a bipolar disorder. Magellan has adopted the American Psychiatric Association's (APA) *Practice Guideline for the Treatment of Patients With Bipolar Disorder (2002),* Second Edition, and the Guideline Watch: *Practice Guideline for the Treatment of Patients With Bipolar Disorder (2005), Second Edition*, to serve as an evidence-based framework for practitioners' clinical decision-making with patients who have bipolar disorder. These documents incorporate developments in pharmacotherapy and other areas of psychiatric management of individuals with bipolar disorder. A research-based resource, the guideline covers the psychiatric management of patients with this disorder, from clinical features and epidemiology to treatment approach and planning.

An extensive literature review suggests that the APA guideline is among the most comprehensive, evidence-based clinical practice guidelines (CPGs) for this disorder, and in general, APA guidelines are widely used. Accepted broadly by managed behavioral healthcare organizations (MBHOs), this adoption will minimize the burden on practitioners serving multiple MBHOs. Due to the aging of the adopted guideline and the Guideline Watch, Magellan has updated this Introduction to reflect current knowledge and practice.

As with all CPGs, the adopted guideline and Magellan's Introduction augment, but do not replace, sound clinical judgment. As a matter of good practice, clinically sound exceptions to the treatment guidelines should be noted in the member's treatment record, with clinical reasoning for the exceptions. Magellan periodically requests clinical files from providers to monitor compliance with adopted guidelines.

Additionally, this guideline does not supersede Food and Drug Administration (FDA) determinations or other actions regarding withdrawal or approval of specific medications or devices, and their uses. It is the responsibility of the treating clinician to remain current on medication/device alerts and warnings issued by the FDA and other regulatory and professional bodies, and to incorporate such information in his or her treatment decisions. This guideline references selected published literature through May 2017. Magellan encourages providers to continually update their own practices to reflect the most current evidence base.

## Additional Recommendations Based on Recent Literature Review

The APA guideline is based on a literature review through 2001 and the guideline watch is based on a literature review up to its publication in November 2005. Magellan conducted further review of the clinical literature on assessment and treatment of bipolar disorder published through May 2017. We have summarized key recommendations from this more recent literature review below. Magellan encourages providers to be familiar with this information, as well as the information in the APA guideline.

## Executive Summary

(Discussion of changes/new information in this updated guideline)

### *Bipolar Disorder Spectrum*

Based on 2015 population estimates, the lifetime prevalence of bipolar disorder (BD) in the general population is 4.4% in the United States, representing approximately 14 million individuals (Cerimele et al., 2017). Across ethnicities and races, there is little difference in the prevalence of this disorder, which is a leading cause of disability. Cerimele et al. reported that the time of first symptoms, (often occurring in late adolescence) to diagnosis averages six to eight years. Approximately 89% and 95% of individuals with bipolar I disorder or bipolar II disorder, respectively, are treated for bipolar disorder at a minimum of once during their lifetimes; however, only approximately two-thirds are treated by a psychiatrist. In contrast, only about two-thirds of individuals with bipolar I disorder or bipolar II disorder reported receiving treatment in the past 12-months. "Individuals who received treatment were about equally divided between those who received treatment from a psychiatrist and those who received treatment from a general medical clinician, such as a primary clinician" (Cerimele et al., p. 192). Only one-third of individuals with subthreshold bipolar disorder reported receiving any treatment, and only 8% of those received treatment from a psychiatrist (Cerimele et al., 2017). This chronic illness has a two-year recurrence rate of approximately 50% in individuals receiving treatment (Pikalov et al., 2017). Harrison et al. noted that a recent systematic review of literature reported that suicide occurs in approximately 5% of individuals with bipolar disorder, and that mortality rates from natural causes, e.g., cardiovascular disease, increase in patients with bipolar disorder. Bipolar disorder reduces life expectancy by 10 years or more (Harrison et al., 2016).

In a review of literature, authors noted the need for innovative approaches to bipolar disorder and its treatment, highlighting three approaches. Firstly, they called for a "reevaluation of the phenotype, with an emphasis on mood instability rather than on discrete clinical episodes" (Harrison et al., p. 76). Although classically described as "significant episodes of depression and elevated mood (mania or hypomania) with intervening periods of normal mood (euthymia)…the profile of bipolar disorder is complex and heterogeneous, both longitudinally and cross-sectionally, and includes mixed mood states, persistent mood instability, and cognitive dysfunction" (Harrison et al., p. 76). Next, they suggested a reason for the paucity of new drug treatments for bipolar disorder is the lack of a good understanding of etiology and biological basis of the disorder. Noting that bipolar disorder "has a high heritability (over 80%), with a complex non-Mendelian genetic basis," authors emphasized the need for genomic data "to inform and improve bipolar disorder treatments, both by highlighting targets and pathways and by enabling personalized medicine" (Harrison et al., p. 76). They suggested moving forward from descriptive psychopathology to "a more valid nosology and treatments that are based on rational understanding of pathophysiology, the later requiring advances in molecular genetics and neuroscience" (Harrison et al., p. 83).

A recent study mined electronic health records (EHRs) from a large healthcare system, using a diagnostic algorithm for classifying bipolar disorder, to identify variants underlying the heritability of bipolar disorder (Castro et al., 2015). This study found that text mining of EHRs could help in developing specific and predictive diagnostic algorithms comparable to those achieved by direct interview. Authors noted, "With the increasingly widespread implementation of EHRs, this study supports the application of high-throughput *in silico* phenotyping for epidemiologic, genetic, and clinical research" (Castro et al., p. 371).

A recent clinical synthesis focusing on data from neuroimaging and genetic studies highlighted current knowledge about the complicated neurobiology of bipolar disorder (Mahon et al., 2015). Examination of structural and functional brain alterations using magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI), respectively, have found alterations in frontal and subcortical regions involved in emotion regulation. Postmortem morphometric alterations provide further evidence of these alterations. Authors noted that although bipolar disorder has a strong genetic component, the bipolar disorder phenotype is unlikely caused by one or only a few genetic mutations. "Twin studies demonstrate that monozygotic twins have a higher concordance rate (38.5% - 43.0%) for BD than dizygotic twins (4.5% - 5.6%), and family studies show that adopted children with a biological parent with BD have a higher relative risk of developing the disorder than adopted children whose biological parents do not have BD (4.3 versus 1.3)" (Mahon et al., p. 5). Genome-wide association studies (GWAS), pathway analysis, gene expression profile, examination of structural alterations in the genome, and the investigation of epigenetics are different methodologies providing some understanding of the genetics of bipolar disorder. They emphasized that the development of novel treatment strategies are dependent upon an understanding of the neurobiology of bipolar disorder, hindered by the "large degree of phenotypic heterogeneity inherent in the disorder" (Mahon et al., p. 8). Another more recent study provided evidence that limbic brain areas are impacted by bipolar disorder diagnosis and elevated body mass index (BMI) (Bond et al., 2017). Authors suggested that magnetic resonance spectroscopy (MRS) may provide information about the impact of higher BMI on neurochemistry, stating, "Longitudinal studies are urgently needed to determine whether higher BMI and/or increasing BMI over time lead to progression of neurochemical abnormalities in BD" (Bond et al., p. 6).

A large longitudinal study compared diagnostic differences in the offspring of parents with bipolar disorder ("high-risk" offspring), (n=391) with the offspring of community comparison parents without bipolar disorder (n=248). Follow-up assessments were over a mean duration of 6.8 years with a 2.5-year mean follow-up interval (Axelson et al., 2015). Researchers sought to describe "the trajectory of mood episodes and identify diagnostic precursors of full-threshold bipolar disorder (defined as the presence of manic, mixed, or hypomanic episodes, which we refer to hereafter as 'mania/hypomania' in the offspring of parents with bipolar disorder" (Axelson et al., p. 639). High-risk offspring were less likely to be living with both biological parents while their mothers' mean age at time of their birth was significantly lower, compared with community parents' offspring. Parents with bipolar disorder were younger, of lower socioeconomic status, less likely to be married and more likely to be white compared with the community parents. Compared to community parents, they were more likely to have history of a major depressive disorder and a non-mood axis I disorder, e.g., anxiety disorders, ADHD, disruptive behavior disorders and substance use disorders (Axelson et al., 2015). Findings of this study included the following:

- High-risk offspring – higher rates of subthreshold mania or hypomania (13.3%) compared with 1.2% in community offspring;
- High-risk offspring – higher rates of manic, mixed, or hypomanic episodes (9.2%) compared with 0.8% in community offspring;

- High-risk offspring – higher rates of major depressive episodes (32.0%) compared with 14.9% in community offspring; and
- High-risk offspring – subthreshold manic or hypomanic episodes, major depressive episodes, and disruptive behavior disorders associated with subsequent manic, mixed, or hypomanic episodes.

Researchers emphasized the importance of targeting subthreshold manic or hypomanic episodes in the offspring of parents with bipolar disorder, as they are a risk factor for development of manic, mixed, or hypomanic episodes. They also indicated close clinical monitoring of major depressive episodes and disruptive behavior disorders in offspring of parents with bipolar disorder (Axelson et al., 2015).

An epidemiological population-based cohort study investigated the risk of bipolar disorder associated with the occurrence of adverse life events during childhood, e.g., familial disruption, parental psychiatric and somatic illness, parental labor market exclusion, parental imprisonment, parental loss, placement in foster care (Bergink et al., 2016). Familial disruption included household composition other than where the child lived with both legal parents at any time from the child's 1st to 15th birthday (Bergink et al., 2016). Researchers studied associations between various adverse life events before age 15 and risk of bipolar disorder utilizing a nationwide register (Denmark) that included persons in the exposed cohort (n=980,554). Analysis found the most prevalent adverse life events in childhood included family disruption (the most common event), parental somatic illness and parental psychopathology. Parental psychiatric illness, not just bipolar disorder, was associated with the highest risk of bipolar disorder. Researchers noted how psychopathology in parents is considered as both an early-life stressor and a genetic liability marker, and they cautioned that their study does not fully "disentangle whether our findings are the result of heritability, environmental influences or both" (Bergink et al., p. 5). They found no increased risk for bipolar disorder associated with somatic diseases in parents. As their study was designed to assess overall effects of *any type* of parental mental disorder, researchers concluded that "broadly defined parental psychopathology is by far the most important risk factor for bipolar disorder in the offspring" while also noting that "bipolar disorder is a disease with a strong genetic loading" (Bergink et al., p. 5). Other studies have provided evidence that adversities, e.g., physical and sexual abuse, are associated with an elevated risk of mania (Gilman et al., 2015). Due to lack of sufficient statistical power, this study did not conduct analysis of specific adversities. Researchers discussed "stress-related pathways in the etiology of mania, and proposed that these pathways have developmental origins" (Gilman et al., p. 338).

Although bipolar disorder has often been considered largely a genetic disorder, social environmental factors, e.g., early adversity and trauma, negative life events during adulthood, low social support, and poor family functioning, may influence its course (Johnson et al., 2016). Authors noted research findings suggesting that "genetic vulnerability to mania does not explain the vulnerability to depressive symptoms within bipolar disorder," and they argued that "psychosocial risk factors are a critical part of this puzzle" (Johnson et al., p. 2). Authors further noted the difficulty in disentangling "the aftermath of episodes from factors that trigger symptoms" (Johnson et al., 2016).

A recent study including individuals (n=78,809) from the general population in cross-sectional and prospective analyses with a median follow-up time of 5.9 years examined the role of inflammation, indicated by elevated C-reactive protein (CRP), in late-onset bipolar disorder (Wium-Andersen et al., 2016). This "first study to examine the prospective and possible causal associations between elevated CRP and late-onset bipolar disorder in the general population" found that "Elevated plasma levels of CRP were associated cross-sectionally and prospectively with late-onset bipolar

disorder in the general population, after multifactorial adjustment for lifestyle factors, socioeconomic status and chronic disease" (Wium-Andersen et al., 2016, p. 144). Although they found only an association, they indicated that they could not exclude that the association may be causal.

### *Psychiatric Comorbidity*

A recent meta-analysis quantitatively summarized the lifetime prevalence of anxiety disorders in co-occurrence bipolar disorder (mostly bipolar type I) in psychiatric inpatient and outpatient populations as follows: panic disorder 16.8%, generalized anxiety disorder 14.4%, social anxiety disorder 13.3%, post-traumatic stress disorder 10.8%, specific phobia 10.8%, obsessive compulsive disorder 10.7%, and agoraphobia 7.8% (Nabavi et al., 2015). The study found a lifetime prevalence of any anxiety disorder in bipolar disorder of 42.7% with some individuals having more than one identified anxiety disorder comorbidity. Noting the difficulty of diagnosis and treatment due to symptoms overlap, authors summarized the clinical implications of the study. These include: 1) anxiety symptoms and high anxiety scores increase risk for suicide and for alcohol misuse in patients with bipolar disorder; 2) alcohol use may represent attempt to modulate mood lability associated with bipolar disorder; and 4) anxiety may be either a protective factor or an aggravating factor for impulsiveness (Nabavi et al., 2015).

Co-morbidity of bipolar disorder with a range of other psychiatric conditions, e.g., anxiety disorders, substance use disorder, and borderline personality disorder, can create difficulty in diagnosis, poor treatment response, and outcomes (Goodwin et al., 2016). Authors cited a recent meta-analysis of studies suggesting that as many as 45% of bipolar I patients have had an anxiety disorder, and another study showed that anxiety disorder co-morbidity worsens outcomes, e.g., increased suicide rates, rapid cycling, poorer quality of life, worse functioning, and transition from unipolar to bipolar depression. Authors suggested regular monitoring of anxiety in addition to the usual focus on depression and mania as anxiety in bipolar disorder influences treatment. They suggested considering, during assessment, anxiety-provoking mental imagery involving "seeing the mind's eye" which may be related to 'flash back' or 'flash forward' experiences (Goodwin et al., p. 35).

In recent evidence-based guidelines for treating bipolar disorder (from the British Association for Psychopharmacology), authors cited reports that as many as 20% of patients with bipolar disorder may have borderline personality disorder associated with worse outcomes. These include hospitalization, suicidal ideation, deliberate self-harm, increased utilization of services, substance use, poor outcomes, and poor adherence and treatment response (Goodwin et al., 2016). Authors emphasized that clinicians often attempt to make "an exclusive diagnosis of one or other disorder" without systematically enquiring about borderline disorder symptoms, which may overlap with bipolar spectrum and rapid cycling bipolar disorder. Noting that symptoms in the two disorders are very different, with *episodic* symptoms in bipolar disorder and *pervasive and enduring* symptoms in borderline personality disorder, they suggested, "It is a grave clinical error to interpret bipolar episodes as pervasive and personality driven if they are not" (Goodwin et al., p. 37).

The most recent guidelines referred to above also referenced alcohol and drug use as another common and clinically significant comorbidity of bipolar disorder (predominately in bipolar I). Authors noted that excessive use of alcohol or drugs is common in individuals with bipolar disorder and creates difficulty in both diagnosis and treatment. "Drug induced psychosis" is sometimes diagnosed rather than a correct diagnosis of bipolar disorder due to the mania induced by a range of stimulant drugs in patients with this comorbidity. Authors stated, "A true drug-induced psychosis

should either wane with the clearance of the offending drug or be a transient effect associated with drug withdrawal" (Goodwin et al., p. 36).

### *Medical Comorbidity*

Studies have shown that the prevalence of obesity and metabolic disorders is twice as great in individuals with bipolar disorder as in the general population (Mansur et al., 2015). Comorbid obesity significantly affects individuals in early as well as in later stages of bipolar disorder. Mansur et al. cited studies indicating that obesity and metabolic syndrome predispose patients with bipolar disorder to a predominantly depressive illness, which is also more severe with higher functional disability, increased risk of suicide, and negative impact on treatment outcomes. Higher body mass index has been associated with poorer response to pharmacological treatment, e.g., lithium and valproate (Depakote®, Depakene®, Stavzor®) (Mansur et al., 2015). Overweight/obese patients with bipolar disorder also may have more severe neurocognitive dysfunction (measures of attention and psychomotor processing speed) than patients with a mood disorder who have normal weight. Authors noted an "unmet need for the development of empirically based therapeutic strategies specifically focused on the management of weight and lifestyle" in the management of patients with bipolar disorder (Mansur et al., 2015).

Studies have shown that individuals with bipolar disorder have greater mortality rates than the general population and that these deaths are mainly due to chronic medical illnesses, e.g., cardiovascular disease, diabetes mellitus, autoimmune diseases, and cancer, rather than suicide (Mansur et al., 2015). Levin et al. reported studies indicating that individuals with serious mental illness, including bipolar disorder, have a life expectancy shortened by 10 to 30 years and are three times more likely to die prematurely than the general population (Levin et al, 2015). A recent descriptive study, part of a clinical trial promoting medication (psychotropic and non-psychotropic) adherence among patients with bipolar disorder and general medical conditions, assessed the relationship between nonadherence to psychotropic and non-psychotropic medications in participants (n=88) with hypertension, rheumatologic diseases, respiratory diseases, hyperlipidemia, and diabetes (Levin et al., 2015). Results showed that adherence to non-psychotropic medications was low, although somewhat better than adherence to bipolar medications. Low adherence to non-psychotropic medications was associated with greater number of psychiatric hospitalizations, suggesting that mental health instability may negatively affect adherence to non-psychotropic medications. The majority of patients reported difficulty taking their non-psychotropic medications. Authors suggested that although their sample was selective and generalizability may be limited, "High rates of cardiovascular factors in our sample suggest that addressing poor adherence to cardiovascular medications is an area worth targeting to reduce cardiovascular risk and premature mortality in bipolar disorder" (Levin et al., 2015).

### *Collaborative Care for Bipolar Disorder*

Magellan's guideline for the treatment of patients with major depressive disorder reported studies showing the benefits of a collaborative care program for primary care patients with *major depressive disorder* (Magellan Health, 2017). Two large effectiveness trials have demonstrated "that individuals with *bipolar disorder* can also participate successfully in, and benefit from, highly collaborative chronic care models" (Bauer et al., 2015). **Core principles of the collaborative care model for integrating physical and mental healthcare include**:

- Patient-centered team care;
- Population-based care;
- Evidence-based care, accountable care; and
- Measurement-based care/scale-based care (Advancing Integrated Mental Health Solutions [AIMS] Center, 2017).

**Chronic care models** include:

- Emphasis on continuity of care over episodic response to acute symptoms;
- Enhancement of patient self-management skills;
- Support of provider decision making; and
- Improvement in system responsiveness to patient needs (Bauer et al., p. 85).

Measurement-based care, sometimes called scale-based care or stepped care, affects clinical care as it relies on data collected throughout treatment, and it is a core component of evidence-based practices (Scott and Lewis, 2015). It "provides insight into treatment progress, highlights ongoing treatment targets, reduces symptom deterioration, and improves client outcomes" (Scott and Lewis, 2015, p. 49). In a study addressing whether collaborative care for bipolar disorder improves outcomes, Bauer et al. discussed the importance of measurement-based care. In this study, they utilized the following measures: **Longitudinal Interval Follow-Up Examination, Social Adjustment Scale-II, Medical Outcomes Study 36-item Short Form Health Survey** and **National Institute of Mental Health Collaborative Study** (Bauer et al., 2015). These outcome measures provided ratings of symptoms of mania and depression, subthreshold symptoms or episodes; ratings of impairment in work, social and leisure, marital, parental, and extended family; ratings of mental and physical quality of life; and intensity of bipolar-specific pharmacotherapy.

