Bipolar Disorder: Evidence Based Practice

Although diagnosis and treatment of BD illness is complex, effective treatment can lead to good outcomes for many patients. Primary care providers are in a key position to render early diagnosis and treatment of BD. This disease should always be considered as part of the differential diagnosis for depression or anxiety. Over the last few years, the care of severe mental illness has shifted from inpatient treatment to community based care. Significant advances in medications for BD, including the introduction of new therapies and the refinement of treatment protocols using older medications have occurred since the last guideline. There has also been increasing recognition of the contribution of psychological therapies to symptom relief, relapse prevention, optimal function, and quality of life.

Since bipolar depression is the most common presentation of bipolar disorder, some patients with BD are diagnosed and treated as unipolar depression. Given the low detection and recognition rates of BD, it is essential that mental health practitioners have the required skills to assess patients with depression, their history, social circumstances and relationships, and the risk they may pose to themselves and to others. This is especially important in view of the fact that BD is associated with an increased suicide rate, a strong tendency for recurrence and high personal and social costs. The effective assessment of a patient, including risk assessment, and the subsequent coordination of the patient’s care, is likely to improve diagnosis and lead to improved outcomes.

OVERVIEW

The guideline for Bipolar Disorder is organized in 3 modules describing the management of patients:

Module A: Acute Mania, Hypomania or Mixed Episode
Module B: Acute Depressive Episode
Module C: Maintenance Phase

Each of the above modules includes an algorithm. The algorithms describe the step-by-step process of clinical decision-making and intervention that should occur when managing patients with BD. General and specific recommendations for each step in the algorithm are included in an annotation section following the algorithm. The links to these recommendations are embedded in the relevant specific steps in the algorithm.

Two additional Modules include specific recommendations and appraisal of the evidence for treatment intervention used in the management of patients with BD. The interventions are organized in the following modules:

Module D: Psychosocial Interventions
Module E: Specific Recommendations for Management of Older Persons with BD

BURDEN OF DISEASE - BIPOLAR DISORDER

Bipolar disorder (BD) is a major cause of impaired quality of life, reduced productivity, and increased mortality. Social difficulties are common (e.g., social stigma, loss of employment, marital break-up). Associated problems, such as anxiety symptoms and substance misuse, may cause further disability.

Bipolar disorder is an episodic, potentially life-long, disabling disorder. Diagnostic features include periods of acute mania, hypomania and depression. Bipolar disorder is characterized by periods of abnormally elevated mood or irritability, which may alternate with periods of depressed mood or a mix of symptoms. These episodes are distressing and often interfere with occupational or educational functioning, social activities and relationships.

Most patients with bipolar disorder can achieve substantial stabilization of their mood swings and related symptoms with proper (continuous) treatment. Because bipolar disorder is a recurrent illness,
long-term preventive treatment is strongly recommended and almost always indicated. A strategy that combines medication and psychosocial treatment is optimal for managing the disorder over time.

The etiology of the disorder is uncertain but genetic and biological factors are important. The environmental and lifestyle features can have an impact on severity and course of illness. Bipolar disorder is often comorbid with a range of other mental disorders (for example, substance misuse and anxiety disorders) and this has significant implications for both the course of the disorder and its treatment.

The lifetime prevalence of bipolar I disorder (depression and mania) is estimated at 0.8% of the adult population, with a range between 0.4% and 1.6%. Bipolar II disorder (depression and hypomania) affects approximately 0.5% or more of the population. Bipolar II disorder is more common in women, bipolar I disorder appears to be evenly distributed between men and women.

This material was developed using the following evidence-based guidelines:

Practice Guideline for the Treatment of Patients with Bipolar Disorder, Second Edition; American Psychiatric Association (APA) Steering Committee on Practice Guidelines, 2002; APA Practice Guidelines. [Referred throughout this document as APA, 2002]

EVIDENCE RATING SYSTEM

<table>
<thead>
<tr>
<th>SR</th>
<th></th>
<th>A strong recommendation that clinicians provide the intervention to eligible patients. Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td>A recommendation that clinicians provide (the service) to eligible patients. At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td>No recommendation for or against the routine provision of the intervention is made. At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation.</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>Recommendation is made against routinely providing the intervention to asymptomatic patients. At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits.</td>
</tr>
<tr>
<td>D</td>
<td></td>
<td>The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. Evidence that the intervention is effective is lacking, or poor quality, or conflicting, and the balance of benefits and harms cannot be determined.</td>
</tr>
<tr>
<td>I</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SR = Strength of recommendation

GRADING RECOMMENDATIONS

If evidence exists, the discussion following the recommendations for each annotation includes an evidence table that identifies the studies that have been considered, the quality of the evidence, and the rating of the strength of the recommendation [SR]. The Strength of Recommendation [SR], based on the level of the evidence and graded using the USPSTF rating system (see Table: Evidence Rating System), is presented in brackets following each guideline recommendation.

Where existing literature was ambiguous or conflicting, or where scientific data was lacking on an issue, recommendations were based on the clinical experience of the WG. Although several of the recommendations in this guideline are based on weak or no evidence [SR = I], some of these recommendations are strongly recommended based on the experience and consensus of the clinical experts
and researchers of the Working Group. Recommendations that are based on consensus of the Working Group include a discussion of the expert opinion on the given topic. No [SR] is presented for these recommendations.

