



Introduction to the Practice Guideline for the Treatment of Bipolar Disorder

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Purpose of This Document

This document is an introduction and update to Magellan Health Services' (Magellan) 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*, Second Edition, and the Guideline Watch: *Practice Guideline for the Treatment of Patients With Bipolar Disorder*, Second Edition to augment providers' clinical decision-making pertaining to members 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.

Adopted Guideline

As with all CPGs, the adopted guideline and this introduction are intended to augment, not replace, sound clinical judgment. As a matter of good practice, clinically sound exceptions to this practice guideline should be clearly noted in the member's treatment record, documenting the clinical reasoning used in making the exception. 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 that are issued by the FDA and other regulatory and professional bodies, and to incorporate such information in his or her treatment decisions.

Additional Recommendations Based on Recent Literature Review

The APA guideline is based on a literature review through 2001. The guideline watch is based on a literature review up to its publication in November 2005. Magellan conducted a further review of the clinical literature on assessment and treatment of bipolar disorder published through March 2011. Key relevant recommendations from this more recent literature review are summarized here. Magellan encourages providers to be familiar with this information, as well as the information in both guidelines.

Bipolar Disorder Spectrum

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 antimanic medication is uncommon, especially in general medical settings. Other significant findings in the study showed that while nearly everyone who had bipolar I or II (89 to 95 percent) received some type of treatment, 69 percent of those with BD-NOS were getting treatment. Those with bipolar I or II were commonly treated by psychiatric specialists, while those with BD-NOS were more commonly treated by general medical professionals (Merikangas et al. 2007).

Another study in this area 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 coaggregate 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 entirely discrete entities but may support a disease continuum model (Van Snellenberg et al. 2009).

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. 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.

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 posttraumatic 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 (Steinbuechel 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 more recently 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).

Findings from a clinical trial examining the effects of pharmacotherapy plus family interventions for patients with BP-I showed that patients with a remitted SUD showed a poorer acute treatment response, a longer time to remission of their 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 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 that 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).

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 comorbidity 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).

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, the risk of violent crime in bipolar disorder was studied in a longitudinal investigation conducted in Sweden. 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 that there is 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 lead investigators to recommend routine risk assessment when evaluating or treating this patient subgroup (Fazel et al. 2010).

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. 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).

Since publication of the adopted APA guideline and watch, two relevant FDA Alerts were issued notifying health care professionals that antiepileptic drugs (AEDs) or anticonvulsant drugs are associated with an increased risk of suicidal thoughts or actions and 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 that current use of AEDs was not associated 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).

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) was conducted 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 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 that they also 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 on 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 also shown to have an impact on treatment adherence (Scherk et al. 2007).

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 and lamotrigine. 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.

More recently, 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 notes that it is only recently that mixed depressions and their implications for treatment have been given the clinical focus that is warranted.

In light of the issues surrounding a possible diagnostic entity of mixed depression, a longitudinal naturalistic study by Goldberg et al. was designed using 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 that have been discussed include 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 (Asnari 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. Asnari 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 (Asnari et al. 2010).

Major changes to PAPHSS Bipolar Depression Algorithm revision included the 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), a 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 (Asnari et al. 2010).

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 to include: (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 should be considered 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.

Another naturalistic follow-up study using patients in the STEP-BD study was conducted to prospectively observe 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 prestudy 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).

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.

More recently, a large study evaluated the efficacy and safety of quetiapine in combination with lithium or divalproex in the prevention of recurrent mood events in patient 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).

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).

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 a highly recurrent, 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).

Psychosocial Treatment

The guideline watch affirms that knowledge of the utility of psychosocial interventions has expanded in recent years. This document summarized findings of randomized clinical trials that demonstrated 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 either an intensive psychosocial intervention (i.e., 30 sessions over nine months of CBT or family-focused therapy or interpersonal and social rhythm therapy emphasizing regularity of sleep/wake rhythms to maintain mood stability) or were assigned to collaborative care (i.e., three session psychoeducational treatment) while receiving 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, no effects of the psychosocial intervention were observed on work/role functioning after a depressive episode. In light of these findings, researchers suggest that alternative interventions

focused on the specific cognitive deficits of individuals with bipolar disorder may be necessary to enhance vocational functioning after a depressive episode (Milkowitz et al. 2007).

A similar study on 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 (Milkowitz et al. 2008).

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:

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