Bauer et al. compared a collaborative chronic care model (**The Bipolar Disorders Program Intervention**) with usual care for bipolar disorder across 11 Veterans Affairs medical centers in a three-year randomized controlled single-blind trial. Participants with bipolar disorder admitted to psychiatric wards at 11 sites were randomly assigned at discharge to a three-year follow-up to the collaborative care intervention or to usual care. The collaborative care intervention (clinic based) included a specialty team with a nurse care coordinator and a psychiatrist in an outpatient clinic, providing care via regular appointments supplemented as needed by phone and clinic contact. Components of care included enhancement of patients' ability to self-manage illness using group psychoeducation; an algorithm and reference manual (VA Bipolar Practice Guidelines) to support providers and enhance evidence-based pharmacotherapy; and a nurse care coordinator enhancing access to care as well as continuity of care. The care manager facilitated information flow of laboratory results, clinical assessments, etc. to the psychiatrist. Usual care participants continued with their previous psychiatrist or, if new to VA, they received assignment to a new psychiatrist. **Benefits of collaborative care vs. usual care** included: 1) significant reduction in weeks of manic episodes (non-significant reduction in weeks of depressive episodes); 2) significant improvement in overall social function (work, parental and extended family roles); improved mental, but not physical, quality of life; and 3) higher treatment satisfaction from the first six-month assessment. 'Pharmacotherapy intensity' did not differ between the two treatment groups. Researchers noted how these results are "consistent with a concurrent two-year trial of a similar collaborative chronic care model for bipolar disorder. Compared with usual care in a staff-model HMO, that intervention also demonstrated significant effects on mania but not depression" (Bauer et al., 2015, p. 89). (These two trials covered over 700 participants.) Noting that pharmacotherapy did not differ in the two groups and was adequate, researchers suggested the possibility that psychoeducation alone

may have enhanced outcomes and that "multiple components contributed with improved access and continuity facilitating pharmacotherapy and patient self-management" (Bauer et al., p. 90). Researchers concluded that individuals with bipolar disorder benefit from collaborative chronic care models and rejected the "paternalistic assumptions" that have separated mental from other medical illnesses concerning the insight and self-management capabilities of individuals with severe mental illness. Researchers suggested the need for studies of collaborative care programs for primary care patients with bipolar disorder (Bauer et al., 2015). Other studies have found that "collaborative or participatory communication style" between physician and patient increases medication adherence and has a positive impact on treatment (Stubbe, 2015). Stubbe emphasized that adherence to treatment with medications is usually partial or intermittent in bipolar disorder, and that the interpersonal aspects of the patient-physician relationship may improve treatment success.

### *Treatment for Acute Mania and Mixed Features or Mixed Episodes*

Manic episodes distinguish bipolar disorder from recurrent unipolar depression. Treatment for manic and hypomanic episodes includes mood stabilizers, i.e., lithium, valproate, and carbamazepine (Tegretol®) and atypical antipsychotics. On September 17, 2015, the U.S. Food and Drug Administration approved cariprazine (Vraylar®) to treat both schizophrenia and bipolar disorder in adults (FDA, 2015). The safety and efficacy of cariprazine in treatment of acute bipolar I mania was shown in a post hoc analysis of pooled data from 3 three-week randomized, double-blind, placebo-controlled, flexible-dose (3-12 mg/d) trials including patients (n=1065) with manic or mixed episodes of bipolar disorder (Earley et al., 2017). Results of this study found that cariprazine was well tolerated and generally safe, although discontinuations due to adverse events, e.g., akathisia and extrapyramidal symptoms, were somewhat greater in the cariprazine group than placebo. However, most of the adverse events were mild to moderate in severity and did not lead to discontinuation of the study. Researchers noted that cariprazine was not associated with hyperprolactinemia, often reported to be a major cause for poor adherence to medications. Scores from the Young Mania Rating Scale (YMRS) showed greater efficacy of cariprazine than placebo. At the end of treatment, more patients in the cariprazine group had mild or no symptoms compared with patients in the placebo group (Earley et al., 2017).

An initial treatment for acute mania usually requires short-term pharmacological treatment; psychotherapy is not effective for management (Goodwin et al., 2016). The most current evidence-based guidelines from the British Association for Psychopharmacology advised that in the treatment of severe mania, dopamine antagonists, e.g., haloperidol (Haldol®), olanzapine (Zyprexa®), risperidone (Risperdol®), and quetiapine (Seroquel®) provide rapid antimanic effect (Goodwin et al., 2016). Valproate may be an alternative treatment; however, the guidelines noted that it should not be used in treatment of women of childbearing potential. Other options also include aripiprazole (Abilify®), other dopamine antagonists and partial agonists, carbamazepine and lithium. To control behavior of an agitated patient without their consent, the guidelines suggested treatment with the lowest dose necessary of dopamine antagonists/partial agonists and GABA modulators, e.g., benzodiazepines. If acute mania begins while receiving maintenance treatment of lithium, the guidelines suggested adding a dopamine antagonist or partial agonist (Goodwin et al., 2016). Authors reported that data from trials support the same treatment for mixed features as in mania. The guidelines also advised tapering and discontinuance of antidepressant drugs in a manic episode.

### *Treatment of Acute Depressive Episode*

Evidence-based guidelines from the British Association for Psychopharmacology noted the uncertainty of choosing antidepressants in patients with bipolar disorder who are having an acute depressive episode (Goodwin et al., 2016). They recommended treatment of acute depressive episode with quetiapine, lurasidone (Latuda®) or olanzapine in patients with bipolar disorder not already receiving treatment for the disorder. Although antidepressants are not an established treatment for acute depressive episode in bipolar disorder and there is a risk of a switch to mania during treatment for depression, they appear unlikely to induce mania when combined with a drug for mania (Goodwin et al., 2016). The guidelines referred to above also indicated consideration of electroconvulsive therapy (ECT) for the treatment of patients with psychosis, treatment resistance, high suicidal risk, and severe depression during pregnancy. When the depressive episode is less severe, authors recommend considering lithium for treatment. According to the guidelines, **additional** psychological treatment, i.e., family-focused, cognitive behavior therapy or interpersonal rhythm therapy may shorten the acute depressive episode. The guidelines noted the lack of evidence of efficacy of these treatments without combined pharmacotherapy.

The guidelines advised that when an antidepressant as monotherapy treats an acute depressive episode in bipolar II disorder, the dose should only be increased gradually and closely monitored for any adverse reactions.

Researchers compared medication-induced mood switch risk in three acute phase treatments, i.e., lithium monotherapy, sertraline monotherapy, and combined lithium and sertraline in a 16-week, double-blind, multisite comparison study including participants (n=142) with bipolar II depression (Altshuler et al., 2017). This prospective, randomized double-blind trial found "no difference in risk of hypomanic switch across sertraline monotherapy, lithium monotherapy, or combination therapy" and none of the participants had a manic switch (Altshuler et al., p. 272). Between treatment groups, there was no significant difference in response rates, although there was a significantly higher dropout rate in the combination treatment group.

The long-term safety, tolerability, and effectiveness of lurasidone was evaluated in an 18-month, open-label, continuation study including individuals whose initial presentation was a major depressive episode associated with bipolar I disorder, and who had completed six or more months of initial treatment with lurasidone (Pikalov et al., 2017). Three initial, double-blind, placebo-controlled trials (lurasidone monotherapy; adjunctive therapy with lurasidone; and lithium or valproate) enrolled individuals (n=1199) with bipolar I depression over six weeks, and 78.5% of the enrollees completed the trials. Almost 87% of these individuals then entered a six-month extension study of lurasidone and 68.4% completed the trial. Of those completing the six-month extension study, almost 22% entered the 18-month continuation trial. The mean dose of lurasidone during the continuation trial was 61.8 mg/day. Of the participants in the continuation trial, almost 19.7% discontinued (6.6% due to adverse events and 1.6% due to insufficient efficacy). Results of this continuation study found relatively low levels of both weight gain and adverse metabolic effects, comparable with results reported in studies of lurasidone in patients with schizophrenia. The majority of patients maintained improvement in depressive symptoms. In conclusion, researchers stated, "In summary, up to 2 years of treatment with lurasidone monotherapy or adjunctive therapy was found to be safe and well tolerated in this bipolar I disorder population that presented initially with a major depressive episode. Researchers observed minimal effects on weight and metabolic parameters consistent with previous long-term trials in patients with a diagnosis of schizophrenia. Improvement in depressive symptoms was maintained in the majority of patients during long-term lurasidone treatment, with relatively low rates of relapse" (Pikalov et al., p. 7).

### *Treatment of Rapid Cycling*

Studies have suggested that individuals with bipolar disorder and comorbid migraine, more likely to be female and have panic attacks, have a higher prevalence of rapid cycling (Gordon-Smith et al., 2014). The rate of rapid cycling in bipolar disorder, defined as having four or more episodes in a 12-month period, has been reported to comprise 34.7% of patients in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) (El-Mallakh et al., 2015). An analysis of a randomized clinical trial within the STEP-BD analyzed rapid cycling to determine whether antidepressants (ADs) caused or worsened it in patients (n=68) randomized to continue or discontinue antidepressant treatment after initial response to an acute depressive episode treated with an antidepressant and a mood stabilizer (El-Mallakh et al., 2015). Authors noted that individuals with rapid cycling generally are younger, have greater disease burden, and more exposure to antidepressants than those without rapid cycling. Results found that patients with rapid cycling receiving continuation antidepressant treatment experienced a greater (268% more) number of mood episodes per year as well as more (293% more) depressive episodes per year than those without rapid cycling. They also had less time in remission than those without rapid cycling. No significant differences existed in the patients discontinuing antidepressant treatment. Authors concluded, "Despite preselection for good antidepressant response and concurrent mood stabilizer treatment, antidepressant continuation in rapid-cycling was associated with worsened maintenance outcomes, especially for depressive morbidity, versus antidepressant discontinuation" (El-Mallakh et al., p. 319). They further stated, "This decreased efficacy of antidepressants supports previous claims of limited clinical utility and lack of safety in long term treatment of BD patients with ADs" (El-Mallakh et al., p. 323).

### *Maintenance Treatment*

The recommendations from the British Association for Psychopharmacology indicate that long-term treatment of bipolar disorder includes continuous, not intermittent, treatment with medications to prevent new mood episodes (Goodwin et al., 2016). Randomized controlled trials have supported the efficacy of different medications to prevent *manic relapse:* lithium, olanzapine, quetiapine, risperidone long-acting injection (LAI), and valproate. For the prevention of *depressive relapse*, the guidelines report that the following medications are effective: lamotrigine, lithium, quetiapine, and lurasidone. The guidelines also recommend GABA modulators, i.e., benzodiazepines, or dopamine antagonists/partial agonists in the presence of an acute stressor, early relapse symptoms, or if anxiety is prominent. As initial monotherapy, the guidelines recommend lithium due to its effectiveness against manic, depressive and mixed relapse, and its association with reduced relapse and reduced suicide/self-harm. The guidelines suggest valproate, considered equivalent to lithium, to stabilize mood, if patients do not tolerate lithium or if it is not effective. Although carbamazepine is not as effective as lithium in maintenance treatment, the guidelines suggests its use when lithium is ineffective. Recommendations include combinations of predominantly anti-manic agents when there is no effective response to monotherapy for patients whose burden of disease is mania. Where the burden is depressive, "a combination of lithium, lamotrigine, quetiapine, lurasidone or olanzapine may be more appropriate" (Goodwin et al., p. 505). Cautioning a lack of support in long-term trials for use of antidepressants in long-term treatment, the guidelines suggest effective use of antidepressants in the long term for a small number of patients. For treatment of refractory mania, the guidelines suggest consideration of clozapine (Goodwin et al., 2016). The guidelines recommend considering maintenance electroconvulsive therapy (ECT) for patients who do not respond well to oral agents if they have responded to ECT during an acute episode. Although relapse risk continues even after years of

sustained remission, the guidelines emphasize an informed assessment of potential dangers of discontinuation. Noting that psychoeducation is a component of good clinical practice, the guidelines suggest family-focused therapy, cognitive behavior therapy, and interpersonal social rhythm therapy to enhance care and reduce subthreshold symptoms.

Most Repetitive Transcranial Magnetic Stimulation (rTMS) studies have focused on treatment of unipolar major depressive disorders rather than on bipolar depression. Magellan Health considers the use of (rTMS) for treatment of bipolar disorder to be investigative at this time, as trials in bipolar depression are too limited for meaningful conclusions (Magellan Health, 2015).

In a double-blind, placebo-controlled, randomized withdrawal study, researchers evaluated efficacy, safety, and tolerability of long-acting injectable (LAI) antipsychotic aripiprazole (Abilify Maintena®) once-monthly 400 mg as maintenance treatment for bipolar I disorder (Calabrese et al., 2017). After a screening for current manic episode, patients converted to oral aripiprazole (15-30 mg/day) for 4-6 weeks followed by oral aripiprazole stabilization over 2-8 weeks. After assessment for stability, patients entered the single-blind stabilization phase over a period of 12-28 weeks during which they received injectable LAI aripiprazole every 4 weeks. The double-blind phase included patients (n=266) who met a stability criteria and were randomized to 52 weeks of treatment with either injectable LAI aripiprazole or placebo. The study found significant delay in time to recurrence of mood episodes and fewer patients experiencing any mood episode in patients treated with LAI aripiprazole once monthly compared with placebo. Researchers noted that treatment was generally safe, well tolerated, and resulted in few discontinuations due to adverse events of treatment. The adverse events reported at higher rates with treatment compared to placebo were weight increase, akathisia, insomnia, and anxiety of which most were mild or moderate. Researchers discussed the serious challenge of adherence in the treatment of patients with bipolar I disorder, suggesting the need for additional studies of the potential of LAIs in bipolar disorder. They concluded that this study demonstrated LAI aripiprazole's efficacy in the maintenance treatment for Bipolar I disorder, and that it is generally safe and well tolerated (Calabrese et al., 2017). Currently the only long-acting injectable antipsychotic approved by the FDA for the maintenance treatment of bipolar disorder is risperidone (Risperdal Consta®).

Noting that bipolar disorder is associated with 10 and 15 times greater risk of suicide acts and lifetime suicide, respectively, than the general population, researchers compared rates of self-harm, unintentional injury, and suicide in patients (n=6671) diagnosed with bipolar disorder and prescribed lithium, valproate sodium, olanzapine, or quetiapine fumarate as maintenance mood stabilizer treatment (Hayes et al., 2016). They completed this large nationally representative cohort study covering a period of 18 years by examining primary care electronic health records of patients with two or more consecutive prescriptions of these drugs for treatment lasting at least 28 days. Results found lower rates of self-harm in individuals prescribed lithium than in those receiving valproate, olanzapine and quetiapine as maintenance treatment; rates of unintentional injury were lower in those prescribed lithium than those prescribed valproate and quetiapine, but not olanzapine. The small number of suicides in the cohort did not allow researchers to estimate rates accurately between the various treatments, although the rate was lower in the lithium group. Researchers indicated that these findings augment results of other studies and "support the hypothesis that lithium use reduces impulsive aggression in addition to stabilizing mood" (Hayes et al., p. 630).

### *Psychosocial Treatment*

A recent survey of non-physician mental health clinicians from community mental health clinics examined knowledge about bipolar disorder, treatment approaches and perceived barriers that

may interfere with optimal treatment (Stein et al., 2015). Authors used responses on the clinician self-report version of the validated Psychotherapy Practice Scale for Interpersonal and Social Rhythm Therapy (IPSRT) and the Clinician Techniques and Beliefs (CTB) measures for assessment. Most of the mental health clinicians were social workers along with other disciplines, e.g., psychology, marriage and family, and child counseling. Results of the survey showed cognitive behavior therapy (CBT) was the most commonly used therapeutic approach. Other therapies utilized included counseling (self-rated highest), psychoeducation, and the identification of warning signs of possible recurrence. Of the participants (n=55), 67% acknowledged that they were very knowledgeable in the treatment of individuals with bipolar disorder, while only 33% of clinicians were able to correctly answer more than 84% of true-false questions about bipolar disorder. Clinicians viewed substance use problems as interfering with treatment of bipolar disorder, and 44% of clinicians perceived these problems as more pressing than symptoms of bipolar disorder. Authors noted that although it was encouraging to see clinicians embracing CBT techniques, they did not utilize alternative techniques, e.g., sleep-wake routines, where they could have been beneficial. They suggested enhancement of additional knowledge of non-physician mental health clinicians about psychotropic medication used in the treatment of bipolar disorder to encourage patient adherence to medication and for monitoring of side effects. They also suggested education about and encouragement for the use of other interventions, such as motivational interviewing and motivational enhancement. Authors concluded, "Our findings suggest that they would benefit from additional training in effective therapeutic approaches for bipolar disorder beyond CBT, as well as pharmacotherapy" (Stein et al., 2015).

A recent article reviewed randomized trials of adjunctive psychotherapy, i.e., CBT; group psychoeducation; family-focused treatment; and IPRST in delaying or preventing relapses and stabilizing illness episodes (Miklowitz and Gitlin, 2015). While noting that progress in psychological interventions was slow, compared to the growth in numbers of pharmacological options for bipolar disorder, studies have reported that the addition of psychotherapy to pharmacotherapy during the post-episode phase or the maintenance phase of treatment reduces rates of recurrence by 50% or more compared with usual care. Treatment reported to be more effective than usual care is commonly over a period of 4-6 months and includes 12 or more sessions. Authors noted that treatment guidelines for bipolar disorder recommend psychotherapy, e.g., psychoeducation sessions focusing on illness management and stress reduction, combined with medications. Treatment strategies including adjunctive psychotherapy and discussed in this article include the following:

- ***CBT*** – includes behavioral activation, relapse prevention, and cognitive restructuring; CBT is the most frequent psychotherapy examined in randomized controlled trials, although its protocols may vary (Miklowitz and Gitlin, 2015);
    - Authors reported a trial in patients (n=103) comparing CBT plus pharmacotherapy to pharmacotherapy alone, finding 75% of patients in the pharmacotherapy alone group had relapsed at one year compared to 44% of those in the adjunctive CBT group; at 30 months, patients in the CBT plus pharmacotherapy group had fewer depressive relapses and days in mood episodes than patients in the pharmacotherapy alone group (Miklowitz and Gitlin, 2015);
    - Another study compared 22 sessions of CBT to treatment as usual (TAU) in patients (n=253) with bipolar disorder and found no difference in time to recurrence over 18 months; patients with fewer prior episodes were less likely to have recurrence in CBT than in TAU; among those having many prior episodes, those in the CBT group were more likely to have recurrences than the TAU group; authors suggested "CBT may be best suited to the earliest phases of the disorder, or CBT may be unsettling and agitating

to patients who are unstable, have a more refractory illness, or have more cognitive impairment" (Miklowitz and Gitlin, p. 39);

- Another study found no differences in symptom severity or recurrence rates between individual CBT or six sessions of group psychoeducation in patients (n=204) who were in full or partial remission (Miklowitz and Gitlin, 2015);
- In a study including patients (n=76) with subthreshold manic or depressive symptoms randomized to CBT combined with pharmacotherapy or individual supportive therapy adjunctive to pharmacotherapy, no differences in relapse rates were evident over 33 months; authors noted common elements of the two approaches (Miklowitz and Gitlin, 2015).