Management of Persons with Bipolar Disorders
A: Current Mania, Hypomania or Mixed Episode

1. Person meets DSM-IV criteria for bipolar manic, hypomanic or mixed episode [A1]

2. Complete assessment
   Review current medication
   Assess risk for suicide [A2]

3. Is patient taking antidepressants or mania-inducing medication? [A3]
   Yes
   Reduce/stop antidepressants [A5]
   No

4. Severe mania or psychotic features present? [A4]
   Yes
   Refer for hospitalization [A5]
   Initiate/adjust treatment with combination of antipsychotic and antimanic medications [A6]
   Reassess every 2-3 days until symptoms improve
   No

5. Is patient receiving clinical effective medications for bipolar mania/mixed [A7]
   Yes
   Modify dose or medication if indicated [A8]
   No

6. Initiate/adjust treatment with an antimanic medication [A9]

7. Reassess every 1-2 weeks for 6 weeks [A10]

8. Is patient responding to therapy? [A11]
   Yes
   Continue current treatment
   Monitor regularly for 6 weeks
   No

9. Assess adherence, needs for psychosocial and/or family interventions, adverse effects, and psychosocial barriers to therapy
   Assess risk for suicide [A12]

10. Add/change antimanic medication until stable or consider alternative therapy [A14]

11. Is patient in full remission? [A12]
   Yes
   Continue to Module C Maintenance Therapy
   No

12. Reevaluate diagnosis and treatment
    Consider hospitalization and or consultation
    Consider ECT
MODULE A: BIPOLAR ACUTE MANIC, HYPOMANIC, OR MIXED EPISODE

A-1. Person Meets DSM-IV Criteria for Bipolar Manic, Hypomanic, or Mixed Episode

BACKGROUND

Patients with a Bipolar Disorder may have a myriad of presentations. They can present with a major depressive episode, manic episode, hypomanic episode or a combination of manic and depressive symptoms (mixed episode). This module is intended for patients who are currently displaying a mania, hypomania, or a mixed episode.

DEFINITIONS

The APA (2002) adapted the following definitions from The Diagnostic and Statistical Manual of Mental Disorders - IV edition Text Revision (DSM-IV-TR)⁴

Diagnostic Criteria for a Manic Episode

- A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).
- During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:
  - Inflated self-esteem or grandiosity
  - Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
  - More talkative than usual or pressure to keep talking
  - Flight of ideas or subjective experience that thoughts are racing
  - Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
  - Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
  - Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
- The symptoms do not meet criteria for a mixed episode.
- The mood disturbance 1) is sufficiently severe to cause marked impairment in occupational functioning, usual social activities, or relationships with others, 2) necessitates hospitalization to prevent harm to self or others, or 3) has psychotic features.
- The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Diagnostic Criteria for a Hypomanic Episode

- A distinct period of persistently elevated, expansive, or irritable mood, lasting at least 4 days, that is clearly different from the usual non-depressed mood.
- During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:
  - Inflated self-esteem or grandiosity
  - Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
More talkative than usual or pressure to keep talking

Flight of ideas or subjective experience that thoughts are racing

Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)

Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation

Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

- The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic.
- The disturbance in mood and the change in functioning are observable by others.
- The episode 1) is not severe enough to cause marked impairment in social or occupational functioning, 2) does not necessitate hospitalization, and 3) does not have psychotic features.
- The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Diagnostic Criteria for a Mixed Episode

- The criteria are met both for a manic episode and for a major depressive episode (except for duration) nearly every day during at least a 1-week period
- The mood disturbance 1) is sufficiently severe to cause marked impairment in occupational functioning, usual social activities, or relationships with others, 2) necessitates hospitalization to prevent harm to self or others, or 3) has psychotic features
- The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

*Episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, ECT, light therapy) should not count toward a diagnosis of either bipolar I or, II disorders.*

A-2. Complete Assessment; Review Current Medication; Assess Suicide Risk

BACKGROUND

A full psychiatric history, assessment of mental status, and physical examinations are necessary to confirm diagnosis, exclude underlying organic conditions (e.g., hypothyroidism), identify physical complications, and ascertain the risk of self-harm.

Individuals experiencing mania, hypomania, or particularly mixed episode have an elevated acute and chronic risk of suicide. These individuals can be intensely dissatisfied with their life and experience profound disruptions of their psychosocial support systems. Individuals with mania, hypomania, and mixed episode are also at an increased risk of substance abuse that further increases their potential for suicide. Because of these acute and chronic risks, it is essential that providers assess their patients for suicide risk.
Table A-1 Clinical Status Assessment

<table>
<thead>
<tr>
<th>Areas to be assessed</th>
<th>Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical comorbidity</td>
<td>Comorbid medical problems can contribute to mood dysregulation</td>
</tr>
<tr>
<td>Psychiatric comorbidity</td>
<td>It is important to assess for and treat all psychiatric comorbid conditions</td>
</tr>
<tr>
<td>Psychosocial Stressors</td>
<td>Current stressors can contribute to mood problems and adherence to treatment</td>
</tr>
<tr>
<td>Current medications</td>
<td>Assess the frequency and dosages of all prescribed and over-the-counter medications the patient is taking</td>
</tr>
<tr>
<td>Past medications</td>
<td>Check for previous historical response to mood stabilizers; note reasons for discontinuation, including side effect problems and nonresponse</td>
</tr>
<tr>
<td>Medication compliance</td>
<td>Evaluate whether the patient has been compliant in the past with medication treatment</td>
</tr>
<tr>
<td>Suicide risk</td>
<td>Evaluate risk factors for suicide including family history, previous attempts, and co-occurring substance use</td>
</tr>
<tr>
<td>Substance Use</td>
<td>Substance abuse can contribute to or precipitate a relapse; it can also be a reason for medication nonresponse</td>
</tr>
</tbody>
</table>

**ACTION STATEMENT**

Patients with a bipolar mania, hypomania or mixed episode require a thorough evaluation to determine level of risk and appropriate acute treatment.

**RECOMMENDATIONS**

1. A complete clinical assessment should be obtained for patients with a manic, hypomanic, or mixed episode to include:
   a. Clinical status
   b. Medical comorbidities
   c. Psychiatric comorbidities
   d. Psychosocial status
   e. Current medications
   f. Past medications
   g. Medication compliance
   h. Substance use.