- ***Group Psychoeducation*** - Authors reported that group psychoeducation "enlivens psychoeducation with real-life examples" and "takes advantage of the social support provided by other patients" (Miklowitz and Gitlin, 2015, p. 39). Authors also noted that its role is more consistent in treating and preventing manic symptoms than depressive symptoms.
  - A study evaluating group psychoeducation similar to CBT but with only minimal use of behavioral activation or cognitive restructuring found that 22 sessions of structured psychoeducation was associated with better psychosocial functioning and fewer recurrences than the use of a support group alone. Compared with those in the support group, those receiving the structured psychoeducation had fewer days of acute illness over a period of five years (Miklowitz and Gitlin, 2015).
  - Another study found that patients (n=306) in Department of Veterans Affairs sites who received mood monitoring from a nurse care coordinator and group psychoeducation had fewer weeks in manic episodes than those receiving usual care; multicomponent care resulted in significant improvements in social functioning and quality of life (Miklowitz and Gitlin, 2015).
  - Another very large randomized trial in patients (n=441) with bipolar disorder found patients receiving group psychoeducation with multicomponent care had lower mania scores and less time in episodes of mania or hypomania than patients in usual care. Group psychoeducation did not significantly affect depressive symptoms (Miklowitz and Gitlin, 2015).
  - "Functional remediation treatment," an adaptation of structured psychoeducation emphasizing cognitive functioning, was tested in a randomized trial including patients (n=268) with bipolar disorder who received group sessions of functional remediation, standard group psychoeducation, or TAU in 21 weekly sessions. The functional remediation group showed greater improvements in psychosocial functional functioning than in TAU, but the improvement was only slightly better than in standard psychoeducation (Miklowitz and Gitlin, 2015).
- ***Family Focused Treatment (FFT)*** - strives to lead to faster stabilization while reducing likelihood of recurrences of bipolar disorder, and includes assistance in stabilization of sleep/wake cycles and adherence to medications (Miklowitz and Gitlin, 2015).
  - Results of nine randomized trials of family-focused treatment for patients (n=959) with bipolar disorder found, "Overall, FFT and pharmacotherapy have been associated with a 35-40% reduction over 2 years in recurrence rates compared with brief psychoeducation and pharmacotherapy" (Miklowitz and Gitlin, p. 40).

- FFT was associated with greater survival rate than comparison groups;
- FFT was associated with fewer patients re-hospitalized than individual therapy;
- FFT combined with interpersonal therapy was associated with less depression and longer time to relapse;
- Recovery at one year was greater in FFT (77%) than in IPSRT (65%), CBT (60%), and collaborative care (52%) with better functioning in FFT, IPSRT and CBT versus collaborative care;
- Recovery of adolescents in FFT was faster than in those in enhanced care;
- Compared with health program, both caregivers and patients in FFT had decreases in depression;
- Recovery from depression was faster in children in FFT than children in TAU;
- FFT was associated with less severe manic symptoms in adolescents than enhanced care; and
- Greater reductions in positive symptoms occurred in patients in FFT than in enhanced care.

- ***Interpersonal and Social Rhythm Therapy (IPSRT)*** - includes strategies, integrated into interpersonal problem solving, to improve social rhythm regularity and nightly routine regularity by preventing disruptions in the rhythms that may precipitate episodes of mood disorder (Miklowitz and Gitlin, 2015).
  - In a large trial of IPSRT, patients (n=175) who were randomized to IPSRT during an acute mood episode had a longer time to recurrence in the maintenance phase than those assigned to intensive clinical management, while also showing greater ability to stabilize sleep/wake cycles and social routines during acute treatment (Miklowitz and Gitlin, 2015).
- Authors concluded that psychotherapy is an effective adjunctive to pharmacotherapy and that more effective treatment includes 12 or more sessions lasting 4-6 months. They acknowledged that there is lack of knowledge about which form of psychotherapy is the most effective for the different phases of bipolar disorder, and that knowledge is scant about the mechanisms affecting the improvement of patients in the different treatments. In conclusion, they stated, "Integrating the study of psychotherapy with brain imaging techniques may also help determine what patients are the best candidates for intensive care."

### *Complexities of Treatment of Bipolar Disorder*

Psychiatrists are challenged in treating women with bipolar disorder through pregnancy and the postpartum period due to risk of relapse and recurrence postpartum (Wesseloo et al., 2017). Although lithium is considered the gold standard for treatment of bipolar disorder, decisions about its use during pregnancy are complicated due to inconclusive data on the associated risks of adverse neonatal outcomes. A recent population-based cohort study investigated whether lamotrigine, increasingly used as an alternative to lithium during pregnancy, is as effective as lithium in the prevention of severe postpartum episodes. Researchers compared the risk of inpatient psychiatric admission within three months postpartum in two groups: women (n=55) using lamotrigine and women (n=59) using lithium during pregnancy (Wesseloo et al., 2017).

Researchers found the overall risk for postpartum psychiatric admission was 11.4%, with no significant difference between the two groups. Overall, the polarity of postpartum episodes was 53.8% for mania or psychosis and 46.2% for depression or other diagnoses with no significant difference between the groups. Limitations of this study noted by researchers included the small sample size as well as "confounding by indication because lithium was predominantly prescribed in patients with a history of manic episodes, while lamotrigine was primarily prescribed to women with a particular vulnerability for depressive episodes. Notably, this is consistent with the current bipolar disorder treatment guidelines" (Wesseloo et al, p. 396). Researchers also noted, "The perinatal effectiveness of lamotrigine is largely unknown for patients with predominantly manic episodes in history" (Wesseloo et al, p. 396).

Authors emphasized challenges in psychopharmacologic treatment of anxiety disorders in bipolar disorder, e.g., the concern that antidepressants may destabilize mood in patients, and that benzodiazepines may present problems in treating patients with comorbid alcohol/substance use disorders. They suggested the use of medication, e.g., a typical or atypical antipsychotic that may cover both conditions, and cautioned, "effect of atypical antipsychotics (e.g., olanzapine, quetiapine and lurasidone) on anxiety during bipolar depression should be viewed with caution and as preliminary" (Nabavi et al., p. 1415). Authors advised the use of psychological interventions, e.g., cognitive behavioral therapy (CBT) and mindfulness-based cognitive therapy in the treatment of anxiety comorbid to bipolar disorder while noting that the co-occurrence of more than one anxiety disorder may discourage the use of psychotherapy in patients with bipolar disorder. Noting the challenge in treating co-existing conditions, authors stated the need for advancing knowledge on patterns of response to psychological and psychopharmacological treatments among patients with bipolar disorder with or without anxiety disorders (Nabavi et al., p. 1415).

***Summary of New Recommendations since Magellan's Last Update (2015) Based on Current Literature***

- **Bipolar Disorder Spectrum**
    - Emphasize mood instability instead of discrete clinical episodes in re-evaluation of phenotype.
    - Increase understanding of etiology and biological basis of bipolar disorder.
    - Increase understanding of pathophysiology of bipolar disorder to make better treatment decisions.
    - Use text mining of electronic health records to assist in development of diagnostic algorithms.
    - Increase understanding of the impact of increased body mass index on progression of neurochemical abnormalities in bipolar disorder.
    - Increase awareness of diagnostic differences in "high risk" offspring of parents with bipolar disorder with offspring of parents without the disorder; target subthreshold manic or hypomanic episodes in offspring of parents with bipolar disorder as these are risk factors for development of manic, mixed, or hypomanic episodes; closely monitor major depressive episodes and disruptive behavior disorders in offspring of parents with bipolar disorder.
    - Increase awareness of associations between adverse life events, e.g., parental loss, child not living with parents from age 1 to age 15, and parental psychopathology,

during childhood and risk of bipolar disorder; increase awareness of both genetic and environmental risks associated with bipolar disorder.

- Consider how inflammation indicated by elevated C-reactive protein (CRP) is associated with late-onset bipolar disorder.

- **Psychiatric Comorbidity**
  - Increase awareness of how anxiety symptoms and high anxiety scores may increase risk of suicide and alcohol misuse in patients with bipolar disorder; worsen rapid cycling; decrease quality of life; decrease level of functioning; and lead to a transition from unipolar to bipolar depression.
  - During assessment, consider anxiety-provoking mental imagery involving "seeing the mind's eye" related to flashbacks or flash forward experiences.
  - Enquire about borderline disorder symptoms that often overlap with bipolar spectrum and rapid cycling bipolar disorder while being aware that episodic symptoms occur in bipolar disorder while pervasive and enduring symptoms occur in borderline personality disorder.
  - Be careful not to confuse diagnosis of bipolar disorder with diagnosis of drug induced psychosis; mania may be induced by a range of stimulant drugs in patients with bipolar disorder.

- **Medical Comorbidity**
  - Consider how obesity, increased body mass, and metabolic disorders affect patients with bipolar disorder, predisposing them to a predominantly depressive illness, more severe and with higher functional disability, increased risk of suicide, and negative impact on treatment outcomes.
  - Consider how chronic medical illnesses, cardiovascular disease, diabetes mellitus, autoimmune diseases, and cancer increase mortality rates in individuals with bipolar disorder more than suicide.
  - Address poor adherence to non-psychotropic medications, e.g., cardiovascular medications, in patients with bipolar disorder, as mental health instability may negatively affect adherence to non-psychotropic medications, increasing premature mortality.

- **Collaborative Care for Bipolar Disorder**
  - Consider the benefits of collaborative care interventions for patients with bipolar disorder; become familiar with the core principles of the collaborative care model for integrating physical and mental healthcare.
  - Utilize measurement-based care, also called scale-based care or stepped care.
  - Improve the communication style between physician and patient, using a collaborative or participatory communication style to increase medication adherence and have a positive impact on treatment.

- **Acute Mania and Mixed Features**
    - Treat manic and hypomanic episodes in bipolar disorder with mood stabilizers, e.g., lithium, valproate, and carbamazepine, and atypical antipsychotics.
    - Consider the use of cariprazine (Vraylar®), a new drug approved by the U.S. Food and Drug Administration on September 17, 2015, to treat bipolar disorder (also is used to treat schizophrenia).
    - Consider treating acute mania initially with a short-term pharmacological treatment.
    - Consider treating severe mania with dopamine antagonists, e.g., haloperidol (Haldol®), olanzapine (Zyprexa®), risperidone (Risperdol®), and quetiapine (Seroquel®), to provide rapid anti-manic effects; valproate may be an alternative treatment, but should not be used in treatment of women of child-bearing potential.
    - Other treatment options include aripiprazole (Abilify®), and other dopamine antagonists and partial agonists, e.g., carbamazepine and lithium.
    - Consider treatment with the lowest dose necessary of dopamine antagonists/partial agonists and GABA modulators, e.g., benzodiazepines, to control agitated patients without their consent.
    - A dopamine antagonist or partial agonist may be added if acute mania begins while the patient is receiving maintenance treatment of lithium.
    - Consider treating mixed features the same as mania.
    - Consider tapering and discontinuance of antidepressant drugs in a manic episode.

- **Acute Depressive Episode**
    - Consider treating acute depressive episodes with quetiapine, lurasidone, or olanzapine in patients with bipolar disorder not already receiving treatment for the disorder.
    - Consider lithium as treatment for a depressive episode that is not severe.
    - Consider psychological treatment, e.g., family-focused, cognitive behavior therapy or interpersonal rhythm therapy combined with pharmacotherapy, to shorten the acute depressive episode.
    - When treating an acute depressive episode in bipolar II disorder, only gradually increase the dose while closely monitoring for any adverse reactions.

- **Rapid Cycling**
    - Consider avoiding continuing antidepressant treatment due to its association with worsened maintenance outcomes, e.g., depressive morbidity.

- **Maintenance Treatment**
    - Consider continuous, not intermittent, treatment with medications to prevent new mood episodes.

- To prevent manic relapse, consider treatment with lithium, olanzapine, quetiapine, risperidone long-acting injection (LAI) and valproate.
- To prevent depressive relapse, consider lamotrigine, lithium, quetiapine, and lurasidone.
- In the presence of an acute stressor, early relapse symptoms, or if anxiety is prominent, consider treatment with GABA modulators, i.e., benzodiazepines, or dopamine antagonists/partials agonists.
- Consider lithium as initial monotherapy against manic, depressive and mixed relapse.
- Consider valproate to stabilize mood if patients do not tolerate lithium or if it is ineffective.
- When lithium is ineffective, consider carbamazepine for maintenance treatment.
- Consider combinations of predominantly anti-manic agents when there is no effective response to monotherapy for patients whose burden of disease is mania.
- Combined lithium, lamotrigine, quetiapine, lurasidone or olanzapine may be considered for patients whose burden of disease is depressive.
- Exercise caution in using antidepressants in long-term treatment.
- Consider clozapine for the treatment of refractory mania.
- Consider ECT for patients not responding well to oral agents if they have responded to ECT during an acute episode.
- Perform an informed assessment of potential dangers before discontinuation of treatment.
- Consider family-focused therapy, cognitive behavior therapy, and interpersonal social therapy to enhance care and reduce subthreshold symptoms.
- Consider long-acting injectable antipsychotic medications, e.g., LAI aripiprazole and LOA risperidone, for the maintenance treatment of bipolar disorder.
- Consider the use of lithium to reduce impulsive aggression in addition to stabilizing mood.

- **Psychosocial Treatment**
  - Provide training for non-physician mental health clinicians in effective therapeutic approaches for bipolar disorder beyond CBT, and enhance knowledge of psychotropic medications used to treat bipolar disorder to encourage patient adherence and monitoring of side effects.
  - Consider psychotherapy, i.e., CBT, group psychoeducation, family-focused treatment, and IPRST, as an effective adjunctive to pharmacotherapy to delay or prevent relapses and stabilize illness episodes.
  - Increase knowledge about effective forms of psychotherapy for different phases of bipolar disorder.

# Introduction

## Bipolar Disorder Spectrum (BPS)

According to researchers in a study of bipolar patients in the United States using a probability sample of data from the 2007 National Comorbidity Survey Replication (NCS-R), there is a large discrepancy between rates of bipolar disorder found in large-scale community surveys and those derived from prospective longitudinal studies (Merikangas et al., 2007). Study results showed that the lifetime prevalence rate estimates are 1.0 percent for bipolar I (BP-I), 1.1 percent for bipolar-II (BP-II) and 2.4 percent for bipolar disorder not otherwise specified (BD-NOS)—also referred to as subthreshold bipolar disorder. Researchers indicated that most respondents with threshold and subthreshold bipolar disorder had lifetime comorbidity and other Diagnostic and Statistical Manual (DSM) IV-TR Axis I disorders, particularly anxiety. Clinical severity and role impairment were greater for threshold than for subthreshold bipolar disorder and for BP-II than for BP-I episodes of major depression. However, subthreshold cases still have moderate to severe clinical severity and role impairment. The study also revealed that, although most people with bipolar disorder receive lifetime professional treatment for emotional problems, use of anti-manic medication is uncommon, especially in general medical settings. Other significant findings in the study showed that while nearly everyone who had bipolar I disorder or bipolar II disorder, (89 to 95 percent) received some type of treatment, 69 percent of those with BD-NOS were getting treatment. Those with bipolar I disorder or bipolar II disorder were commonly treated by psychiatric specialists, while those with BD-NOS were more commonly treated by general medical professionals (Merikangas et al., 2007).

A later international report presented the lifetime and 12-month prevalence rates for BP-I, BP-II and subthreshold BP from the World Mental Health (WMH) Survey Initiative (Merikangas et al., 2011). This project of the World Health Organization (WHO) obtained cross-national information on the prevalence, patterns of comorbidity, impact and use of mental health services in high-, middle- and low-income countries. Results from this combined sample of approximately 61,000 adults from 11 countries showed total lifetime prevalence of BP-I of 0.6 percent, BP-II of 0.4 percent and subthreshold BP of 1.4 percent. Twelve-month prevalence rates were 0.4 percent, 0.3 percent and 0.8 percent for BP-I, BP-II and subthreshold BP respectively. The United States had a lifetime prevalence rate for BPS of 4.4 percent and a 12-month prevalence rate of 2.8 percent—higher than any other country. Comorbid conditions, e.g., anxiety disorders, behavior disorder and substance use disorders, were present in 75 percent of those with BPS in the 11 countries. Other findings from this report included: severity of manic and depressive symptoms, and suicidal behavior increased from subthreshold to BP-I; severity of symptoms was greater for depressive than manic episodes; and less than 50 percent of those with lifetime BPS received mental health treatment, particularly in low-income countries (Merikangas et al., 2011).

Another study explored the concept of a spectrum of subthreshold affective traits or temperaments. This Argentinean study examined the prevalence of affective temperaments, i.e., depressive, cyclothymic, hyperthymic, irritable and anxious, between clinically unaffected relatives of bipolar patients and investigated the impact of these subaffective forms on their quality of life. Their preliminary findings suggested that the cyclothymic and anxious affective traits are more common in bipolar pedigrees and, except for the hyperthymic type, quality of life was affected by these temperaments in the undiagnosed individuals termed “clinically well” by authors (Vazquez et al., 2008). Similarly, a family study used a community sample (739 young adults and 1,744 relatives) to validate familial transmission of subthreshold psychiatric conditions and determine the relationship between a number of subthreshold conditions and full syndrome (FS) disorders. These

findings showed that subthreshold bipolar disorder was associated only with familial FS anxiety. Researchers suggested that their conclusions seem to confirm other reported findings on the substantial comorbidity between bipolar and anxiety disorders now corroborated by their findings of associated patterns of familial transmission (Shankman et al., 2007).

Genetic linkage was the focus of a systematic review of 77 family studies of probands with schizophrenia and BD conducted to ascertain whether these disorders co-aggregate in families. Reported results from this meta-analysis provided evidence that first-degree relatives (FDR) of either schizophrenia or BD have approximately double the expected risk of the other disorder. Investigators proposed that their findings argue against the view that these disorders are discrete entities, but may support a disease continuum model (Van Snellenberg et al., 2009). In a later genetic study examining the possibility of common genetic markers affecting susceptibility to five psychiatric disorders, i.e., autism spectrum disorder, attention-deficit/hyperactivity disorder, bipolar disorder, major depressive disorder and schizophrenia, researchers found that these disorders share some of the same genetic risk factors (National Institute of Mental Health 2013). Researchers analyzed genome-wide single-nucleotide polymorphism (SNP) data for the five disorders in patients with the disorders (n=33,332) and controls (n=27,888) finding specific variations in two calcium channel genes (CACNA1C and CACNB2) associated with all five disorders. They suggested that alterations in calcium-channel signaling represent a mechanism contributing to a broad vulnerability to psychopathology. According to Jordan Smoller, M.D., "…these results will help us move toward diagnostic classification informed by disease cause…" (National Institute of Mental Health, 2013).

In a later study using the same genome-wide information and data sets as in the NIMH study above, researchers looked for overlap in heritability attributable to genetic variation, calculating the extent to which pairs of disorders link to the same genetic variants (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Findings showed that overlap in heritability due to common genetic variation was greatest between schizophrenia and bipolar disorder at 15 percent and was about 10 percent between bipolar disorder and depression. Researchers noted that these results have important implications for both diagnostics and research, encouraging "investigations into shared pathophysiologies across disorders, including potential clarification of common therapeutic mechanisms" (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013, p. 10).

A recent study involved the creation of a stem cell model for bipolar disorder (Chen et al., 2015). Skin samples from individuals diagnosed with bipolar disorder and from individuals without bipolar disorder were transformed into induced pluripotent stem cells (iPSCs), then into neurons (similar to the ones found in the brain). Researchers compared the neurons from the individuals with bipolar disorder to those of individuals without the disorder, finding that the bipolar neurons "expressed more membrane receptors and ion channel genes than control neurons, particularly transcripts involved in calcium signaling." Researchers noted that this relates to the enhanced tonic excitability that maintains brain rhythms in bipolar disorder. Further, when bipolar disorder neurons were exposed to lithium, calcium signaling was altered. Researchers discussed how examination of the detailed effects of lithium exposure (or the effects of other bipolar disorder drugs) in these cells may be beneficial. They suggested that the results of this study support the concept that bipolar disorder, along with other neuropsychiatric disorders identified later in life, may result from "alteration in neural differentiation that occur in development" (Chen et al., 2014, p. 6).

Although BPS is a highly heritable disorder, other factors, e.g., social and environmental, may influence the onset of disease. The impact of sunlight on the age of onset of bipolar disorder was the topic of a study that obtained data from patients (n=2414) with a diagnosis of BP-I (Bauer et al., 2012). This study's main purpose was the investigation of whether age of onset of BP-I may be associated with sunlight, measured by solar insolation, rather than latitude. Solar insolation refers to the amount of electromagnetic energy from the sun received on the surface of the earth at a given time; locations within the same latitude may differ significantly in measures of solar insolation. The U.S. National Aeronautics and Space Administration (NASA) released solar insolation values for the entire globe in the Surface Meteorology and Solar Energy Version 6.0 database. Bauer et al. found that a large monthly increase in solar insolation was associated with a young onset of BP-I, without regard to latitude. In areas with the largest monthly increase in solar insolation, i.e., Norway, Chile and arid parts of California, the age of onset was about five years less than in areas with the smallest monthly increase. Researchers suggested that in areas experiencing a large increase in sunlight in springtime, clinicians should be aware of the study's implications in identifying symptoms of bipolar disorder in younger patients.

In the newer Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5), the diagnosis "bipolar disorder I – mixed episode" requiring that an individual simultaneously meet full criteria for both mania and major depressive episode has been eliminated. Instead, a new specifier, "with mixed features," includes episodes of mania or hypomania when depressive features are present; it also includes episodes of depression in the context of major depressive disorder or bipolar disorder when features of mania/hypomania are present. Criterion A for both manic and hypomanic episodes includes the addition of increased energy/activity as a core symptom. An anxious distress specifier, identifying patients with anxiety symptoms that are not part of the bipolar diagnostic criteria, is included in the chapter on bipolar and related disorders. Individuals with history of major depressive disorder meeting all criteria for hypomania, except the four consecutive day criterion, are categorized under "other specified bipolar and related disorder." Another specified bipolar and related disorder would include past history of a major depressive disorder where too few symptoms of hypomania are present to meet criteria for the full bipolar II syndrome, although the duration criterion (at least four consecutive days) is sufficient (American Psychiatric Association 2013).

## Psychiatric Comorbidity

The APA guideline indicates that relative to the general population, individuals with bipolar disorder are at greater risk for comorbid anxiety disorders, especially panic disorder and obsessive disorder, and that bipolar disorder with a comorbid substance use disorder (SUD) is a very common presentation. The guideline discusses epidemiological studies showing rates of alcohol abuse or dependence at 46 percent in patients with bipolar disorder compared with 13 percent for the general population and comparable drug abuse and dependence figures at 41 percent and 6 percent respectively. A later report on co-occurring mood and substance use disorders stated that comorbidity of mood disorders and substance use disorders is highest with bipolar disorder (Pettinati et al. 2013). Authors reported lifetime prevalence rate of any bipolar disorder and any substance use disorder of 47.3 percent and lifetime prevalence rate of bipolar I disorder and any substance use disorder of 60.3 percent.

Additionally, the guideline stresses that comorbid personality disorders pose complicated diagnostic pictures because patients are at greater risk for experiencing intrapsychic and psychosocial stressors that can precipitate or exacerbate mood episodes. Since publication of the

guideline, a later study investigated whether rapid-response impulsivity and/or reward-delay impulsivity are greater in combined bipolar disorder and antisocial personality disorder over either alone (Swann et al. 2011). Using laboratory measures of impulsivity, i.e., the Immediate Memory Task (IMT) and the Two-Choice Impulsivity Paradigm (TCIP), researchers measured response inhibition and reward delay in men (n=133) with antisocial personality disorder, bipolar disorder and combined disorders compared to controls with neither condition. Results showed increased impulsivity in the combined disorders over either disorder alone. They suggested that compensatory mechanisms for impulsivity in uncomplicated antisocial personality disorder or bipolar disorder may be compromised when the disorders are combined, leading to more severe impulsivity in the combined disorders.

A study examined whether bipolar disorder and borderline personality disorder confer independent, additive risk for suicide attempts (Zimmerman et al., 2014). Psychiatric outpatients, including those with bipolar disorder, borderline personality disorder, and bipolar disorder combined with borderline personality disorder, underwent semi-structured interviews. In this study, more than one-third of patients with bipolar disorder had history of suicide attempts, and nearly 50 percent of those with borderline personality disorder had previous suicide attempts. However, nearly 60 percent of patients with both bipolar disorder and borderline personality disorder had history of suicide attempts, with the influence of borderline personality disorder greater than that of bipolar disorder. Authors indicated there was an additive, indicative risk of suicide in each of the disorders, but noted that the influence of borderline personality disorder as a risk of suicide was greater than that of bipolar disorder. Authors stress the importance of diagnosing both conditions when they are both present, to identify patients at high risk for suicide attempts (Zimmerman et al., 2015).

The guideline briefly discusses the prevalence of bipolar disorder in children and adolescents and notes that in a community sample of this age group, 1 percent had mood symptoms that met criteria for bipolar disorder and 5.7 percent for BD-NOS. The guideline also adds that child and adolescent bipolar disorder is often comorbid with attention deficit and conduct disorders, and that these individuals are at greater risk for developing substance use disorders. Since publication of the guideline, a more recent epidemiological study found that bipolar disorder places a child at increased risk for the development of post-traumatic stress disorder (PTSD) and that full or subthreshold PTSD in adolescents with BPD increased the risk for SUD. The study showed that in bipolar children with PTSD and SUD, bipolar disorder either precedes or is coincident with the onset of PTSD, followed by the development of SUD and indicate the need to implement early preventative interventions (Steinbuchel et al., 2009).

The guideline also acknowledges that the presence of comorbid attention-deficit/hyperactivity disorder (ADHD) in adults and children with bipolar disorder makes it difficult to monitor changes in mood states. In addition, the guideline indicates that adults with bipolar disorder and comorbid ADHD are likely to have experienced a much earlier age at onset of their mood disorder relative to those without comorbid ADHD. A later analysis of data from the initial assessments of children (n=707) in the National Institute of Mental Health-supported Longitudinal Assessment of Manic Symptoms (LAMS) study included children with ADHD (n=538), bipolar spectrum disorder (n=162), ADHD combined with bipolar spectrum disorder (n=117) and children with neither (n=124). This study found that comorbid bipolar disorder and ADHD did not have significantly younger age of onset of mood symptoms than bipolar disorder without comorbid ADHD (Arnold et al., 2011). Children with comorbid bipolar disorder and ADHD had greater rates of other comorbidities than children with only ADHD or only bipolar disorder, and global functioning was more impaired in children with the comorbid condition than in those with either diagnosis alone. A

published clinical review noted that criteria for a lifetime diagnosis of ADHD was met by approximately 9.5 percent of adult patients with bipolar disorder and that more men than women have these co-occurring conditions (Goodman et al., 2009). This same review also reported that bipolar patients with lifetime ADHD were more likely to have been diagnosed as bipolar I than bipolar II and that social phobia, post-traumatic stress disorder (PTSD) and SUD were other common comorbid conditions in this subpopulation of bipolar patients (Goodman et al., 2009).

Gao et al. studied the independent associations between co-occurring anxiety disorders and SUDs in patients with rapid cycling bipolar disorder I or II (RCBDI or RCBDII) using data from patients enrolled into four randomized, double-blind, placebo-controlled clinical trials (Gao et al., 2010). Results showed that patients with RCBDI had significantly higher rates of anxiety disorders than those with RCBDII and those with anxiety disorders had significantly higher rates of recent and lifetime alcohol and marijuana dependence than those without anxiety disorders. This study also found that the risk for marijuana dependence was significantly higher in bipolar patients with generalized anxiety disorder (GAD) than in those without GAD.

A recent systematic review and meta-analysis examined associations between manic symptoms and cannabis use in individuals with pre-existing bipolar disorder (Gibbs et al., 2015). Authors noted studies suggesting that cannabis use contributes to the development of psychosis and plays a causal role in the development of manic symptoms and episodes. Noting that comorbid cannabis use is more common in individuals experiencing bipolar disorder than those with schizophrenia, they pointed out that the association between cannabis use and mania has received less attention. Based on a review of six studies meeting criteria for inclusion, authors suggested that cannabis use increases the likelihood, severity and duration of manic phases in individuals with pre-existing bipolar disorder. In a proportion of those previously diagnosed with bipolar disorder, the use of cannabis preceded the presence or reoccurrence of manic symptoms. They noted that that "while cannabis use appears to selectively precede manic symptoms, it has not been found to be similarly associated with depression symptoms" (Gibbs et al., 2015, p. 45). Authors summarized that cannabis use has an observed tendency to precede or coincide with mania symptom and suggested a potential causal influence from cannabis use to the development of mania. They suggested more high quality prospective studies to clarify how the use of cannabis may contribute to the development of mania over time (Gibbs et al., 2015).

A clinical trial examining the effects of pharmacotherapy plus family interventions for patients with BP-I combined with a remitted substance use disorder (SUD) found that a remitted SUD is related to poorer acute treatment response. Other effects include longer time to remission of acute mood episode and a greater percentage of time with subthreshold but clinically significant depression and manic symptoms over follow-up compared to those without this comorbidity pattern. Researchers noted that subsequent substance abuse during follow-up could not fully account for the poorer course of illness (Gaudiano et al., 2008). The impact of a SUD was also the focus of a prospective analysis in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) Study where depressive episodes of bipolar I disorder and II subjects (n=3,750) were identified and followed for two years. Subjects with past or current drug/alcohol use disorders were compared with those with no history of drug/alcohol use disorders on time to recovery from depression and time until switch to a manic, hypomanic or mixed episode. During the prospective follow-up period, researchers reported that 2,153 subjects developed a new-onset major depressive episode. A total of 457 of the new-onset depressed subjects switched to a manic, hypomanic or mixed episode prior to recovery. Findings showed current or past SUDs were not associated with longer time to recovery from depression but may have contributed to a greater risk of switch into manic, mixed or hypomanic states (Ostacher et al., 2010).

In a later clinical summary of bipolar and substance use disorder comorbidity, Ostacher suggested that patients with bipolar disorder may initiate the use of alcohol and drugs as a response to their symptoms and as the reward associated with prior use. He further explained how drug and alcohol use in dependent bipolar disorder patients may be associated with the complex interaction between cue-based reward, reward sensitivity, anxiety and mood. Ostacher's clinical summary recommends avoiding over diagnosis of bipolar disorder in patients in addiction treatment settings, providing medical and psychological treatment for substance use disorders in patients with bipolar disorder, and shifting focus from one on mood to improving health outcomes, e.g., treatment to change health risk behavior for patients with co-occurring bipolar and substance use disorders (Ostacher, 2011).

Using data from a community-based sample of both sexes in a case-control family study of Binge Eating Disorder (BED), researchers found that full BED co-occurred significantly with bipolar and major depressive disorder (Javras et al., 2008). Another study of demographic and clinical features of bipolar patients with and without eating disorders by Wildes et al. showed that eating disorder co-morbidity may be a marker for increased symptom load and illness burden in bipolar disorder (Wildes et al., 2007). The analysis also showed that lifetime eating disorder comorbidity was associated with increased Body Mass Index (BMI) and current illness severity, a greater number of depressive episodes and more psychiatric comorbidity in the sample of patients with bipolar disorder. Additionally, the study revealed that bipolar patients with co-occurring eating disorders also endorsed more cognitive correlates of disordered eating, i.e., restraint, eating/shape/weight concern, than did patients with no history of clinically significant eating disturbance. Researchers suggested the need for a renewed emphasis on the evaluation and management of weight and eating in mood disorders (Wildes et al., 2007). In a study assessing the prevalence and clinical correlates of eating disorders in patients with bipolar disorder (n=875), researchers found that eating disorders were associated with an earlier age of onset, a more pathological course of bipolar disorder and higher rates of suicide attempts. No significant eating disorder comorbidity differences were evident in patients with bipolar I disorder as compared with patients with bipolar II disorder (McElroy et al., 2011).

The guideline briefly discusses the presence of violent behavior in bipolar patients and notes that this may be an indication for hospitalization. The guideline also acknowledges that comorbid substance abuse and psychosis contributes to the threat of criminal violence or aggression. Since publication of the guideline, a longitudinal investigation conducted in Sweden studied the risk of violent crime in bipolar disorder. The study analyzed the incidence of violent crime in individuals with two or more hospital discharge diagnoses of bipolar disorder using both the general population and unaffected siblings as control groups. Results showed an increased risk for violent crime among bipolar patients with comorbid substance abuse with no difference however, in rates of violent crime by clinical subgroups, i.e., manic, depressive, psychotic, nonpsychotic. These findings have led investigators to recommend routine risk assessment when evaluating or treating this patient subgroup (Fazel et al., 2010). In a later study that compared the prevalence of aggression in persons with bipolar disorder (n=255) to subjects with other, non-bipolar psychopathology (n=85) and healthy controls (n=84), researchers found that individuals with bipolar disorder display greater rates of aggressive behaviors, independent of the severity of bipolar disorder and polarity of the episode. Aggression as measured using the Aggression Questionnaire was higher in those in a current mood episode (Ballester et al., 2012).

A recent study investigated whether comorbid anxiety moderates the effects of intensive psychotherapy (family-focused therapy, interpersonal and social rhythm therapy, or cognitive-

behavioral therapy) in patients with bipolar depression (Deckersbach et al., 2014). Researchers noted that findings from studies have shown individuals with bipolar disorder and a comorbid anxiety disorder experience greater severity of illness, longer illness duration, higher rates of suicide, and poorer response to treatment compared with individuals without comorbid anxiety disorder. Researchers noted studies showing that although psychosocial interventions are beneficial for the treatment of acute depressive episodes, there is a lack of clarity about how comorbid anxiety disorders may moderate the efficacy of the interventions. Participants (n=269) in this exploratory analysis were a subset of participants meeting criteria of bipolar depression who were enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Researchers evaluated the differential effects of intensive psychotherapy and collaborative care (minimal psychotherapy plus adjunctive pharmacotherapy) for patients including those with and without a lifetime anxiety disorder. Results showed that 66 percent of patients with comorbid anxiety disorder recovered with psychotherapy compared with only 49 percent with collaborative care. There were no differences between rates of recovery for patients without lifetime anxiety disorder who were assigned to psychotherapy compared with collaborative care. Researchers suggested that the more robust response to intensive psychotherapy for bipolar patients with an anxiety disorder is in contrast to findings of poorer response to pharmacologic management for bipolar disorder with comorbid anxiety. They suggested that the identification of anxiety in the context of bipolar disorder suggests different psychosocial approaches for those with and without anxiety (Deckersbach et al., 2014).

## Acute Manic or Mixed Episodes

The use of second-generation antipsychotics (SGAs) in the treatment of mood disorders is broadening. The adopted guideline watch presented findings of numerous studies on the equivalent or superior efficacy of SGAs as monotherapy, i.e., olanzapine, risperidone, ziprasidone, aripiprazole and quetiapine, and as adjunctive treatment with more traditional mood stabilizers for the acute treatment of mania, i.e., olanzapine, risperidone or quetiapine added to either divalproex or lithium. The five aforementioned SGAs all have U.S. Food and Drug Administration (FDA) approval for the treatment of manic and mixed bipolar episodes with quetiapine also having FDA approval for the treatment of bipolar depression. On October 24, 2011, the FDA approved first generic olanzapine (olanzapine tablets and olanzapine orally disintegrating tablets) to treat bipolar disorder and schizophrenia (FDA News Release October 24, 2011). Asenapine (Saphris™), a SGA that acts at dopamine D-2 and a variety of serotonin receptors, was approved by the FDA in the fall of 2009 for the treatment of BP-I and schizophrenia in adults ( FDA News Release August 14, 2009). A review of literature provided an update of published current data about the efficacy and safety of asenapine for the treatment of bipolar disorder (Samalin et al., 2013). Authors reported results from studies showing well toleration of asenapine, especially with regard to metabolic side effects. Unlike other SGAs, it does not appear to have significant impact on weight gain. Other advantages of asenapine over other SGAs include sublingual formulation and early efficacy. Asenapine's efficacy when used as monotherapy or adjunctive therapy in the acute treatment of manic or mixed episodes of patients with bipolar I disorder was demonstrated. Forty-week extension studies assessing the safety of asenapine found that the efficacy of asenapine in patients with acute mania seemed to remain constant during long-term studies.

After publication of the guideline watch, a randomized, double-blind, placebo-controlled study investigated the efficacy and safety of adjunctive ziprasidone in patients with acute mania who had inadequate response to treatment with mood stabilizers, i.e., lithium or divalproex. Participants (n=618) were randomly assigned to one of three groups: mood stabilizer plus placebo, mood

stabilizer plus low-dose ziprasidone or mood stabilizer plus high-dose ziprasidone (Sachs et al., 2012). Although evidence of ziprasidone's antimanic efficacy has been shown in monotherapy trials, the findings of this study did not show a significant benefit of adjunctive ziprasidone over placebo for treatment of acute mania in participants treated with lithium or divalproex. Researchers suggested that ziprasidone may offer advantages, i.e., lower risk of weight gain, undesirable metabolic effects, compared with other SGAs. Prevalence of extrapyramidal symptoms was higher in the mood stabilizer plus high-dose ziprasidone group compared with the mood stabilizer plus low-dose ziprasidone group. Researchers stated their surprise at the lack of efficacy in this study in light of the successful monotherapy studies and suggested the possibility that the study may have failed for reasons other than lack of efficacy.

Since publication of the adopted APA guideline and guideline watch, the FDA issued two relevant Alerts notifying healthcare professionals that antiepileptic drugs (AEDs) or anticonvulsant drugs are associated with an increased risk of suicidal thoughts or actions. The FDA Alerts also cautioned that both conventional and atypical (SGA) antipsychotics are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis (FDA Alert January 31, 2008; FDA Alert June 16, 2008).

Researchers analyzing observational data on more than 5 million patients in The United Kingdom reported results suggesting that the AEDs may not raise the risk for suicide but that the underlying disease for which these drugs are prescribed was more strongly associated with suicide-related events (Arana et al., 2010; Vega, 2010). This study focused on the association between AEDs and attempted or completed suicides in patients with epilepsy, depression or bipolar disease. The investigators conducted the case control analysis adjusting for age, duration of disease, previous/current use of AEDs, lithium, antipsychotic drugs or antidepressants and history of an alcohol use or mental disorder including a chronic disease score. Findings showed no association of current use of AEDs with an increased risk for suicide-related events in patients with epilepsy, bipolar disorder or depression with epilepsy. Other results showed that current use of AEDs was associated with a greater than two-fold increased risk for suicide related events among individuals free of epilepsy, depression or bipolar disorder, e.g. using AEDs for pain management, and in patients with depression alone (without epilepsy). In addition, AEDs appeared slightly protective against suicide-related events among patients with epilepsy alone (Arana et al., 2010; Vega, 2010).

A prospective, longitudinal observational study examined the risk of suicide attempts or suicide deaths associated with antiepileptics, i.e., carbamazepine, lamotrigine and valproate, in patients (n=199) with bipolar disorder (Leon et al., 2012). Participants who were significantly more likely to receive antiepileptics were those with more severe manic or hypomanic symptoms. This study found no significantly elevated risk of suicide attempts or suicides in participants during periods when they were using antiepileptic drugs, as compared to periods when they were not using an antiepileptic. Researchers concluded that regular monitoring of mood episode symptoms, suicidal ideation and behavior in patients treated with antiepileptic drugs is needed.