2. A standardized tool combined with a clinical interview should be used to obtain the necessary information about symptoms, symptom severity, and effects on daily functioning that is required to diagnose BD mania/hypomania based on DSM-IV-TR criteria.

3. Assess the severity of mania episode using a standardized rating scale (e.g., Young Mania Rating Scale).
4. Consider using the same standardized questionnaire to monitor treatment response at follow-up visits, after each change in treatment, and to periodically assess the patient’s response to treatment until full remission is achieved.

Further information on assessment and screening tools for Bipolar Disorder and suicide - see: http://www.cqaimh.org/stable.html

A-3. Is Patient Taking Antidepressants or Mania-Inducing Medication? Reduce/Stop Antidepressant Medications

BACKGROUND

Because of the cyclical nature of Bipolar Disorder patients who are currently experiencing mania, hypomania, or mixed episode may recently have been treated for depression using antidepressants. Other patients may have experienced one or more depressive episodes without ever having displayed any evidence of mania or hypomania and they also might be on antidepressants for their depressive episodes or other manic-inducing medication. A tradition of clinical wisdom suggests that antidepressants might worsen the course of the hypomania or mania.

ACTION STATEMENT

Stop manic-inducing medications in patients who are experiencing a manic, hypomanic or mixed manic episode.

RECOMMENDATION

5. Antidepressants or other manic inducing substances should be stopped in patients experiencing a manic, hypomanic, or mixed manic episode. [B]

6. Antidepressant medications known to be associated with discontinuation syndromes may be tapered over 3 to 5 days rather than being abruptly stopped. [C]

The most common discontinuation symptoms include:

- Dizziness
- Headache
- Paresthesia
- Nausea
- Diarrhea
- Insomnia
- Irritability

RATIONALE

Research shows that antidepressants can induce or worsen manic or hypomanic episodes. Sudden discontinuation of antidepressants can lead to discontinuation syndromes or a worsening of symptoms.

EVIDENCE STATEMENTS

> Bottlender et al., (2001) studied the development of mania and hypomania in a retrospective review of 158 patients. The 69 patients who were on a tricyclic antidepressant but not on a mood stabilizer had a significantly higher switch rate than did those who were on a tricyclic antidepressant and a mood stabilizer. The differences in patients on selective serotonin reuptake inhibitors (SSRIs) and
monoamine oxidase inhibitors (MAOIs) did not reach statistical significance, possibly because of small sample sizes (total of 25 on SSRI and 12 on MAOI).

> Gijsman et al. (2004) in a systematic review of twelve randomized studies with 1,088 randomly assigned patients looked at the use of antidepressants for bipolar depression. This study did not show that patients on antidepressants had a greater switch rate into mania than did patients on placebo. One factor which might have affected this outcome however is the fact that approximately 75 percent of these patients were on another medication to control mania at the time of the study. This would have likely lowered the rate at which these patients developed mania and hypomania.

> A number of reports have described a series of symptoms after discontinuation or dose reduction of serotonergic antidepressant medications. A prospective, double blind, placebo-substitution study confirmed that discontinuation symptoms are most common with short half-life antidepressants, such as paroxetine (Rosenbaum et al., 1998).

EVIDENCE TABLE

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Source</th>
<th>LE</th>
<th>QE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Antidepressants may induce or worsen mania, hypomania, or mixed episode</td>
<td>Amsterdam, 1998 Bottlender et al., 2001 Gijsman et al., 2004 Nemeroff, 2004</td>
<td>I I</td>
</tr>
<tr>
<td>2</td>
<td>Antidepressants may induce or worsen rapid cycling</td>
<td>Altshuler et al., 1995 Bauer et al., 1994 Wehr &amp; Goodwin, 1987</td>
<td>II-3</td>
</tr>
<tr>
<td>3</td>
<td>Antidepressants should be discontinued by slow taper to avoid relapse</td>
<td>Faedda et al., 1993 Suppes et al., 1993 Rosenbaum et al., 1998</td>
<td>II</td>
</tr>
</tbody>
</table>

LE = Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

A-4. Severe Mania, Dangerousness, or Psychotic Features Present?

BACKGROUND

Some patients will present with severe and/or psychotic mania or mixed episode. These patients represent a particular risk of harming themselves or others and of experiencing profound psychosocial impairment because of their symptoms. This impairment can manifest itself in the form of unhealthy decisions, risk taking behaviors, lost jobs or ruined relationships. Because of these concerns, more aggressive treatment strategies should be tried.

The usual reasons for urgent hospitalization include acute suicide risk, acute violence risk due to mental illness, delirium, and acute unstable medical condition. Patients with severe mania will often have psychotic symptoms including:

- Inappropriate affect of a bizarre or odd quality
- Delusions (e.g., fixed false beliefs)
- Visual or (typically) auditory hallucinations
- Catatonic behavior (e.g., motor immobility or excessive agitation) Extreme negativism or mutism Peculiar voluntary movement patients are at risk of harming themselves or others and may have
greater functional impairment.
These patients are at risk of harming themselves or others and may have greater functional impairment.

RECOMMENDATIONS
1. Patients with BD mania, hypomania, or mixed episode should be assessed for suicidality, acute or chronic psychosis or other unstable or dangerous conditions.
2. Any patient with suicidal ideation or suicide attempts necessitating psychiatric hospitalization should be considered for referral to mental health specialty care.
3. Patients with a diagnosis of BD mania who present with severe symptoms with any of the following unstable conditions, need to be referred for urgent/emergent mental health intervention as these are inappropriate for care in the primary care setting:
   a. Delirium
   b. Marked psychotic symptoms
   c. Severe mania symptoms
   d. Suicidality or homicidality
   e. Potential for violence (e.g., ideas about or intent to harm others; history of violent behavior; severe agitation or hostility; active psychosis)
   f. Substance withdrawal or intoxication

DISCUSSION
Psychosis is defined as a mental state in which the patient is significantly out of touch with reality to the extent that it impairs functioning. Patients with psychotic symptoms may present in an acutely agitated state with a recent onset of disturbed and/or disturbing symptoms.
In particular, paranoid concerns that others wish to harm the patient and voices (especially command hallucinations) telling the patient to hurt him or herself or someone else, are indications for an immediate mental health consultation or referral.
It is important to bear in mind that psychotic symptoms may be the direct result of an underlying medical condition, toxic state, alcohol or substance use disorder, or may be associated with a mental health condition such as schizophrenia or affective illness (Kaplan & Sadock, 1995).