Researchers conducted another study on risk of death associated with use of conventional, i.e., haloperidol and thioridazine, and atypical antipsychotic drugs, i.e., clozapine, olanzapine, quetiapine and risperidone among current users of these agents in a large retrospective cohort study of Medicaid enrollees in Tennessee. In their primary analysis, researchers (Ray et al., 2009) included 44,218 and 46,089 baseline users of single typical and atypical drugs, respectively, and 186,600 matched nonusers of antipsychotic drugs. The authors also assessed for residual confounding related to factors associated with the use of antipsychotic drugs and performed a secondary analysis on possible confounders such as medications, substance use, smoking and

existing cardiovascular disease. The conclusions drawn from their analysis showed that current users of atypical antipsychotic drugs had twice the rate of sudden cardiac death than nonusers and similar to the death rate for patients taking typical antipsychotic drugs, i.e., adjusted incidence-rate ratio of 2.26 and 1.99 respectively. Researchers also discussed the apparent dose-response and temporal relationship between taking antipsychotic medication and sudden cardiac death and speculated that that both classes increase the risk of serious ventricular arrhythmias by means of potassium-channel blockade along with other mechanisms (Ray et al., 2009, White, 2009).

The guideline watch stressed the significant clinical concerns for metabolic effects that are associated with the SGAs. Specifically, the guideline watch noted that clozapine and olanzapine are associated with increased risk of developing diabetes mellitus and dyslipidemia and may be responsible for significantly greater weight gain than the other antipsychotics. Further, risperidone and quetiapine are associated with moderate weight gain, and ziprasidone and aripiprazole with minimal weight change. Therefore, the guideline advised clinicians to monitor weight, waist circumference, blood pressure, glucose and lipids at baseline and at monthly intervals in patients on these medications (Hirschfeld, 2005).

Since publication of the guideline watch, a large meta-analysis of 24 randomized controlled trials with 6,187 patients was conducted to examine the efficacy, safety and tolerability of SGAs in the treatment of acute mania. All of the SGAs studied, i.e., olanzapine, risperidone, ziprasidone, aripiprazole and quetiapine, showed superiority to placebo in the treatment of acute mania. The study's comparison of SGAs as a group with mood stabilizers as a group, i.e., lithium, valproate, carbamazepine, showed a trend toward the superiority of SGAs — mainly due to the significant superiority of olanzapine in reducing manic symptoms. Study findings showed, with the exception of ziprasidone, that adding SGAs to mood stabilizers increased the efficacy compared with monotherapy with mood stabilizers alone. Additionally, the SGAs did not show superiority in improving manic symptoms when compared with the conventional antipsychotic haloperidol. The adverse effects of SGAs, e.g., somnolence, weight gain, extrapyramidal symptoms, were shown to have an impact on treatment adherence (Scherk et al., 2007). A later multiple-treatments meta-analysis of 68 randomized controlled trials (n=16073 patients) compared the efficacy and acceptability of the following drugs, either against placebo or against one another, for the treatment of acute mania in adults: aripiprazole, asenapine, carbamazepine, valproate, gabapentin, haloperidol, lamotrigine, lithium, olanzapine, quetiapine, risperidone, topiramate and ziprasidone. Results from this study showed that antipsychotic drugs were significantly more effective than mood stabilizers overall. Haloperidol, olanzapine and risperidone outperformed other drugs in terms of efficacy. Olanzapine, quetiapine and risperidone outperformed haloperidol in terms of dropouts. Researchers suggested that risperidone and olanzapine are superior for efficacy and acceptability for the treatment of acute mania (Cipriani et al., 2011).

A prospective pharmacogenomics study of mood stabilizer response is exploring the predictive value of genetic markers of lithium and valproate response in patients with bipolar disorder (U.S. National Institutes of Health Clinical Trial, 2013). Dunlop et al. suggested that predictors of lithium response identified from large-scale randomized studies such as Lithium Treatment Moderate-Dose Use Study (LiTMUS) for Bipolar Disorder complement the research collaboration of the aforementioned clinical trial (Dunlop et al., 2013). The purpose of LiTMUS, a six-month study, was to address whether a moderate dosage of lithium plus optimized personalized treatment (OPT), compared with OPT alone, results in better outcomes in participants (n=283) with bipolar disorder (Nierenberg et al., 2013). OPT is largely based on the Texas Implementation of Medication Algorithm. Results of this trial showed that low-dosage lithium plus OPT did not provide additional benefits when compared with OPT alone. Outcome measures of mood symptoms, suicidal ideation

and functioning were similar in both groups. One interesting finding inviting follow-up investigation was that participants receiving lithium plus OPT were less likely to receive a SGA, although these participants reported significantly more manic or hypomanic episodes in the year prior to this study. Researchers suggested that clinicians use the results of this study to reconsider lithium for their bipolar patients.

A later study examined relationships between treatment service utilization and demographic and illness characteristics in participants (n=283) with bipolar disorder who were the subjects of the LiTMUS study (Sylvia et al., 2013). Participants were randomized to receive low-dosage lithium plus optimized personalized treatment (OPT) or OPT alone. There were no significant differences in the total number of medical or counseling services used in two 12-week periods between the two groups. Higher manic symptoms (on the Young Mania Rating Scale [YMRS]) and higher depressive symptoms (on the Montgomery Asberg Depression Rating Scale [MADRS]) showed higher rates of using medical services, with manic symptoms having a higher association than depressive symptoms. Authors suggested that mania encourages patients to seek treatment for physical but not psychological problems. Data also showed that patients with more intense, frequent and burdensome side effects sought not only medical services but also counseling services. Authors suggested that physical symptoms, but not psychiatric and mood symptoms, prompt individuals with bipolar disorder to seek counseling services. They cautioned that general medical providers may not be aware of the bipolar diagnosis while treating symptoms or comorbid conditions of bipolar disorder (Sylvia et al., 2013).

A recent systematic review and meta-analysis synthesized data from studies with regard to syndromal and symptomatic recovery after a first manic episode (Gignac et al., 2014). Eight studies represented patients (n=753) with bipolar I disorder identified during a first manic episode or first manic hospitalization. The majority of the patients received treatment with mood stabilizers and antipsychotics; lithium was the most widely used mood stabilizer. Within six months to one year of first-episode mania, the majority of patients (77.4 percent) achieved syndromal recovery; however, only 62 percent of patients achieved symptomatic recovery within one year and they remained at high risk for recurrence. Authors suggested that this difference between syndromal and symptomatic recovery rates is a major challenge in the management of bipolar disorder. Despite symptom remission, occupational impairment and deficits in self-esteem were observed in patients. Based on analysis of the data, authors suggested that risk of recurrence increases to 41 percent at one year and 60 percent by year four. Authors suggested that literature has not focused on protective factors in the 40 percent of patients who stay well for up to four years and suggested that psychosocial interventions may play a disease-altering role in bipolar disorder. Their data also suggested that earlier age at onset has been associated with both longer delay to first treatment as well as to a higher risk of recurrence (Gignac et al., 2014).

In a recent population study using the Swedish national registries, Viktorin et al. found an association between antidepressant monotherapy and increased risk of mania in patients with bipolar disorder (Viktorin et al., 2014). They categorized patients (n=3,240) with bipolar disorder who began treatment with antidepressants, while having no antidepressant treatment during the previous year, into two groups: those receiving antidepressant monotherapy (selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, tricyclic and tetracyclic antidepressants or bupropion), and those receiving both antidepressant and a mood stabilizer (lithium, valproate or lamotrigine). Authors noted that 35 percent of the patients received treatment with antidepressant monotherapy, contrary to clinical guidelines. Results of their analysis found an increase in treatment-emergent mania in patients on antidepressant monotherapy and no increased risk of mania in patients receiving the combination treatment.

Authors highlighted the importance of avoiding antidepressant monotherapy in the treatment of bipolar disorder (Viktorin et al., 2014). Vieta suggested the use of antidepressants (only in combination with mood stabilizers) for treatment of patients with bipolar II disorders and in patients who have demonstrated good response to antidepressants in the past. He further suggested the avoidance of using antidepressants in patients who, in past treatments, have experienced switches to mania (Medscape 2015).

## Depressive Episode Classification Issues and Treatment

The guideline watch emphasizes that the impact of depressive episodes on quality of life and duration of episodes in bipolar patients is substantially worse than the impact of manic episodes. The document also notes that far less research attention has been paid to the treatment of bipolar depression. However, recently published epidemiological and service utilization data for mood disorders in the United States, reported that bipolar disorder is less prevalent but more persistent and more impairing than major depressive disorder (MDD). Kessler et al. argued here that the higher persistence and severity of bipolar disorder results in a substantial proportion of all seriously impairing depressive episodes being due to threshold or subthreshold bipolar disorder rather than to MDD (Kessler et al., 2007).

Updated research information provided in the guideline watch suggested that the medications having the strongest evidence for efficacy for acute treatment of depression in patients with BP-I disorder are the olanzapine-fluoxetine combination, i.e., FDA approved Symbyax™, quetiapine (Seroquel™) and lamotrigine (Lamictal™). Lamotrigine is not FDA approved for acute bipolar depression but is approved for bipolar maintenance therapy. The guideline watch indicated that there was suggestive evidence that the adjunctive use of the dopamine agonist, pramipexole, used with mood stabilizers may be helpful. Additionally, the guideline watch acknowledged a modest evidence basis for the efficacy of an antidepressant with an adjunctive mood stabilizer while also specifying that use of an antidepressant without a mood stabilizer is not recommended for bipolar I patients.

Lurasidone (Latuda™), a new atypical antipsychotic, is the most recently approved medication for the treatment of bipolar depression (Medscape, 2013). On June 28, 2013, the FDA approved lurasidone as monotherapy or with lithium or valproate. Other FDA approved medications for bipolar depression include olanzapine-fluoxetine combination and quetiapine. Clinical trials have shown that lurasidone is less likely to induce weight gain, hyperlipidemia, and glucose impairment than the other approved drugs.

Loebel et al. evaluated the efficacy and safety of lurasidone monotherapy for the treatment of bipolar I depression (Loebel et al., 2014). In this randomized, double-blind, placebo-controlled study, patients (n=505), ages 18-75, with bipolar I disorder who were experiencing a major depressive episode were assigned to receive placebo, low-dose (20-60 mg daily) lurasidone, or high-dose (80-120 mg daily) lurasidone over six weeks of treatment. Those assigned to the low dose lurasidone received 20 mg/day for days 1-7, after which dosing adjustments up to 60 mg/day were allowed to optimize efficacy and tolerability. Patients assigned to the 80-120 mg/day received 20 mg/day for days 1-2, 40 mg/day for days 1-4, 60 mg/day for days 5-6 and 80 mg on day 7. After the first week, the dose could be adjusted within the dosage range. Patients treated with either high- or low-dose lurasidone showed significant reduction in core depressive symptoms from baseline to end of the treatment period compared to those receiving placebo. The proportion of patients achieving remission was significantly higher in the lurasidone 20-60 mg group (42

percent) and the lurasidone 80-120 mg group (40 percent) compared with the placebo group (25 percent). Discontinuation rates due to adverse events were low in the lurasidone groups and similar to placebo. Lurasidone treatment had minimal effect of weight, lipids or measures of glycemic control compared with placebo. Researchers concluded, "lurasidone may be a valuable addition to the therapeutic armamentarium for the treatment of patients with bipolar depression" (Loebel et al., p 167).

Another randomized, double-blind, placebo-controlled study investigated the efficacy of lurasidone as adjunctive therapy with lithium or valproate in the treatment of bipolar I depression (Loebel et al, 2014). In this study, patients (n=348) with bipolar I disorder, who were experiencing a major depressive episode and receiving treatment with lithium or valproate, were randomized to six weeks of either adjunctive lurasidone 20-120 mg/day or placebo. Patients assigned to lurasidone received 20 mg/day on days 1 to 3, 40 mg/day on days 4 to 6 and 60 mg on day 7. Afterwards, the dose was adjusted (as needed) within the dosage range at weekly intervals in 20 mg increments or decrements. Patients treated with lurasidone showed significant reduction in core depressive symptoms from baseline to end of the treatment period compared to those receiving placebo. Comparable treatment effects were associated with adjunctive lithium and valproate. Researchers noted minimal changes in weight, lipids and measures of glycemic control occurred during treatment with lurasidone. They concluded that treatment of patients with bipolar I depression may significantly improve depressive symptoms while being generally well tolerated (Leobel et al., 2014).

In a randomized, double-blind, placebo-controlled study, researchers investigated whether memantine can augment the effects of lamotrigine in patients with bipolar depression (Gunn et al., 2012). Patients with bipolar disorder I or bipolar disorder II and a current episode of depression (n=29) were randomized to receive lamotrigine augmented with either memantine or placebo. The memantine or placebo dose started at 5 mg for the first week and increased by 5 mg each week up to 20 mg, based on response and tolerability. Researchers found memantine was not superior to placebo over the eight-week study, but during the first four weeks when the dose was being titrated up, 57 percent of patients receiving memantine met the response criteria, compared to 20 percent of those receiving placebo. Remission was achieved by 57 percent of those receiving memantine compared with 27 percent of those receiving placebo. Researchers suggested that memantine can augment the effects of lamotrigine in early on in the treatment while the dose is being titrated up, and they suggested further studies to ascertain optimal timing and dosing for memantine augmentation of lamotrigine in the depressive phase of bipolar disorder.

A published clinical review (Schneck, 2009) emphasized that mixed depressions— defined as major depressive episodes accompanied by subsyndromal manic or hypomanic symptoms—have been recognized for many years. However, this is in contrast to the only DSM-IV-TR defined mixed state, which is the simultaneous occurrence of full manic and depressive symptoms lasting at least one week. The author noted that it is only recently that mixed depressions and their implications for treatment have been given the clinical focus that is warranted. In DSM-5, a new specifier, "with mixed features," includes episodes of mania or hypomania when depressive features are present as well as episodes of depression when features of mania/hypomania are present.

In light of the issues surrounding a possible diagnostic entity of mixed depression, a longitudinal naturalistic study by Goldberg et al. included patients that were initially assessed upon entry to the STEP-BD study. This group (N=335) was defined specifically as having bipolar depression with subsyndromal as well as syndromal mania during depression. The study compared outcomes in patients who received a mood stabilizing agent with versus without an antidepressant for a bipolar

depressive episode. Results showed that adjunctive antidepressant use was associated with significantly higher mania symptom severity at the three-month follow-up and did not hasten time to recovery relative to treatment with mood stabilization alone (Goldberg et al., 2007). Along with these findings, evidence signaling caution in the use of antidepressants continues to increase. Other problems using antidepressants discussed included an increase in the frequency of suicidal ideation and mood cycling (Schneck, 2009, Suppes et al., 2006).

In 2010, The Psychopharmacology Algorithm Project at the Harvard South Shore Program (PAPHSS) updated their Bipolar Depression Treatment Algorithm (Ansari et al., 2010). In their supporting clinical review on the use of antidepressants in the treatment of bipolar depression, authors acknowledged the continuing clinical controversy related to the possible risks of antidepressant-related manic induction and longer-term mood destabilization. Ansari and Osser reported that such risks may vary with each antidepressant and noted conclusions from a clinical trial (Leverich et al., 2006) showing that when bupropion, sertraline and venlafaxine used adjunctively with mood stabilizers were compared, bupropion was least associated with subsequent mania. The reported risk was slightly higher with sertraline and significantly higher with venlafaxine. The authors subsequently indicated that antidepressants appear to be better tolerated in patients with bipolar II versus bipolar I depression in that the risk of an antidepressant-induced switch into mania appears to be lower in patients with bipolar II. Also, when manic switches do occur with antidepressant therapy, the severity of mood elevation appears to be milder in patients with bipolar II disorder. While antidepressants may have some merit in treating bipolar II depression, the authors stressed that further controlled research is needed (Ansari et al., 2010).

Researchers performed a systematic literature search and appraisal of results from trials to review the evidence base of available treatment options for bipolar depression under two common scenarios: 1) patient currently not treated with a mood-stabilizing agent and 2) patient already receiving treatment with a mood-stabilizing agent (Bauer et al., 2012). Based upon their review, researchers found that if current treatment does not include a mood-stabilizing agent, quetiapine or olanzapine are treatment choices; lamotrigine or carbamazepine are also considered. When current treatment includes a mood-stabilizing agent such as lithium, lamotrigine is an option. Further, they concluded that there is no evidence for additional benefit from antidepressants when treatment includes a mood stabilizer. Researchers stated that in practice however, antidepressants are often used in combination with antimanic agents.

Major changes to PAPHSS Bipolar Depression Algorithm revision included the following: early consideration of ECT and treatment of psychotic symptoms; optimization of lithium therapy prior to treatment with quetiapine or lamotrigine (in both bipolar I and II depressed patients); low priority of olanzapine-fluoxetine combination because of its long-term metabolic side effects; and the use of antidepressants, i.e., bupropion, very late, if at all, in the algorithm (Ansari et al., 2010). A meta-analysis of six observational studies including patients diagnosed with bipolar or unipolar depression (n=1106) investigated the relative efficacy of ECT in both forms of depression finding ECT to be as equally effective for bipolar depression as compared with unipolar depression (Dierckx et al., 2012). The overall remission rate was 53.2 percent for patients with bipolar depression and 50.9 percent for patients with unipolar depression. Researchers suggested that this finding is encouraging since bipolar depression is often relatively treatment resistant.

In a recent randomized controlled, six-week acute treatment trial, researchers compared the effects of right unilateral (RUL) brief-pulse ECT and algorithm-based pharmacologic treatment (APT) on general neurocognitive function and autobiographical memory consistency in patients (n=73) with

treatment-resistant bipolar depression (Kessler et al., 2014). ECT was conducted in three sessions per week for up to six weeks (0.5 ms pulse width, 900 mA pulse amplitude) during which appropriate dosage adjustments were made in subsequent treatments. The mean dose for the RUL brief-pulse ECT was 233.3 mC. If remission occurred before the end of the treatment period, ECT was terminated and the patient switched to pharmacologic maintenance therapy. In the APT group, patients were treated with medications according to a treatment algorithm for bipolar depression (Goodwin and Jamison, 2007). Results found that patients in both groups showed reduced performance in most neurocognitive domains at pretreatment assessment, and both groups showed improved performance on all measures after treatment. Patients receiving ECT, however, exhibited reduced autobiographical memory compared to patients randomized to APT. Researchers suggested that the clinical implication of this finding is uncertain. They concluded, "general neurocognitive function was unaffected by RUL ECT treatment and positively related to improved mood in bipolar depression. Autobiographical memory consistency was reduced in patients treated with ECT. The results suggest that ECT can be used in treatment-resistant bipolar depression without compromising general neurocognitive function." (Kessler et al., 2014)

A later analysis of the aforementioned study, found that in a linear mixed effect modeling analysis, ECT was significantly more effective than drug therapy (Schoeyen et al., 2015). At the end of the six-week treatment period, the mean Montgomery Asberg Depression Rating Scale (MADRS) score, the mean score on the Inventory of Depressive Symptomatology and the Clinical Global Impressions of Bipolar Disorder (CGI-BP) score were all lower in the ECT group than the APT group at six weeks. No significant difference was found between the remission rates of the ECT group (34.8 percent) and the pharmacological treatment group (30.0 percent). Researchers concluded that the current results show that, in the acute phase of treatment-resistant bipolar depression, ECT is more effective than pharmacological treatment (Schoeyen et al., 2015).