A-5. Refer for Hospitalization

BACKGROUND
Some patients seeking treatment will present with severe mania or mixed episode. Because of the increased impairment experienced by these patients and the increased risk they present to themselves or others, hospitalization should always be considered as perhaps the most appropriate environment for treatment.
Specialized treatments only available, or often best provided, in an inpatient setting include:
   • Electro-convulsive therapy (ECT)
   • Close monitoring and daily titration of medications with disabling side effects or toxicity
Constant staff observation as part of an intensive behavioral modification program
Close monitoring of behavior in an episodic disorder
Close monitoring of vital signs or need for multiple daily laboratory or electrophysiological testing.

ACTION STATEMENT
Ensure that appropriate care, protocols, and regulatory/policy mandates are followed during diagnosis and stabilization of the patient with a severe or an unstable bipolar manic episode.

RECOMMENDATIONS
1. Local, state and federal regulations/mandates, as well as guidelines, should be followed when the patient represents a risk to self or others.
2. Patients with urgent, unstable conditions, severe mania or mixed episode or elevated dangerousness should be referred to a higher level of care (hospitalization).
3. Hospitalization should be considered in patients whose severe mania or mixed episode seriously impairs their ability to care for themselves. [I]

RATIONALE
Patients who experience a severe episode of mania or mixed episode present a number of clinical challenges. By definition, they are experiencing severe impairment in at least one major area of their life and often they experience this impairment in most areas of their life. They are prone to impulsive actions that might intentionally or inadvertently put themselves or others around them at risk. Their altered cognition impairs their ability to make rational and healthy decisions. They may experience delusions or hallucinations that can dramatically and unpredictably alter their behavior. Many with mania and mixed episode will experience thoughts of harming themselves or others and their condition and poor impulse control heightens their risk of acting on these thoughts. For these reasons hospitalization should be considered in these severely ill patients.

A-6. Initiate/Adjust Treatment with Combination of Anti-Psychotic and Anti-Manic Medications

BACKGROUND
Some patients will present with severe and/or psychotic mania or mixed episode. These patients represent a particular risk of harming themselves or others and of experiencing profound psychosocial impairment because of their symptoms. This impairment can manifest itself in the form of unhealthy decisions, risk taking behaviors, lost jobs, or ruined relationships. Because of these concerns, more aggressive treatment strategies should be tried.

ACTION STATEMENT
Patients with severe mania or mixed episode, with or without psychotic features, should be started on a combination of an antipsychotic and another anti-manic agent.

RECOMMENDATIONS
1. Patients with severe mania should be treated with a combination of antipsychotics and lithium or valproate. These antipsychotics include olanzapine, quetiapine, aripiprazole, or risperidone [B] and may include and ziprasidone. [I]
2. Patients with severe mixed episode should be treated with a combination of antipsychotics and lithium or valproate. These antipsychotics include aripiprazole, olanzapine, risperidone, or haloperidol [B] and may include quetiapine or ziprasidone. [I]
3. Clozapine, with its more serious side effect profile, may be added to existing medications for severe mania or mixed episode if it has been successful in the past or if other antipsychotics have failed. [I]
4. Patients who are not hospitalized should be reassessed every 2-5 days until symptoms improve.

RATIONALE
Several recent randomized controlled trials have demonstrated that patients with mania or mixed episode who
are placed on combinations of antipsychotics and non-antipsychotic mood stabilizers have an improved outcome.

There are a number of methodological limitations in the research literature related to treatment of manic/hypomanic BD. Research studies typically do not differentiate by severity of acute illness. Many of the studies looking at combinations of medications were designed to look at individuals who had an inadequate response to monotherapy. Often the dose of the initial medication was not optimized prior to starting the second medication. Starting multiple medications also increases the risks of adverse effects. Although these studies did not focus specifically on severe mania, this is a prudent strategy for the sickest patients. It is believed that all of the second generation antipsychotics (SGAs) are likely to be equally effective in severe mania or severe mixed episode when combined with lithium or valproate, but studies are lacking for several of the antipsychotics.

EVIDENCE STATEMENTS

- Namjoshi et al., (2004) studied 336 patients with mania or mixed episode, all of whom were on either lithium or valproate. Two hundred twenty-four of these patients also received olanzapine while the other 112 received a placebo. Those patients who were on olanzapine plus the antimanic agent had significantly greater improvement in their Young Mania Rating Scale (YMRS), Hamilton Depression rating Scale (HDRS) and Quality of life Assessment (QOL).

- Tohen et al., (2002b) found that patients who were placed on a combination of olanzapine in addition to lithium or valproate had greater improvement in mania and depressive symptoms than did those on lithium or valproate alone.

- Sachs et al., (2004) followed 191 patients with mania, all of whom were on either valproate or lithium. Ninety-one (91) of these patients were also on quetiapine. The quetiapine patients were more likely to experience a response (> 50% reduction of the YMRS) and remission. These patients also had a greater average decrease in their YMRS than did patients who were not on quetiapine. Patients on quetiapine were noted to have significantly more somnolence and dry mouth.