*The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of acute bipolar depression* indicated that there was no consistency in specific time criteria for operationalizing treatment emergent affective switches (TEAS) in clinical trials. The Task Force noted that the International Society for Bipolar Disorders proposes a definition of "the appearance of an episode of the opposite pole directly from/after the index episode occurring up to eight weeks after remission" which needs validation in future clinical trials (Grunze et al., 2010). The WFSBP guideline also summarized new key findings for its revisions including: 1) Clear evidence of the efficacy of quetiapine monotherapy at 300mg/day for the treatment of both bipolar I and II depression; 2) Strong evidence for the efficacy of olanzapine/fluoxetine combination; 3) Fair evidence for the efficacy of fluoxetine and to some degree for other antidepressants when used in combination with an antimanic agent and noting the TEAS issue to "be under control with the combined use of an antimanic agent, at least with SSRIs (Selective Serotonin Reuptake Inhibitors);" and 4) demonstrated efficacy for lamotrigine monotherapy in more severely depressed patients and as an add-on to lithium in non- or partially responding patients (Grunze et al., 2010, p.101).

## Rapid Cycling

The guideline indicates that rapid cycling is generally difficult to treat. The document also emphasizes that an important first step is to assess for and treat medical conditions that may contribute to cycling, such as hypothyroidism or substance abuse. Additionally, the guideline suggests that lithium, divalproex or their combined use are more effective on the manic aspects of rapid-cycling and not for the recurrent depression that principally characterizes rapid cycling. It

also suggests that lamotrigine is effective in rapid cycling and especially for depressive features. A later randomized, placebo-controlled study evaluated the efficacy of lamotrigine as compared with placebo when used as adjunctive treatment for rapid-cycling bipolar depression non-responsive to the combination of lithium plus divalproex (Kemp et al., 2012). In Phase I of the study, patients (n=133) with bipolar I or II disorder and rapid cycling during the year preceding the study were treated with lithium and divalproex for up to 16 weeks during which only 19 patients stabilized on the combination of lithium and divalproex. In Phase II of the study, patients (n=49) who remained in or cycled into the depressed phase after Phase I treatment were randomly assigned to adjunctive lamotrigine or adjunctive placebo. Researchers found that the addition of lamotrigine during Phase II was no more effective than placebo in reducing depression severity and suggested that future studies consider randomizing patients to a positive control treatment, e.g., atypical antipsychotic, rather than placebo.

Another naturalistic follow-up study using patients in the STEP-BD study prospectively observed mood episode frequency for up to one year. Results showed that at entry, 32 percent of the patients met DSM-IV-TR criteria for rapid cycling in the pre-study year. At the end of 12 months, only 5 percent of the patients could be classified as rapid cyclers; 34 percent had no further mood episodes; 34 percent experienced one episode and 27 percent had two or three episodes. Patients who entered the study with earlier illness onset and greater severity were more likely to have one or more episodes in the prospective study year. Antidepressant use during follow-up was associated with more frequent mood episodes. Researchers suggested that cycling is on a continuum and that prevention of recurrences may require early intervention and restricted use of antidepressants (Schneck et al., 2008).

An exploratory analysis of a randomized, double-blind, placebo-controlled trial examined the efficacy and mood conversion rate of long-term fluoxetine versus lithium monotherapy in patients (n=81) with rapid- versus non-rapid-cycling bipolar disorder (Amsterdam et al., 2013). The participants in the study had recovered from a major depressive episode during initial fluoxetine monotherapy. Results of the study showed that after initial stabilization on fluoxetine, depressive relapse and treatment-emergent mood conversion episode rates were similar for fluoxetine monotherapy, lithium monotherapy and placebo during long-term treatment of rapid- and non-rapid-cycling bipolar II disorder. Researchers pointed out that their definition of rapid cycling was based on an average of ≥ 4 affective episodes per year over the course of the illness rather than ≥ 4 affective episodes in the preceding year per the DSM-IV definition. They also pointed out that the findings may question recommendations of practice guidelines to avoid maintenance antidepressants in patients with rapid and non-rapid cycling bipolar II disorder.

Rapid Cycling – Comorbid Bipolar Disorder and Migraine. A recent study examined differences in clinical characteristics between individuals with bipolar disorder and comorbid migraine and those with bipolar disorder without migraine (Gordon-Smith et al., 2015). Authors noted several studies suggesting that the prevalence of migraine headache is higher in affective disorders than in the general population and one study that found individuals with bipolar disorder to be almost three times more likely to have migraine than those with major depressive disorder. Studies have also shown different clinical characteristics between individuals with bipolar disorder and comorbid migraine and those with bipolar disorder without migraine. Conditions found to be associated with bipolar disorder and comorbid migraine include earlier age of onset of bipolar disorder, increased prevalence of comorbid panic disorders, higher rate of suicide attempt, and higher prevalence of bipolar II disorder. Gordon-Smith et al. compared the lifetime clinical characteristics of individuals with bipolar disorder and comorbid migraine (n=375) and bipolar disorder without comorbid

migraine (n=1113). Results showed that individuals in the bipolar disorder and comorbid migraine group compared with the no migraine group were characterized by the following: higher rate of history of panic attacks; higher rate of family history of affective disorders; higher rate of rapid cycling; younger age at illness onset; and higher number of females. Researchers concluded that their findings provide evidence that comorbid bipolar disorder and comorbid migraine is a homogenous subgroup of bipolar disorder associated with unstable rapid cycling, suggesting that the identification of a subgroup of individuals with comorbid bipolar disorder and comorbid migraine may be useful in future research and clinical practice (Gordon-Smith et al., 2015).

## Maintenance Treatment

The guideline watch indicated that both lamotrigine and lithium appear to have substantial utility in the maintenance treatment of patients with bipolar disorder. Specifically, the utility of lamotrigine was somewhat greater for the prevention of depressive compared with manic episodes and the opposite was true for lithium. Additionally, the guideline watch noted that results of clinical trials of olanzapine versus divalproex for maintenance treatment of manic or mixed episodes did not show differences in remission rates except that time to remission was shorter for olanzapine than for divalproex. Similarly, the guideline watch discussed study results showing that olanzapine versus lithium maintenance treatment did not show statistically significant relapse rates into manic or depressed states. However, olanzapine showed superiority to lithium in rates of symptomatic recurrence of mania or mixed episodes, but rates of depression recurrence did not differ. The guideline watch also indicated that monotherapy and combination therapy, i.e., lithium or valproate plus olanzapine, did not show differences in time to relapse into mania or depression, but combination therapy was more effective in the prevention of symptomatic relapse.

At the recent European Psychiatric Association (EPA) 23rd Congress, Dr. Simhandl noted that, generally, after four years, bipolar disorder patients have a relapse (Medscape, 2015). He recommended strategies to reduce relapse, e.g., better adherence and self-monitoring by patients, psychoeducation, mindfulness training, cognitive behavioral therapy, and interpersonal and social therapies. Dr. Völlm indicated that lithium is still the best medication for preventing relapse and agreed that psychological interventions, in addition to medications, are worth trying although evidence of their efficacy is lacking (Medscape, 2015).

A large study evaluated the efficacy and safety of quetiapine in combination with lithium or divalproex in the prevention of recurrent mood events in patients with bipolar I disorder where the index episode was manic or depressed. Their results revealed that patients who respond to quetiapine plus lithium or divalproex in acute treatment, continued treatment with the combination appears to be beneficial as maintenance therapy and was associated with a significant risk reduction in the time to recurrence of any mood event (Suppes et al., 2009).

The novel drug N-acetyl cysteine (NAC) was studied as an add-on to existing maintenance drugs in the treatment and prevention of depressive symptoms in bipolar disorder. Berk et al. studied NAC as the bioavailable precursor to glutathione—the main antioxidant substrate in all tissue (Berk et al., 2008). Researchers noted that perturbed glutathione metabolism has been increasingly described as a feature of major psychiatric disorders. Key conclusions from this trial was that NAC (1 gram twice daily) adjunctive to usual medication caused a prominent reduction over a six-month period in depressive symptoms, improvement in function/quality of life with some effect in symptoms of mania and that further study is warranted (Berk et al., 2008). In a later double-blind randomized placebo-controlled trial including participants with bipolar disorder (n=149),

researchers investigated the efficacy of adjunctive NAC, in addition to treatment as usual, in the maintenance treatment of bipolar depression (Berk et al., 2012). Participants were randomized to adjunctive NAC or placebo while also receiving treatment as usual. The findings showed no significant differences in recurrence, or symptomatic outcomes, or quality of life measures during the maintenance phase of the trial between the groups receiving adjunctive NAC or placebo in addition to treatment as usual.

Magellan has reviewed the literature and evaluated published research studies on the use of ketamine in the treatment of bipolar disorder. Ketamine is a high-affinity, noncompetitive N-Methyl-D-aspartate (NDMA)-glutamate receptor that is theorized to be instrumental in the neurobiology of depression. Ketamine has demonstrated antidepressant-like properties but the exact biologic mechanism underlying its antidepressant activities is unclear. Ketamine has been employed in clinical practice as a nonbarbiturate adjunct to anesthesia and procedural sedation for use in human and veterinary medicine. It is also used illicitly in order to intensify social experiences by giving a reported sense of physical closeness, empathy and euphoria. Small randomized, placebo-controlled studies have been conducted on patients with major depressive episodes where intravenous treatment with ketamine in sub-anesthetic doses, i.e., 0.5 mg/kg, has been studied. Preliminary evidence from these studies demonstrated robust effects for ketamine, but the duration of the therapeutic effect was very short term. Investigators have concurred that the sustainability of ketamine's antidepressant effect and its long-term safety in repeated exposure in patient's remains unknown, e.g., risk of severe psychosis and more dissociate and psychotomimetic effects. Much research now focuses on what can prevent post-ketamine relapse. Other clinical studies are examining augmentation of ketamine with other glutamate-modulating agents, i.e., riluzole, to prevent relapse. Magellan considers the use of ketamine in the treatment of bipolar depression highly investigational (Magellan Healthcare Technology Assessments Report, 2013).

A recent randomized, placebo-controlled, double-blind study examined the effect of a single ketamine infusion on anhedonia levels in patients (n=36) with treatment resistant bipolar depression, who were currently experiencing a major depressive episode (Lally et al., 2014). This National Institutes of Health trial was conducted over a four-week period, with two weeks between each infusion. Using rating scales for both anhedonia and depression to detect resultant mood changes, researchers discovered that ketamine, compared to placebo, more rapidly reduced the levels of anhedonia. Within 40 minutes of receiving ketamine, levels of anhedonia plummeted and lasted up to 14 days. This result was independent from the reductions in general depressive symptoms. Positron emission tomography imaging in a subset of patients to explored the neurobiological mechanisms underpinning the effects of ketamine on anhedonia levels. Researchers found that the greatest clinical reduction in anhedonia levels were found in individuals with the largest increase in glucose metabolism in the dACC and the putamen, but not the ventral striatum. Researchers emphasized the importance of the glutamatergic system in the treatment of symptoms of treatment-refractory bipolar depression, e.g., anhedonia. Limitations of this study acknowledged by the authors included the following: lack of baseline PET image; potential invalidation of the placebo arm of study as patients may have realized which infusion they received; and the fact that all patients continued receiving lithium or valproate which may have affected the effect of ketamine. As this was a very small study, further larger studies to replicate and extend the findings are needed (Lally et al., 2014).

An observational study using STEP-BD baseline data from BP-I patients (N=1,943) from 2000-2004 was used to examine the association between patient characteristics and patient-reported use of any antimanic medication in an effort to clarify the usage of SGAs in pharmacologic treatment as replacement or augmenting agents. Researchers reported that at study entry, more than 80 percent

of participants reported receiving at least one antimanic medication; 73 percent a mood stabilizer specifically. Findings showed that measures of psychiatric severity or complexity were more likely to be associated with differences in the drugs used whereas co-occurring medical conditions were not. Depressed states were associated with similar odds of antipsychotic monotherapy as elevated or mixed states. Additionally, compared to whites, blacks had greater odds of entering on antipsychotic monotherapy as a mood stabilizer. Researchers concluded that despite increasing pharmacotherapy options, there was no evidence that over time more patients received antimanic medication and found that not all prescribing differences were consistent with the medical literature (Busch et al., 2009).

Tsai et al. performed a literature search to identify double-blind, randomized controlled trials of aripiprazole for the maintenance treatment of bipolar disorder (Tsai et al., 2011). Aripiprazole, approved by the FDA for the maintenance treatment of bipolar disorder, is used increasingly in the maintenance treatment of bipolar disorder. Authors found that the evidence base supporting ariprazole's use in maintenance treatment relies on results from a single trial conducted (Keck et al 2006). Several substantive methodological limitations in the trial, e.g., insufficient duration, limited generalizability and low overall completion rate, were described by Tsai et al. Authors suggested alternative modifications or study designs to generate useful data to inform the maintenance treatment of patients with bipolar disorder in the future.

*The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2012 on the long-term treatment of bipolar disorder* indicated that areas of uncertainty still exist in the prevention of depressive episodes and long-term treatment of bipolar II patients (Grunze et al., 2013). The guidelines note that although no single agent shows equally good efficacy throughout the bipolar spectrum, the broadest base of evidence continues to be lithium for the long-term treatment of bipolar disorder. The guidelines did not present an overall recommendation for long-term treatment of bipolar disorder, but discussed various treatments in different scenarios, noting the need for examination of different scenarios separately. The guidelines identified medications with the highest recommendation grades, i.e., aripiprazole for patients with episode of mania; lamotrigine for the prevention of depressive recurrences; lithium for any relapse and mania; quetiapine for mania, depression and any episode. The guidelines did not recommend typical antipsychotics in the treatment of bipolar patients due to the absence of reliable evidence and unfavorable side effect profile.

A systematic review and network meta-analysis investigated the efficacy and tolerability of bipolar treatment strategies for bipolar disorder (Miura et al., 2014). The meta-analysis included 33 randomized controlled trials comparing pharmacological agents with placebo or active comparator, with at least 12 weeks of follow-up, for the maintenance treatment of patients (n=6846) with bipolar disorder. Pharmacological agents included mood stabilizers, antipsychotics, antidepressants, and antiepileptic drugs, and combination or augmentation studies were included. Efficacy outcomes measures included the number of participants with recurrent mood episode, number of participants who dropped out of treatment due to adverse events, and number of participants who completed suicide. Below are some of the findings from this meta-analysis:

- Except for imipramine, all drugs or combinations were significantly more efficacious in preventing any mood episode relapse or recurrence than placebo.
- Quetiapine and lithium were the only drugs that prevented relapse or recurrence of both polarities of the mood episode compared with placebo.

- Olanzapine, lithium plus valproate, and risperidone long-acting injection were more prophylactic for manic episodes than for depressive episodes.
- Lamotrigine was more prophylactic for depressive episodes.
- This study showed the superiority of lithium in all three efficacy outcomes.

Authors concluded that the most reasonable candidate for a first-line treatment option for the long-term treatment of bipolar disorder is lithium. They emphasized that all of the drugs have very different side effect profiles and that this must be considered at the individual patient level.

## Predictors of Recurrence

Researchers analyzed prospective follow-up data from the STEP-BP study to investigate recurrence among patients (N=1,469) who initially achieved recovery from a mood episode. The study aimed to estimate the effectiveness of guideline-based treatment with contemporary pharmacotherapies and to examine the association between patient clinical features and risk of recurrence. Results showed 58.4 percent of patients subsequently achieved recovery. During the two years of follow-up, 48.5 percent of these individuals experienced recurrences with more than twice as many developing depressive episodes (34.7 percent) as those who developed manic, hypomanic or mixed episodes (13.8 percent). The time until 25 percent of the individuals experienced a depressive episode was 21.4 weeks and until 25 percent experienced a manic/hypomanic/mixed episode was 85 weeks. Additionally, the study revealed that residual depressive or manic symptoms at recovery and proportion of days depressed or anxious in the preceding year were significantly associated with shorter time to depressive recurrence. Similarly, residual manic symptoms at recovery and proportion of days of elevated mood in the preceding year were significantly associated with shorter time to manic, hypomanic, or mixed episode recurrence. Researchers concluded that in spite of modern evidence-based treatment, bipolar disorder remains an illness with high recurrence, and is a predominantly depressive illness. They also suggested that risk of recurrence might be useful in stratifying patients to more or less intensive maintenance follow-up and treatment, with the ultimate goal of full remission as in major depressive disorder (Perlis et al., 2006).

In a randomized, double-blind, controlled trial of olanzapine versus lithium in bipolar I disorder, patients with an index manic or mixed episode (n=431) who had completed acute therapy with olanzapine plus lithium, a mediators-and-moderators approach was applied to identify predictors of relapse (Tohen et al., 2012). Risk factors for relapse identified for lithium-treated patients included smoking status, previous episode history and country of residence, but no mediators/moderators were identified. Risk factors indicated for olanzapine-treated patients included: smoking status, previous number of bipolar episodes, depressive symptom severity prior to remission and Hamilton Depression Rating Scale-21 (HDRS-21) score at randomization. Researchers found that olanzapine-treated patients with the same number of previous episodes (manic/depressive) but with more severe depressive symptoms had higher rates of relapse than those with less severe depression. Patients with the same severity of depressive symptoms, but whose first episode was mania were more likely to relapse than those with depressive or mixed first episode. The effect of the number of previous episodes on relapse rate was mediated by the severity of depressive symptoms.

## Psychosocial Treatment

The guideline watch affirms that knowledge of the utility of psychosocial interventions has expanded in recent years. It summarized findings of randomized clinical trials demonstrating efficacy for family-focused therapy, cognitive behavioral therapy (CBT) in conjunction with pharmacotherapy, psychoeducation and psychosocial interventions for interpersonal problems/regulation of social rhythms in the treatment of patients with bipolar disorder. Since publication of the guideline watch, other studies of psychosocial treatment have been published with positive results.

Depressed outpatients with bipolar disorder who were participants in the STEP-BD study (N=152) were randomized to receive one of two treatments: 1) intensive psychosocial interventions including interpersonal and social rhythm therapy or family-focused therapy; or 2) collaborative care, i.e., three-session psychoeducational treatment. All patients, in both treatment groups, received adjunctive pharmacotherapy. Results confirmed that patients in intensive psychotherapy had better total functioning, relationship functioning and life satisfaction scores over nine months than patients in collaborative care. However, there were no observed effects of the psychosocial intervention on work/role functioning after a depressive episode. In light of these findings, researchers suggested that alternative interventions focusing on the specific cognitive deficits of individuals with bipolar disorder may be necessary to enhance vocational functioning after a depressive episode (Miklowitz et al., 2007).

A similar study of intensive psychosocial interventions was conducted for adolescents with both BP-I and BP-II disorder where patients received either Family-focused Therapy for Adolescents (FFT-A) or enhanced care (EC) along with protocol pharmacotherapy. FFT-A consisted of 21 sessions over nine months with goals to have families develop a common understanding of bipolar illness, i.e., etiology, course of illness and precipitants to recurrence, encourage adherence with drug treatment and learn relapse prevention strategies. The EC consisted of three family sessions focused on relapse prevention. Much like the STEP-BD study discussed above, the present study found stabilizing effects of FFT-A on depression symptoms, but not mania symptoms. Here, also, researchers recommended that in order to establish full recovery, FFT-A may need to be supplemented with systematic care interventions effective for manic symptoms (Miklowitz et al., 2008).