- Yatham et al., (2004) also reported on 402 patients who were on lithium or valproate for their manic episode. One hundred ninety seven of these patients were also on quetiapine. The patients taking quetiapine were more likely to achieve a clinical response by day 21 and were more likely to enter remission. They also had a statistically greater improvement in their YMRS than did patients who were not on quetiapine.

- Yatham et al., (2003) studied 151 patients with mania or mixed episode on mood stabilizers. Seventy five of these patients received risperidone. The patients receiving risperidone had a greater rate of response (> 50% reduction of YMRS) and had greater improvement as measured by the Brief Psychiatric Rating and Clinical Global Improvement scales.

- Sachs et al., (2006) studied 272 patients with mania or mixed episode in a 3-week multicenter trial. One hundred thirty seven were randomly assigned to receive aripiprazole 15 - 30 mg per day and 135 were to receive placebo. Only 53% of the patients completed the three week study (55% of aripiprazole group and 52% of the placebo group). The aripiprazole group experienced greater reduction in YMRS scores as well as a greater response rate as measured by the YMRS (> 50% reduction). They also experienced greater improvement on the Clinical Global Impression - Bipolar Version Severity and Improvement scores.

- Vieta et al, (2008c) studied patients with manic or mixed manic episodes who had partial nonresponse to either lithium or valproate monotherapy. In this multicenter randomized trial patients were randomized to receive either aripiprazole (N=253) or placebo (N=131). The target dose of lithium was 0.6-1.0 mmol/liter and for divalproic acid was 50-125 mcg/ml. After being weaned off of other psychotropic medications, the patients received open label lithium or valproate. After confirming nonresponse they were started on placebo or aripiprazole at 15 mg per day. The dose of aripiprazole could then be increased to 30 mg per day. At the end of week six the blood concentration of lithium or valproate was similar in the treatment group and placebo group. At week 6 the aripiprazole group had a significantly greater decrease in YMRS (-13.3 vs. -10.7). Adjunctive aripiprazole was also associated with significant improvement as measured by the CGI-BP and PANSS. Discontinuation rates because of adverse effects were higher in the
aripiprazole group. Akathisia was statistically more likely in the aripiprazole group as well.

EVIDENCE TABLE - SEVERE MANIA OR MIXED EPISODE

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Source</th>
<th>LE</th>
<th>QE</th>
<th>SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Olanzapine with valproate or lithium</td>
<td>Namjoshi et al., 2004 Tohen et al., 2002b</td>
<td>I</td>
<td>Fair</td>
<td>B</td>
</tr>
<tr>
<td>2 Quetiapine with valproate or lithium for severe mania</td>
<td>Sachs et al., 2004 Yatham et al., 2004</td>
<td>I</td>
<td>Fair</td>
<td>B</td>
</tr>
<tr>
<td>Quetiapine with valproate or lithium for mixed episode</td>
<td></td>
<td>III</td>
<td>Poor</td>
<td>I</td>
</tr>
<tr>
<td>3 Ziprasidone may be combined with valproate or lithium</td>
<td>Panel Consensus</td>
<td>III</td>
<td>Poor</td>
<td>I</td>
</tr>
<tr>
<td>4 Aripiprazole with valproate or lithium</td>
<td>Sachs et al., 2006 Vieta et al., 2008b</td>
<td>I</td>
<td>Fair</td>
<td>B</td>
</tr>
<tr>
<td>5 Risperidone with valproate or lithium for mixed episode</td>
<td>Yatham et al., 2003</td>
<td>I</td>
<td>Fair</td>
<td>B</td>
</tr>
<tr>
<td>6 Clozapine with valproate or lithium if it was successfully used in the past or if other antipsychotics have failed</td>
<td>Panel Consensus</td>
<td>III</td>
<td>Poor</td>
<td>I</td>
</tr>
</tbody>
</table>

LE = Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

A-7. Is Patient Receiving Clinical Effective Medications for Bipolar Mania/Mixed?

Patients with BD acute mania/hypomania or mixed episode should be treated with medications that have been shown to be effective. Some patients may have been treated in the past with medications that have not been shown to be efficacious in trials. These patients may benefit from adjusting their therapy to include efficacious treatment.

For recommended medications see Annotation A-9
A-8. Modify Dose of Medication As Needed

BACKGROUND

Because the medications used to treat mania and mixed episode may have significant side effects, they are usually not started at a full therapeutic dose. Patients, who develop symptoms of mania/hypomania despite currently receiving medication, may need adjustment of dose to a therapeutic concentration or a change in medication to maintain maximum benefits while minimizing side effects. Lithium, valproate and carbamazepine have plasma concentrations at which they are known to be the most effective. Those plasma concentrations will play a part in determining the dosages of those medications. Providers need to monitor serum concentration closely and adjust medications appropriately during the initial months of treatment.

A significant percentage of patients will not respond to a single medication for mania or mixed episode even when the medication is taken regularly in proper dosages. For these patients the provider will need to try different strategies in order to maximize benefits and obtain remission. Unfortunately little data exists to guide the provider in the exact sequence of steps. Possible strategies include switching to a different monotherapy agent or combining agents.

ACTION STATEMENT

Adjust anti-manic agents to minimize adverse effects while maximizing clinical effectiveness and maintaining therapeutic plasma concentrations when those are known.

RECOMMENDATIONS

1. If patient is having intolerable side effects switch to another effective treatment. [I]
2. Assess compliance and blood serum concentration to assess if medications are in therapeutic range [I]
   a. The serum trough concentration of lithium should be maintained between 0.8 - 1.2 mEq/L
   b. The serum trough concentration of valproate should be maintained between 50-125 mcg/ml
   c. The serum trough concentration of carbamazepine should be maintained between 4 - 12 mcg/ml.
3. Medications without known therapeutic plasma concentrations should be increased until significant improvement is seen, side effects become intolerable or the dose reaches the manufacturer’s suggested upper limits. [I]

RATIONALE

> Lithium, valproate, and carbamazepine have well established therapeutic plasma concentrations. Maintaining the plasma concentration in this range provides the best opportunity for significant improvement. If patients have been started on one of these three medications, the dosages should be adjusted until the serum trough concentration is in the therapeutic range as long as these doses are tolerated by the patient. If these dosages are not tolerated, then consider changing to another medication.