A later randomized, clinical trial evaluated the efficacy of a novel group intervention, functional remediation, in enhancing functioning in patients (n=239) with bipolar I and II disorder (Torrent et al., 2013). Patients were randomized to one of three groups: treatment with functional remediation in daily routines, psychoeducation and treatment as usual. Patients in each group also received pharmacological treatment. Functional remediation, a neurocognitive intervention designed specifically for bipolar patients, addressed neurocognitive issues, e.g., memory, executive functions and attention, and a focus on ecological tasks performed while interacting with other members of the group as well at home. The practical effectiveness of interventions on daily life is emphasized in ecological tasks. Training included memory exercises, problem solving, organization and multitasking to improve functional outcome. Researchers found that functional remediation improved psychosocial functioning significantly as compared to treatment as usual and was associated with greater improvement compared with psychoeducation, but not significantly. Functional remediation was also associated with improvement in occupational functioning, but did not result in greater cognitive improvement (Torrent et al., 2013).

Another study examined whether a mindfulness-based cognitive therapy (MBCT) increases mindfulness, emotion-regulation abilities, psychological well-being, positive affect and interpersonal functioning while reducing residual mood symptoms in patients with bipolar disorder (Deckersbach et al., 2011). Patients (n=12) with bipolar disorder with residual mood symptoms were treated with 12 group sessions of MBCT including cognitive-behavioral treatment elements, mindful movement exercises, problem solving, formal mindfulness exercises, compassionate self-coaching and loving-kindness meditation. Investigators found that patients receiving MCBT showed increased mindfulness, lower residual depressive mood symptoms, increased emotion-regulation abilities, positive affect, psychological well-being, psychosocial functioning and less attentional difficulties at the end of the three-month treatment period. Researchers advised further studies on the efficacy of MCBT are warranted using larger samples and comparative treatment arms in order to fully evaluate its usefulness as a treatment option (Deckersbach et al., 2011).

In a review summarizing the available data on psychosocial interventions for adults with bipolar disorder, Swartz et al. conducted a literature search of outcome studies for the interventions (Swartz et al., 2014). Their study included randomized controlled trials (n=28) testing either individual or group psychosocial interventions for adults with bipolar disorder. Interventions included individual psychoeducation (PE), group PE, individual CBT, group CBT, family therapy, interpersonal and social rhythm therapy, and integrated care management. Three studies of **individual PE**, collectively including 201 patients with bipolar disorder, showed that individual PE resulted in fewer manic relapses and higher functioning over 18 months compared with treatment as usual (TAU). Other results showed that CBT combined with individual PE resulted in fewer days of depressed mood than with individual PE alone, and family focused therapy (FFT) was associated with lower recurrence rates and hospitalization rates than individual PE. In four studies of **group PE**, collectively including 720 patients with bipolar disorder, group PE was associated with longer time to recurrence and decreased rates of hospitalization compared with TAU. When group PE was compared with either individual CBT or functional remediation, symptoms were improved in both groups, although the functional remediation (FR) group showed greater improvement. **Individual cognitive therapy (CT)** or CBT was evaluated in seven trials including patients (n=777) with bipolar disorder. These studies found that, generally, CBT or CT was associated with lower depression severity and lower relapse rates compared to TAU, but had comparable effects to other therapies, e.g., supportive psychotherapy. **Cognitive behavioral group therapy (CBGT)** was studied in four studies including patients (n=199) randomized to CBGT or TAU, or CBGT or pharmacotherapy alone. CBGT was superior to TAU on measures of depressive symptoms, time to relapse, anxiety symptoms, and functioning. One study showed that CBGT adjunctive to pharmacotherapy resulted in fewer depression and anxiety symptoms than pharmacotherapy alone. In two studies of **family therapy** including 193 patients, family focused therapy resulted in lower relapse rates than crisis management. Other therapies shown to be beneficial in the treatment of patients with bipolar disorder were Interpersonal and Social Rhythm Therapy and Integrated Care Management. Authors concluded that individual or group psychotherapy added to medication for the treatment of bipolar disorder has advantages over medication alone. Generally, studies have shown psychotherapies to have a larger impact on depressive symptoms than manic symptoms. In their conclusion, authors noted that studies have shown little difference between evidence-based psychotherapies and suggested that any of the bipolar disorder-specific psychotherapies will be beneficial (Swartz et al., 2014).

## Complexities in Treatment of Bipolar Disorder

Psychiatrists are challenged in treating women with bipolar disorder through pregnancy and the postpartum period due to risk of relapse and recurrence postpartum (Wesseloo et al., 2017). Although lithium is considered the gold standard for treatment of bipolar disorder, decisions about its use during pregnancy are complicated due to inconclusive data on the associated risks of adverse neonatal outcomes. A recent population-based cohort study investigated whether lamotrigine, increasingly used as an alternative to lithium during pregnancy, is as effective as lithium in the prevention of severe postpartum episodes. Researchers compared the risk of inpatient psychiatric admission within three months postpartum in two groups: women (n=55) using lamotrigine and women (n=59) using lithium during pregnancy (Wesseloo et al., 2017). Researchers found an overall risk for postpartum psychiatric admission was 11.4%, with no significant difference between the two groups. Overall, the polarity of postpartum episodes was 53.8% for mania or psychosis and 46.2% for depression or other diagnoses, with no significant difference between the groups. Limitations of this study noted by researchers included the small sample size as well as "confounding by indication because lithium was predominantly prescribed in patients with a history of manic episodes, while lamotrigine was primarily prescribed to women with a particular vulnerability for depressive episodes. Notably, this is consistent with the current bipolar disorder treatment guidelines" (Wesseloo et al, p. 396). Researchers also noted, "the perinatal effectiveness of lamotrigine is largely unknown for patients with predominantly manic episodes in history" (Wesseloo et al, p. 396).

Authors emphasized challenges in psychopharmacologic treatment of anxiety disorders in bipolar disorder, e.g., the concern that antidepressants may destabilize mood in patients, and that benzodiazepines may present problems in treating patients with comorbid alcohol/substance use disorders. They suggested the use of medication, e.g., a typical or atypical antipsychotic that may cover both conditions, and cautioned, "effect of atypical antipsychotics (e.g., olanzapine, quetiapine and lurasidone) on anxiety during bipolar depression should be viewed with caution and as preliminary" (Nabavi et al., p. 1415). Authors advised the use of psychological interventions, e.g., cognitive behavioral therapy (CBT) and mindfulness-based cognitive therapy in the treatment of anxiety comorbid to bipolar disorder while noting that the co-occurrence of more than one anxiety disorder may discourage the use of psychotherapy in patients with bipolar disorder. Noting the challenge in treating co-existing conditions, authors stated the need for advancing knowledge on patterns of response to psychological and psychopharmacological treatments among patients with bipolar disorder with or without anxiety disorders (Nabavi et al., p. 1415).

## Healthcare Effectiveness Data and Information Set (HEDIS®) Measures

## Follow-Up after Hospitalization (FUH)

The Healthcare Effectiveness Data and Information Set (HEDIS®) is a set of performance measures developed and maintained by the National Committee for Quality Assurance (NCQA). A HEDIS measure that includes bipolar disorder diagnoses is Follow-Up after Hospitalization for Mental Illness (FUH.) This measure, like almost all HEDIS measures, focuses on processes, rather than on outcome measures. Individuals with bipolar disorder who have been treated in an acute inpatient setting should receive a follow-up visit within 30 days of discharge, preferably within the first seven days after the discharge.

## Diabetes Screening for People with Schizophrenia or Bipolar Disorder Who are Using Antipsychotic Meds (SSD)

Another HEDIS measure that includes bipolar disorder diagnoses is Diabetes Screening for People with Schizophrenia or Bipolar Disorder Who are Using Antipsychotic Meds. This measure, like almost all HEDIS measures, focuses on processes, rather than on outcome measures. Individuals with a diagnosis of bipolar disorder and who are using antipsychotic medicines should have a diabetes screening during the calendar year in which care is rendered.

## Obtaining Copies of the APA Guideline

Copies of the Practice Guideline for the Treatment of Patients with Bipolar Disorder, Second Edition may be obtained through the APA at http://psych.org/, or by calling (800) 368-5777, or by U.S. mail at:

American Psychiatric Publishing, Inc.
1000 Wilson Blvd., Suite 1825
Arlington, VA 22209-3901

## Provider Feedback

Magellan welcomes feedback on our clinical practice guidelines. We consider suggestions and recommendations in our ongoing review of the guidelines. Submit comments to:

Clinical Operations Coordinator
Re: CPG
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## References


1. Accessed website at http://www.fda.gov/cder/drug/InfoSheets/HCP/antipsychotics_conventional.htm, on April 14, 2009.

2. Advancing Integrated Mental Health Solutions (AIMS Center) 2017. Accessed online at https://aims.uw.edu/collaborative-care/principles-collaborative-care.

3. Altshuler LL, Sugar CA, McElroy SL, Calimlim B, Gitlin M, Keck PE, Aquino-Elias AA, Martens BE, Fischer EG, English TL, Roach J, Suppes T. Switch rates during acute treatment for bipolar II depression with lithium, sertraline, or the two combined: a randomized double-blind comparison. *Am J Psychiatry* 2017; 174(3): 266-276.

4. American Psychiatric Association (2002). Practice Guideline for the Treatment of Patients with Bipolar Disorder, Second Edition. *Am J Psychiatry* April 2002.

5. American Psychiatric Association. Highlights of Changes from DSM-IV-TR to DSM-5 2013. Accessed website on May 18, 2013 at http://www.psychiatry.org/practice/dsm/dsm5.

6. Amsterdam JD, Luo L, Shufts J. Efficacy and mood conversion rate during long-term fluoxetine. Lithium monotherapy in rapid- and non-rapid-cycling bipolar II disorder. *BR J Psychiatry*; 2013; 301-306.

7. Ansari A, Osser DN. The Psychopharmacology Algorithm Project at the Harvard South Shore Program: An Update on Bipolar Depression. *Har Rev Psychiatry*, Volume 18, Number 1.

8. Arana A, Wentworth CE, Ayuso-Mateos JL, Arellano FM. Suicide-Related Events in Patients Treated with Antiepileptic Drugs. *The New England Journal of Medicine*, 1533-4406, 2010 Aug 5, Vol. 363, Issue 6.

9. Arnold LE, Demeter C, Mount K, Frazier T, Youngstrom E, Fristad M, Birmaher B, Findling RL, Horwitz S, Kowatch R. Pediatric bipolar spectrum disorder and ADHD: comparison and comorbidity in the LAMS clinical sample. *Bipolar Disord* 2011; 13(5-6):509-521.

10. Axelson D, Goldstein B, Goldstein T, Monk K, Haifeng Y, Hickey MB, Sakolsky D, Diler R, Haferman D, Merranko J, Iyengar S, Brent D, Kupfer D, Birmaher B. Diagnostic precursors to bipolar disorder in offspring of parents with bipolar disorder: a longitudinal study. *Am J Psychiatry* 2015; 172(7): 638-646.

11. Ballester J, Goldstein T, Goldstein B, Obreja M, Axelson D, Monk K, Hickey MK, Ivengar S, Farchione T, Kupfer DJ, Brent D, Birmaher B. Is bipolar disorder specifically associated with aggression? *Bipolar Disord* 2012; 14(3): 283-90.

12. Bauer M, Glenn T, Alda M, Andreassen OA, Ardau R, Bellivier F, Berk M, Bjella TD, Bossini L, Del Zompo M, Dodd S, Fagiolini A, Frye MA, Gonzalez-Pinto A, Henry C, Kapczinski F, Kliwicki S, Konig B, Kunz M, Lafer B, Lopez-Jaramillo C, Manchia M, Marsh W, Manrinez-Cengotitabengoa M, Melle I, Morken G, Munoz R, Nery F, O'Donovan C, Pfennig A, Quiroz D, Rasgon N, Reif A, Rybakowski J, Sagduyu K, Simhandl C, Torrent C, Vieta E, Zetin M, Whybrow PC. Impact of sunlight on the age of onset of bipolar disorder. *Bipolar Disord* 2012; 14(6):654-663.

13. Bauer M, Ritter P, Grunze H, Pfennig A, Treatment options for acute depression in bipolar disorder. *Bipolar Disorders* 2012; 14 (Suppl2): 37-50.

14. Bauer MS, McBride L, Williford WO, Glick H, Kinosian B, Altshuler L, Beresford T, Kilbourne AM, Sajatovic M, et al. Collaborative care for bipolar disorder: part II. Impact on clinical outcome, function, and costs. *FOCUS* 2015; 13: 85-93.

15. Bergink V, Larsen JT, Hillegers MHU, Dahl SK, Stevens H, Mortensen PB, Petersen L, Munk-Olsen T. Childhood adverse life events and parental psychopathology as risk factors for bipolar disorder. *Transl Psychiatry* 2016.

16. Berk M, Copolov DL, Dean O, Lu K, Jeavons S, Schapkaitz, Anderson-Hunt M, Bush AI. N-Acetyl Cysteine for Depressive Symptoms in Bipolar Disorder – A Double-Blind Randomized Placebo-Controlled Trial. *Biol Psychiatry* 2008; 64:468-475.

17. Berk M, Dean OM, Cotton SM, Gama CS, Kapczinski F, Fernandes B, Kohlmann K, Jeavons S, Hewitt K, Moss K, Allwang C, Schapkaitz I, Cobb H, Bush AI, Dodd S, Malhi GS. Maintenance N-acetyl cysteine treatment for bipolar disorder: a double-blind randomized placebo controlled trial. BMC Med 2012. Accessed on website on May 18, 2013 at http://www.ncbi.nlm.nih.gov/pubmed/22891797.

18. Bond DJ, Silveira LE, MacMillan EL, Torres U, Lang DJ, Su W, Honer WG, Lam RW, Yatham LN. Diagnosis and body mass index effects on hippocampal volumes and neurochemistry in bipolar disorder. *Transl Psychiatry* 2017.

19. Busch AB, Frank RG, Sachs G, Normand SL. Bipolar-I Patient Characteristics Associated with Differences in Antimanic Medication Prescribing. *Psychopharmacol Bulletin* 41(2): 35-49, 2009.

20. Calabrese JR, Sanchez R, Amatniek J, Cox K, Johnson B, Perry P, Hertel P, such P, Salzman PM, McQuade RD, Nyilas M, Carson WH. Efficacy and safety of aripiprazole once-monthly in the maintenance treatment of bipolar I disorder: a double-blind, placebo-controlled, 52-week randomized withdrawal study. *J Clin Psychiatry* 2017; 78(3): 324-331.

21. Castro VM, Minnier J, Murphy SN, Kohane I, Churchill SE, Gainer V, Cai T, Hoffnagle AG, Dai Y, Block S, Weill SR, Nadal-Vicens M, Pollastri AR, Rosenquist JN, Goryachev S, Ongur D, Sklar P, Perlis RH, Wmoller JW, International Cohort Collection for Bipolar Disorder Consortium. Validation of electronic health record phenotyping of bipolar disorder cases and controls. *Am J Psychiatry* 2015; 172(4): 363-371.

22. Cerimele JM, Fortney JC, Unützer J, Bipolar Disorder and population health. *Psychiatric Services* 2017; 68(2): 192-194.

23. Chen HM, DeLong CJ, Bame M, Rajapakse I, Herron TJ, Mcinnis MG, O'Shea KS. Transcripts involved in calcium signaling and telencephalic neuronal fate are altered in induced pluripotent stem cells from bipolar disorder patients. *Transl Psychiatry* 2014; 1-8.

24. Cipriani A, Barbui C, Salanti G, Rendell J, Brown R, Stockton S, Purgato M, Spineli LM, Goodwin GM, Geddes JR. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *Lancet* 2011; 378:1306-1315.

25. Cross-Disorder Group of the Psychiatric Genomics Consortium. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet* 2013; 45(9):984-94.

26. Deckersbach T, Holzel B, Eisner LR, Stange JP, Peckham AD, Dougherty DD, Rauch SL, Lazar S, Nierenberg AA. Mindfulness-based cognitive therapy for nonremitted patients with bipolar disorder. *CNS Neurosci Ther* 2012; 18(2): 133-141.

27. Deckersbach T, Peters AT, Sylvia L, Urdahl A, Magalhães PVS, Otto MW, Frank E, Miklowitz DJ, Berk M, Kinrys G, Nierenberg A. Do comorbid anxiety disorders moderate the effects of psychotherapy for bipolar disorder? Results from STEP-BD. *Am J Psychiatry* 2014; 171:178-186.

28. Dierckx B, Heijnen WT, van den Broek WW, Birkenhager TK. Efficacy of electroconvulsive therapy in bipolar versus unipolar major depression: a meta-analysis. *Bipolar Disorders* 2012; 14:146-150.

29. Dunlop BW, Rakofskyk JJ, Rapaport MH. A simple question answered: adding moderate-dosage lithium does not help patients with bipolar disorder. *Am J Psychiatry* 2013; 170:1. Accessed website on May 18, 2013 at http://ajp.psychiatryonline.org/article.aspx?articleid=1555623.

30. Earley W, Durgam S, Lu K, Bebelle M, Laszlovszk7y I, Vieta E, Yatham LN. Tolerability of cariprazine in the treatment of acute bipolar I mania: A pooled post hoc analysis of 3 phase II/III studies. *Journal of Affective Disorders* 2017; 205-212.

31. El-Mallakh RS, Vöhringer PA, Ostacher MM, Baldassano CF, Holtzman NS, Whitham EA, Thommi SB, Goodwin FK, Ghaemi SN. Antidepressants worsen rapid-cycling course in bipolar depression: A STEP-BD randomized clinical trial. *J Affect Disord* 2015; 184: 318-321.

32. Fazel S, Lichtenstein P, Grann M, Goodwin GM, Langstrom N. Bipolar Disorder and Violent Crime. New Evidence From Population-Based Longitudinal Studies and Systematic Review. *Arch Gen Psychiatry*. 2010; 67 (9): 931-938.

33. FDA Alerts Health Care Providers to Risk of Suicidal Thoughts and Behavior with Antiepileptic Medications. Accessed website on May 3, 2011 at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm100190.htm.

34. FDA Approves Saphris to Treat Schizophrenia and Bipolar Disorder. Accessed website on March 22, 2011 at http://www.fda.gov/NewsEvents/Newroom/PressAnnouncements/2009/ucm177401.htm.

35. Food and Drug Administration (FDA). FDA News Release: FDA approves first generic olanzapine to treat schizophrenia, bipolar disorder. October 24, 2011. Accessed website on May 18, 2013 at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm277022.htm.

36. Food and Drug Administration (FDA). For Immediate Release September 17, 2015. FDA approves new drug to treat schizophrenia and bipolar disorder. Accessed online on April 14 2017 at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm463103.htm.

37. Gao K, Chan P, Verduin ML, Kemp DE, Tolliver BK, Ganocy SJ, Bilali S, Brady KT, Findling RL, Calabrese JR. Independent predictors for lifetime and recent substance use disorders in patients with rapid cycling bipolar disorder: focus on anxiety disorders. *Am J Addict* 2010; 19(5): 440-449.

38. Gaudiano BA, Uebelacker LA, Miller IW. Impact of remitted substance use disorders on the future course of bipolar I disorder: findings from a clinical trial. *Psychiatry Research* 160 (2008) 63-71.

39. Gibbs M, Winsper C, Marwaha S, Gilbert E, Broome M, Singh SP. Cannabis use and mania symptoms: a systematic review and meta-analysis. *J Affect Disord* 2015; 171: 39-47.

40. Gignac A, McGirr A, Lam RW, Yatham LN. Recovery and recurrence following a first episode of mania: a systematic review and meta-analysis of prospectively characterized cohorts. *J Clin Psychiatry* 2015.

41. Gilman SE, Ni MY, Dunn EC, Breslau J, McLaughlin KA, Smoller JW, Perlis RH. Contributions of the social environment to first-onset and recurrent mania. *Mol Psychiatry* 2015; 20(3): 329-36.

42. Goldberg JF, Perlis RH, Ghaemi SN, Calabrese JR, Bowden CL, Wisniewski S, Miklowitz DJ, Sachs GS, Thase ME. Adjunctive Antidepressant Use and Symptomatic Recovery among Bipolar Depressed Patients with Concomitant Manic Symptoms: Findings from the STEP-BD. *Ma J Psychiatry* 164:9; September 2007.

43. Goodwin GM, Haddad PM, Ferrier IN, Aronson JK, Barnes TRH, Cipriani A, Coghill DR, Fazel S, Geddes JR, Grunze H, Holmes EA, Howes O, Hudson S, Hunt N, Jones I, Macmillan IC, McAllister-Williams H, Miklowitz DM, Morriss R, Munafo M, Paton C, Saharkian BH, Saunders KEA, Sinclair JMA, Taylor D, Vieta E, Young AH. Evidence-based guidelines for treating bipolar disorder: revised third edition. Recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2016; 30(6): 495-553).

44. Goodman DW, Thase ME. Recognizing ADHD in Adults with Comorbid mood Disorder: Implications for Identification and Management. *Postgraduate Medicine*, Volume 121, Issue 5, September 2009.

45. Goodwin FK, Jamison KR. Manic-depressive illness: bipolar disorders and recurrent depression. 2nd edition. Cary NC: Oxford University Press, 2007.

46. Gordon-Smith K, Forty L, Chan C, Knott S, Jones I, Craddock N, Jones LA. Rapid cycling as a feature of bipolar disorder and comorbid migraine. *J Affect Disord* 2015; 175: 320-324.

47. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Moller HJ, Kasper S, and WFSBP Task Force on Treatment Guidelines for Bipolar Disorders. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of acute bipolar depression. *The World Journal of Biological Psychiatry*, 2010; 11: 81-109.

48. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Moller HJ, Kasper S. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2012 on the long-term treatment of bipolar disorder. 2013. Accessed website on May 18, 2013 at http://www.wfsbp.org/fileadmin/user_upload/Treatment_Guidelines/Grunze_et_al_2013.pdf.

49. Gunn A, Barkay G, Karne HS, Nurnberger JI, Mathew SJ, Ghosh S. Early antidepressant effect of memantine during augmentation of lamotrigine inadequate response in bipolar depression: a double-blind, randomized, placebo-controlled trial. *Bipolar Disorders* 2012; 14:64-70.

50. Hayes JF, Pitman A, Marston L, Walters K, Geddes JR, King M, Osborn DP. Self-harm, unintentional injury, and suicide in bipolar disorder during maintenance mood stabilizer treatment: a UK population-based electronic health records study. *JAMA Psychiatry* 2016; 73(6): 630-637.

51. Harrison PJ, Cipriani A, Harmer CJ, Nobre AC, Saunders K, Goodwin GM, Geddes JR. Innovative approaches to bipolar disorder and its treatment. *Ann N.Y. Acad Sci* 2016; 76-89.

52. Hirschfeld RM. (2005). Guideline Watch: Practice Guideline for the Treatment of Patients with Bipolar Disorder, Second Edition. Arlington, VA: American Psychiatric Association. Available online at http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm.

53. Javras KN, Harrison GP, Lalonde JK, Roberts GP, Roberts JL, Nillni YI, Laird NM, Bulik CM, Crow SJ, McElroy SL, Walsh BT, Tsuang MR, Rosenthal NR, Hudson JI. Co-occurrence of Binge Eating Disorder with Psychiatric and Medical Disorders. *J Colin Psychiatry* 2008; 69: 266-273.

54. Johnson SL, Cuellar A, Gershon A. The influence of trauma, life events, and social relationships on bipolar depression. *Psychiatr Clin North Am* 2016; 39(1): 87-94.

55. Keck PE, Jr., Calabrese JR, McQuade RD, Carson WH, Carlson BX. A randomized, double-blind, placebo-controlled 26-week trial of aripiprazole in recently manic patients with bipolar I disorder. *J Clin Psychiatry* 2006; 67:626-637.

56. Kemp DE, Gao K, Fein EB, Chan PK, Conroy C, Obral S, Ganocy SJ, Calabrese JR. Lamotrigine as add-on treatment to lithium and divalproex: lessons learned from a double-blind, placebo-controlled trial in rapid-cycling bipolar disorder. *Bipolar Disorders* 2012; 14:780-789.

57. Kessler RC, Merikangas KR, Wang PS. Prevalence, Comorbidity, and Service Utilization for Mood Disorder in the United States at the Beginning of the Twenty-first Century. *Annu. Rev. Clin. Psychol*. 2007. 3:137-58.

58. Kessler U, Schoeyen HK, Andreassen OA, Eide G, Malt UF, Oedegaard KJ, Morken G, Sundet K, Vaaler AE. The effect of electroconvulsive therapy on neurocognitive function in treatment-resistant bipolar disorder depression. *J Clin Psychiatry* 2014; 75(11); e1306-e1313.

59. Lally N, Nugent AC, Luckenbaugh DA, Ameli R, Roiser JP, Zarate CA. Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression. *Transl Psychiatry* 2014; 1-9.

60. Leon AC, Solomon DA, Li C, Fiedorowicz JG, Coryell WH, Endicott J, Keller MB. Antiepileptic drugs for bipolar disorder and the risk of suicidal behavior: a 30-year observational study. *Am J Psychiatry* 2012; 169(3):285-291.

61. Leverich GS, Altshuler LL, Frye MA, Suppes T, McElroy SL, Keck PE, Kupka RW, Denicoff KD, Nolen WA, Grunze H, Martinez MI, Post RM. Risk of Switch in Mood Polarity to Hypomania or Mania in Patient With Bipolar Depression During Acute and Continuation Trials of Venlafaxine, Sertraline, and Bupropion As Adjuncts to Mood Stabilizers. *Am J Psychiatry* 2006; 163: 232-239.

62. Levin JB, Aebi ME, Tatsuoka C, Cassidy KA, Sajatovic M. Adherence to psychotropic and nonpsychotropic medication among patients with bipolar disorder and general medical conditions. *Psychiatric Services* 2016; 67(3): 342-345.

63. Loebel A, Cucchiaro J, Silva R, Kroger H, Sarma K, Xu J, Calabrese JR. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry* 2014; 171:169- 177.

64. Loebel A, Cucchiaro J, Silva R, Kroger H, Hsu J, Sarma K, Sachs G. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry* 2014; 171:160- 168.

65. Magellan Healthcare Technology Assessment Report. Ketamine for the treatment of treatment-resistant depression. 2013.

66. Mahon K, Russo M, Perez-Rodriguez M, Burdick KE. The neurobiology of bipolar disorder: Neuroimaging and genetics update. *FOCUS* 2015; 13(1): 3-11.

67. Mansur RB, McIntyre RS. Metabolic comorbidity and physical health implications for bipolar disorder: an update. *FOCUS* 2015; 13(1): 12.18.

68. McElroy SL, Frye MA, Hellemann G, Altshuler L, Leverich GS, Suppes T, Keck PE, Nolen WA, Kupka R, Post R. Prevalence and correlates of eating disorders in 875 patients with bipolar disorder. *J Affect Disord* 2011; 128(3):191-8.

69. Medscape. Lithium still best medication for preventing bipolar relapse. April 06, 2015. Accessed online on June 3 2015 at http://www.medscape.com/viewarticle/842612.

70. Medscape Medical News. Lurasidone approved for bipolar depression. July 01 2013. Accessed online on June 3 2015 at http://www.medscape.com/viewarticle/807204.

71. Medscape. Should antidepressants ever be used in bipolar disorder? February 04, 2015. Accessed online on June 3 2015 at http://www.medscape.com/viewarticle/838861.

72. Merikangas KR, et al. (2007) Lifetime and 12-month Prevalence of Bipolar Spectrum Disorder in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 64:543-552.

73. Merikangas KR, Jin R, He JP, Kessler RC, Lee S, Sampson NA, Viana MC, Andrade LH, Hu C, Karam EG, Ladea M, Medina-Mora ME, Ono Y, Posada-Villa J, Sagar R, Wells JE, Zarkov Z. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry* 2011; 68(3):241-51.

74. Miklowitz DJ, Axelson DA, Birmaher B, George EJ, Taylor DO, Schneck CD, Beresford CA, Dickinson LM, Craighead E, Brent DA. Family-Focused Treatment for Adolescents with Bipolar Disorder. *Arch Gen Psychiatry*. 2008: 65(9): 1053:1061.

75. Miklowitz DJ, Gitlin MJ. Psychosocial approaches to the treatment of bipolar disorder. *FOCUS* 2015; 13(1): 37-46.

76. Miklowitz DJ, Otto MW, Frank E, Reilly-Harrington NA, Kogan JN, Sachs GS, Thase ME, Calabrese JR, Marangell LB, Ostacher JM. Intensive Psychosocial Intervention Enhances Functioning in Patients with Bipolar Depression Results from a 9-Month Randomized Controlled Trial. *Am J Psychiatry* 2007; 164:1340-1347.

77. Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, Salanti G, Motomura K, Shimano-Katsuki S, Leuht S, Cipriani A, Geddes JR, Kanba S. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. *The Lancet* 2014; 1:351-359.

78. Nabavi B, Mitchell AJ, Nutt D. A lifetime prevalence of comorbidity between bipolar affective disorder and anxiety disorders: a meta-analysis of 52 interview-based studies of psychiatric population. *EBioMedicine* 2015; 1405-1419.

79. National Institute of Mental Health. Science Update March 01, 2013. Accessed website on May 18, 2013 at http://www.nimh.nih.gov/news/science-news/2013/five-major-mental-disorders-share-genetic-roots.shtml.

80. Nierenberg AA, Friedman ES, Bowden CL, Sylvia LG, Thase ME, Ketter T, Ostacher MJ, Leon AC, Reilly-Harrington N, Iosifescu DV, Pencina M, Severe JB, Calabrese JR.. Lithium treatment moderate-dose use study (LiTMUS) for bipolar disorder: a randomized comparative effectiveness trial of optimized personalized treatment with and without lithium. *Am J Psychiatry* 2013; 102-110.

81. Ostacher MJ, Perlis RH, Nierenberg AA, Calabrese J, Stange JP, Salloum I, Weiss RD, Sachs GS for the STEP-BD Investigators. Impact of Substance Use Disorder on Recovery From Episodes of Depression In Bipolar Disorder Patients: Prospective Data From the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry* 2010; 167: 289-297.

82. Ostacher MJ. Bipolar and substance use disorder comorbidity: diagnostic and treatment considerations. *FOCUS* 2011; 9:428-434.

83. Perlis RH, et al. (2006). Predictors of Recurrence in Bipolar Disorder: Primary Outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry* 163:217-224.

84. Perlis RH, Ostacher MJ, Patel JK, Marangell LB, Zhang H, Wisniewski SR, Ketter TA, Miklowitz DJ, Otto MW. Predictors of Recurrence in Bipolar Disorder: Primary Outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry* 2006; 163-217-224.

85. Pettinati HM, O'Brien CP, Dundon WD. Current status of co-occurring mood and substance use disorders: a new therapeutic target. *Am J Psychiatry* 2013; 170(1):23-30.

86. Pikalov A, Tsai J, Mao Y, Silva R, Cucchiaro J, Loebel A. Long-term use of lurasidone in patients with bipolar disorder: safety and effectiveness over 2 years of treatment. *Int J Bipolar Disord* 2017; 5-9.

87. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical Antipsychotic Drugs and the Risk of Sudden Cardiac Death. *N Engl J Med* 2009; Med. 290; 360:225-235.

88. Sachs GS, Vanderburg G, Karayal ON, Kolluri S, Bachinsky M, Cavus I. Adjunctive oral ziprasidone in patients with acute mania treated with lithium or divalproex, Part 1: results of a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2012; 73:1412-1419.

89. Samaliln L, Charpeaud T, Liorca PM. Asenapine in bipolar I disorder: evidence and place in patient management. *Ther Adv Chronic Dis* 2013; 4(1):5-14.

90. Scherk H, et al. (2007). Second-Generation Antipsychotic Agents in the Treatment of Acute Mania: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Arch Gen Psychiatry* 64:442-455.

91. Schneck CD, Miklowitz DJ, Miyahara S, Araga M, Wisniewski S, Gyulai L, Allen MH, Thase ME, Sachs GS. The Prospective Course of Rapid-cycling Bipolar Disorder: Findings from the STEP-BD. *Am J Psychiatry* 165:3, March 2008.

92. Schneck CD. Mixed Depression: The Importance of Rediscovering Subtypes of Mixed Mood States. *Am J Psychiatry* 166:2, February 2009.

93. Schoeyen HK, Kessler U, Andreassen OA, Auestad BH, Bergsholm P, Malt UF, Morken G, Oedegaard KJ, Vaaler A. Treatment-resistant bipolar depression: a randomized controlled trial of electroconvulsive therapy versus algorithm-based pharmacological treatment. *Am J Psychiatry* 2015; 172:41-51.

94. Scott K, Lewis CC. Using measurement-based care to enhance any treatment. *Cogn Behav Pract* 2015; 22(1); 49-59.

95. Shankman SA, Klein DN, Lewinsohn PM, Seeley JR, Small JW. Family study of subthreshold psychopathology in a community sample. *Psychological Medicine* (2008), 38, 187-198.

96. Stein BD, Celedonia KL, Swartz HA, Burns RM, Sorbero MJ, Brindley R, Frank E. Psychosocial treatment of bipolar disorder: clinician knowledge, common approaches, and barriers to effective treatment. *Psychiatric Services* 2016; 66(12): 1361-1364.

97. Steinbuchel PH, Wilens TE, Adamson JJ, Sgambati S. Posttraumatic stress disorder and substance use disorder in adolescent bipolar disorder. *Bipolar Disorders* 2009: 11: 198-204.

98. Stubbe D. The roller coaster ride: optimizing the therapeutic alliance with patients with bipolar disorder. *FOCUS* 2015; 13: No. 1.

99. Suppes T, Kelly D. Update of the Texas Implementation of Medication Algorithms for Bipolar I Disorder. *Medscape Psychiatry and Mental Health*. 2006; 11(1).

100. Suppes T, Vieta E, Liu S, Brecher M, Paulsson B. Maintenance Treatment for Patients with Bipolar I Disorder: Results from a North American Study of Quetiapine in Combination with Lithium or Divalproex. (Trial 127). *Am J Psychiatry* March 16, 2009 (doi: 10.1176/appi.ajp.2008.08020189).

101. Swann AC, Lijffijt M, Lane SD, Steinberg JL, Moeller G. Interacting mechanisms of impulsivity in bipolar disorder and antisocial personality disorder. *J Psychiatr Res* 2011; 45(11):1477-1482.

102. Swartz HA. Psychotherapy for bipolar disorder in adults: a review of the evidence. *FOCUS* 2014; XII(3): 251-266.

103. Sylvia LG, Iosifescu D, Friedman ES, Bernstein EE, Bowden CL, Ketter TA, Reilly-Harrington NA, Leon AC, Calabarese JR, Ostacher MJ, Rabideau DJ, Thase ME, Nierenberg AA. Use of treatment services in a comparative effectiveness study of bipolar disorder. *Psychiatric Services* 2013; 64(11); 1119-1126.

104. Tohen M, Wang WV, Leboyer M, Jen KY. Variables as mediators or moderators in predicting relapse to any type of mood episode in a bipolar maintenance study. *J Clin Psychiatry* 2012; 73(7). Accessed website on May 18, 2013 at http://www.ncbi.nlm.nih.gov/pubmed/22901362.

105. Torrent C, Bonnin CDM, Martinez-Aran A, Valle J, Amann BL, Gonzalez-Pinto A, Crespo JM, et al. Efficacy of functional remediation in bipolar disorder: a multicenter randomized controlled study. *Am J Psychiatry* 2013. Accessed website on May 18, 2013 at http://ajp.psychiatryonline.org/article.aspx?articleid=1669838.

106. Tsai AC, Rosenlicht NZ, Jureidini JN, Parry PI, Spielmans GI, Healy D. Aripiprazole in the maintenance treatment of bipolar disorder: a critical review of the evidence and its dissemination into the scientific literature. *PLoS Med* 2011; 8(5). Accessed on website on May 18, 2013 at http://www.ncbi.nlm.nih.gov/pubmed/?term=aripiprazole+in+the+maintenance+treatment+of+bipolar+disorder%3A+a+critical+review+of+the+evidence+and+its+dissemination+into+the+scientific+literature.

107. U.S. National Institutes of Health. Pharmacogenomics of Mood Stabilizer Response in Bipolar Disorder (PGBD): Clinical Trial 2013. Accessed website on May 18, 2013 at http://clinicaltrials.gov/show/NCT01272531.

108. Van Snellenberg JX, de Candia T. Meta-analytic Evidence for Familial Coaggregation of Schizophrenia and Bipolar disorder. *Arch Gen Psychiatry*, Vol. 66 (No. 7), July 2009.

109. Vazquez G, Kahn C, Schiavo CE, Goldchluk A, Herbst L, Piccione M, Saidman N, Ruggeri H, Silva A, Leal J, Bonetto GG, Zaratiegui R, Padilla E, Vilaprino JJ, Calvo M, Guerrero G, Strejilievich SA, Cetkovich-Bakman MG, Akiskal KK, Akiskal HS. Bipolar disorders and affective temperaments: A national family study testing the "endophenotype" and "subaffective" theses using the TEMPS-A Buenos Aires. *Journal of Affective Disorder* 108 (2008) 25-32.

110. Vega CP. Underlying Illness May Be More Important Than Antiepileptic Use for Suicide Risk. Medscape Education Clinical Briefs. Accessed website on May 2, 2011 http://www.medscape.org/viewarticle/726525_print.

111. Viktorin A, Lichtenstein P, Thase ME, Larsson H, Lundholm C, Magnusson PKE, Landén. The risk of switch to mania in patients with bipolar disorder during treatment with an antidepressant alone and in combination with a mood stabilizer. *Am J Psychiatry* 2014; 171:1067-1073.

112. Wesseloo R, Liu X, Clark CT, Kushner SA, Munk-Olsen T, Bergink V. Risk of postpartum episodes in women with bipolar disorder after lamotrigine or lithium use during pregnancy: A population-based cohort study. *Journal of Affective Disorders* 2017; 394-97.

113. White RF. Medscape Psychiatry and Mental Health. Accessed website at www.medscape.com/viewarticle/558811 on March 17, 2009.

114. White RF. Recent Research in Antipsychotic Therapy CME/CE. Efficacy and Safety of First-Generation Compared with Second-Generation Antipsychotics. Accessed website at http://cme.medscape.com/viewprogram/19071 on May 5, 2009.

115. Wildes JE, Marcus MD, Fagiolini A. Eating Disorders and Illness Burden in Patients with Bipolar Spectrum Disorders. *Compr Psychiatry*. 2007; 48(6): 516-521.

116. Wium-Andersen MK, Ørsted DD, Nordestgaard BG. Elevated C-reactive protein and late-onset bipolar disorder in 78 809 individuals from the general population. *BJ Psych* 2016; 208: 138-45.

117. Zimmerman M, Martinez J, Young D, Chelminski I, Morgan TA, Dalrymple K. Comorbid bipolar disorder and borderline personality disorder and history of suicide attempts. *J Pers Disord* 2014; 28(3): 358-364.