> The second generation antipsychotics do not yet have established therapeutic plasma concentrations ranges. For those medications the dosage should be adjusted until there is evidence of efficacy, the patient experiences side effects that cannot be tolerated, or the medication reaches the manufacturer’s upper limits.
EVIDENCE TABLE

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Source</th>
<th>LE</th>
<th>QE</th>
<th>SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Maintain lithium concentrations between 0.8 and 1.2 mEq/L</td>
<td>Gelenberg et al., 1989; Goodwin &amp; Jamison 2007</td>
<td>III</td>
<td>Good</td>
<td>A</td>
</tr>
<tr>
<td>2. Maintain valproate concentrations between 50 to 125 mcg/ml</td>
<td>Gilman et al., 1990</td>
<td>II</td>
<td>Good</td>
<td>A</td>
</tr>
<tr>
<td>3. Maintain carbamazepine concentrations between 4 and 12 mcg/ml</td>
<td>Arana &amp; Hyman, 1991</td>
<td>II</td>
<td>Good</td>
<td>A</td>
</tr>
</tbody>
</table>

LE = Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

A-9. Initiate/Adjust Treatment with an Anti-Manic Medication

BACKGROUND

Patients with mania, hypomania or mixed episode can experience a wide variety of psychosocial impairments. In addition to dramatic mood swings and debilitating cognitive changes these impairments can include substance abuse, lost relationships and financial ruin. Prompt, effective treatment of manic and mixed manic symptoms can minimize this impairment and dramatically improve the patient’s long-term outcome.

ACTION STATEMENT

Patients with mania/hypomania or mixed episode should be started on a medication proven to effectively treat manic and mixed manic symptoms.

RECOMMENDATIONS

General considerations

1. Pharmacotherapy for bipolar mania or mixed episode should start with initiation or optimization of a medication that has been shown to be the most effective in treating bipolar manic episodes while minimizing the potential risks. [I] (see Table A - 2)

2. Consider using the agent(s) that have been effective in treating prior episodes of mania or mixed episode. [I]

3. Ensure that the patient has stopped taking any antidepressant or mania inducing substances. [B]

4. In selecting a drug treatment regimen for patients with bipolar disorder, clinicians should be aware of the patient’s other psychiatric and medical conditions and should try to avoid exacerbating them.

5. In selecting a drug treatment regimen for patients with diabetes or obesity consider the risk and benefit of utilizing medications that are less associated with weight gain.

Mania

6. Patients with mania should be started on one of the following: lithium, valproate, carbamazepine, aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone. [A]

Mixed episode

7. Patients with mixed episode should be started on one of the following: valproate, carbamazepine olanzapine, aripiprazole, risperidone, or ziprasidone. [A]

Mania or Mixed episode

8. Clozapine, haloperidol and oxcarbazepine may be considered in patients with mania or mixed episode. [I]

9. Lithium, or quetiapine may be considered in patients with mixed episode. [I]
10. Medications NOT recommended in patients with mania or mixed episode include topiramate, lamotrigine, and gabapentin. [D]

RATIONALE

- Lithium has been the gold standard treatment for mania for the last three decades. Over the past fifteen years, numerous studies have demonstrated the efficacy of certain antiepileptic and antipsychotic medications in controlling mania. These medications should be considered first-line treatments for acute mania.
- Fewer studies have been performed with patients experiencing a mixed manic state. The limited data suggests that valproate may be more effective than lithium in these populations. Lithium was found to be less effective in mixed episode in placebo control trials (Swann et al., 1997). Several studies of patients with mania and mixed episode support the use of aripiprazole, olanzapine, risperidone, or ziprasidone in patients with mixed episode.
- Studies evaluating the use of topiramate, lamotrigine, or gabapentin have failed to show efficacy for these medications in treating mania or mixed episode and these can expose the patient to unnecessary side effects.

Table A - 2. Effectiveness of Medication in Bipolar Mania/Hypomania or Mixed episode

<table>
<thead>
<tr>
<th></th>
<th>Likely to be Beneficial [SR]</th>
<th>Trade off between Benefit and Harm [SR]</th>
<th>Unknown</th>
<th>Unlikely to Be Beneficial OR May be Harmful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combining (lithium or valproate) with aripiprazole, olanzapine, quetiapine, or risperidone [A]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SR = S trength of Recommendation (See Appendix A)
A-10. Reassess Every One to Two Weeks for at least 6 Weeks

BACKGROUND

Medications for mania and mixed episode will often take 5-10 days before they start to show a significant positive effect. The early stages of treatment for mania and mixed episode can be an extremely fluid period with patients having rapid, dramatic changes in their symptoms, including the development of new symptoms. Providers need to monitor these changes closely until a clear pattern of positive response has been demonstrated.

After any change in dose or medication, the patient should be monitored for positive and adverse effects. If no effectiveness is noted, it is sometimes useful to obtain medication concentrations for some treatments to assure adequate dosing and medication compliance.

RECOMMENDATIONS

1. Ongoing assessment of patients starting treatment for acute bipolar mania, hypomania or mixed episodes should include a reassessment for: [I]
   a. The development of depressive symptoms, suicidal ideation or homicidal ideation
   b. Emergence or change in psychotic symptoms
   c. Substance use
   d. Adverse effects of medications
   e. Medication adherence
   f. Medical Stability (e.g., blood pressure)
   g. Significant changes in psychosocial circumstances.

2. Reassess patient every 1 to 2 weeks for at least 6 weeks. [I]

3. Ongoing assessment of patients starting treatment for acute bipolar mania or mixed episode may include pertinent laboratory studies (e.g., medication plasma concentrations, urine drug screening, CBC, blood glucose, liver panel, lipid panel) and weight.

A-11. Is Patient Responding to Therapy?

BACKGROUND

To assess response to treatment, the patient’s symptoms should be carefully assessed at follow-up visits. A standardized, validated questionnaire that is self- or interviewer-administered that assesses DSM-IV-TR criterion, symptoms, effects on functioning, and suicidal ideation can be used as a continuous measure to assess severity and monitor treatment response.

RECOMMENDATIONS

1. Monitor treatment response at 4 to 8 weeks after initiation of treatment, after each change in treatment, and periodically until full remission is achieved. [B]

2. In patients who reach full remission, assessment of symptoms should be continued periodically to monitor for relapse or recurrence. [B]

3. Patients with suicidal ideation should have a careful evaluation of suicide risk. [A]
4. Providers should give simple educational messages regarding medication therapy (e.g., take daily, understand gradual nature of benefits, continue even when feeling better, do not stop without checking with the provider, and specific instructions on how to address issues or concerns) in order to increase adherence to treatment. [I]

5. Patient, family and/or caregiver should be educated about the risk of relapse to mania or hypomania that may occur. They should be instructed on identifying symptoms and the importance of contacting their provider immediately if they notice these symptoms. [I]

A-12. Is Patient in Full Remission

BACKGROUND

It is important that clinical efforts do not stop when the patient begins to show improvement. The goal of treatment should be full remission. Continuing to aggressively treat mania and mixed episode until the patient enters a full remission can make a vast improvement in the patient’s quality of life.

Although many standardized rating scales will give ranges for normal or non-symptomatic scores, remission is best determined by a thorough clinical evaluation. DSM-IV-TR defines Full Remission from mania as “a period of at least 2 months in which there are no significant symptoms of mania”. The DSM-IV-TR defines Full Remission from mixed episode as, “a period of at least 2 months in which there are no significant symptoms of mania or depression”.

RECOMMENDATIONS

1. Patients with mania who have been without any significant symptoms of mania for two months should be considered to be in full remission. [I]

2. Patients with mixed episode who have been without any significant symptoms of mania or depression for two months should be considered to be in full remission. [I]

A-13. Assess Adherence, Need for Psychosocial and/or Family Interventions, Adverse Effects, and Psychosocial Barriers to Therapy; Assess risk for suicide

BACKGROUND

Medications for mania and mixed episode will often take 5-10 days before they start to show a significant positive effect. Several weeks may be required to see the full therapeutic effect of the medication. During the first few weeks of treatment, patients will require frequent monitoring. This monitoring will look for positive and adverse effects of the medications as well as for changes in patient symptoms and psychosocial circumstances. This monitoring will help identify those who are not improving despite following the treatment recommendations. These patients may require more intensive interventions. For some medications, it is essential to monitor their plasma drug concentrations.

ACTION STATEMENT

Assess adherence to therapy, and other possible causes for partial response or non-response.

RECOMMENDATIONS

1. Patients should be followed by a scheduled visit to the clinic periodically, depending on their response to therapy, for a thorough assessment that includes:
   a. Adherence to therapy. Reasons for noncompliance should be explored with the patient. [A]
b. Assessment of potential adverse effects. [A]

c. Monitoring of serum concentration for lithium, valproate, or carbamazepine, and other appropriate blood work to maintain efficacy and avoid toxicity [A/B] (See Annotation A-8)

d. For patients receiving antipsychotic medications, monitor weight, BMI, waist circumference, blood pressure, plasma glucose and fasting lipids [A]. e. Assessment of any changes in patient’s family and community support (housing, care givers, employment, income, social networks). [B]

2. Assess for improvement or change of the core symptoms of mania and mixed episode through a clinical interview or the use of a standardized rating scale (e.g., Young Mania Rating Scale). [I]

3. Patients with suicidal ideation should have a careful evaluation of suicide risk. [A]

RATIONALE

Patients not demonstrating improvement may be appropriate for more intensive interventions. Medication compliance, often closely linked to adverse effects of the medications, is one of the chief determinants of patient response and therefore needs to be closely monitored. Patients experiencing mania and mixed episode are at increased risk for substance abuse which can complicate or confuse the clinical picture. Patients should be assessed for use of alcohol and drug abuse. Many of the medications used in the treatment of mania and mixed episode can have broad systemic effects and might affect blood pressure, glucose metabolism, weight, and liver function. These will also need to be monitored.

The use of standardized rating scales for the monitoring of symptoms is often a helpful way to document progress of therapy. Patients should also be asked about their current life circumstances. Fluctuations in psychosocial stress such as changes in employment or support systems may have a significant impact on their condition or their ability to follow through with treatment recommendations.

A14. Add/Change Anti Manic Medication until Stable or Consider Alternative Therapy

BACKGROUND

A significant percentage of patients will not respond to a single medication for mania or mixed episode even when the medication is taken regularly in proper dosages. For these patients the provider will need to try different strategies in order to maximize benefits and obtain remission. Unfortunately, little data exists to guide the provider in the exact sequence of steps. Possible strategies include switching to a different monotherapy agent or combining agents.

ACTION STATEMENT

Patients whose mania or mixed episode does not respond to adequate doses of a single medication should be receiving more aggressive medication treatment or hospitalization.

RECOMMENDATIONS

1. Patients whose mania does not respond to monotherapy should be considered for consultation/referral with specialty care. For patient with severe mania or mixed episode - see Annotation A-6
2. Reassess for co-occurring medical conditions that may also contribute to greater bipolar illness severity and reduced recovery. [C]

3. Escalating pharmacotherapy may be considered for patients whose mania/mixed episode or hypomania does not respond to monotherapy. The possible options for escalating pharmacotherapy include:
   a. Switching to another monotherapy may be considered if the patient did not respond to the first medication. [I]
   b. In patients with mania/hypomania who do not respond to monotherapy, consider combining a non-antipsychotic mood stabilizer (lithium or valproate) with a second generation antipsychotic such as aripiprazole, olanzapine, quetiapine, or risperidone [A] or ziprasidone. [I]
   c. In patients with mixed episode who do not respond to monotherapy, consider a combination of non-antipsychotics mood stabilizer (lithium or valproate) and a second generation antipsychotic such as aripiprazole, olanzapine, or risperidone [B] or quetiapine or ziprasidone. [I]

4. Clozapine, with its more serious side effect profile, may be combined with valproate or lithium as a treatment of severe mania or mixed episode, if it has been successful in the past or if other antipsychotics have failed. [I]

5. Adjust medications if there is no response within 2–4 weeks on an adequate dose of medication.

6. Electroconvulsive therapy (ECT) may be considered for patients with severe mania patients or whose mania is treatment resistant, those patients who express a preference for ECT, and patients with severe mania during pregnancy. [C]

7. Risks and benefits of long-term pharmacotherapy should be discussed prior to starting medication and should be a continued discussion item during treatment. [A]

RATIONALE

In some situations the medical condition or the treatment of a medical condition can mimic or exacerbate bipolar disorder. Co-occurring general medical conditions may also contribute to greater bipolar illness severity and reduced recovery, impaired quality of life and increased/premature mortality (Carney & Jones 2006; McIntyre et al. 2007). Chronic medical disorders are associated with a more severe course of BD, increased burden of disease and psychosocial stressors (employment adjustment, disability reimbursement, and increased frequent utilization of health services). Comorbid medical disorders in bipolar disorder are associated with several indices of harmful dysfunction, decrements in functional outcomes, and increased utilization of medical services (McIntyre et al. 2006).

Medical condition may exacerbate and increase the severity of bipolar disorder. For example, the use of corticosteroids (e.g., asthma, inflammatory disease) or disorders that leads to abnormal thyroid functioning. Medications such as stimulants and corticosteroids may be associated with secondary mania (Peet & Peters 1995; Arora & Daughton 2007). The treatment of BD may be complicated by conditions such as chronic kidney disease or hypertension that require the use of diuretics, angiotensin-converting enzyme inhibitors. Treatment of conditions that are associated with abnormal cardiac conduction or rhythm or that affect hepatic function may further limit the choice or dosage of effective BD medications (APA 2002).

Many patients with BD will not respond to the first medication they receive. If they do not adequately respond to usual therapeutic doses of an effective medication, then switching from one single medication to another medication is a logical step, although there is little evidence to direct what medication should be tried next. Randomized trials have consistently found that second generation antipsychotics (SGAs) combined with lithium or valproate are more effective than lithium or valproate alone. Most of these studies were conducted in a general population of patients and did not focus solely on patients who failed monotherapy. Despite this limitation, however, combination strategies are also a logical choice for patients who have failed monotherapy. Although this may be a class effect among all of the second generation
antipsychotics, we specifically reviewed the evidence showing the increased efficacy of augmentation with aripiprazole, olanzapine, quetiapine, and risperidone for manic episodes and aripiprazole, olanzapine, or risperidone for a mixed episode.
Management of Persons with Bipolar Disorders
B: Current Bipolar Depressive Episode

1. Person meets DSM-IV criteria for bipolar depressive episode [B1]
   Complete assessment
   Review current medications
   Assess risk for suicide [B2]

2. Is the patient at high risk of harming self or others? [B3]
   Yes: Refer for hospitalization [B4]
   No:

3. Is patient currently receiving clinical effective medications for bipolar depression? [B5]
   Yes:
   No:

4. Initiate pharmacotherapy with medication effective for bipolar depression [B6]
   Modify dose or medication if indicated using medications effective for bipolar depression [B7]

5. Reassess every 1 to 2 weeks for 6 weeks [B8]

6. Provide psychoeducation, psychotherapy and family intervention as indicated [B9]

7. Is patient responding to treatment? [B10]
   Yes:
   Continue current treatment
   Monitor regularly for 6 weeks
   Is patient in full remission? [B11]
   No:

8. Assess adherence, side effects and psychosocial barriers to therapy
   Assess risk for suicide [B12]

9. Augment or combine drugs [B13]
   Consider ECT or alternative therapies [B14]
   Ensure prevention of induced mania

10. Is patient in full remission? [B15]
    Yes:
    No:

11. Reevaluate diagnosis and treatment
    Consider hospitalization and/or consultation
    Consider ECT

12. Continue on Module C Maintenance Therapy
MODULE B: BIPOLAR ACUTE DEPRESSIVE EPISODE

B-1. Person Meets DSM-IV-TR Criteria for Bipolar Depressive Episode

BACKGROUND

To enter this module a patient must have met DSM-IV-TR criteria for a manic or hypomanic episode at some point in their life and currently be meeting DSM-IV-TR criteria for a bipolar depressive episode. Most patients with a bipolar disorder will experience at least one depressive episode during their lifetime. These depressive episodes can be just as severe in BD Type II as they are in BD Type I. The depressive episode must last at least two weeks but can extend for months. The depressive phase of bipolar disorder is a significant cause of suffering, disability, and mortality and represents a major challenge to the treating clinicians. The depressive and manic (or hypomanic) episodes may alternate, but many patients will experience a string of one type of episode before experiencing the other. The care of bipolar depression can be further complicated by the fact that many of the medications used to treat mania can induce depressive like symptoms such as changes in weight, energy, or sleeping patterns.

Bipolar depression is associated with a wide range of symptoms. Recent longitudinal studies suggest a higher prevalence of depressive symptoms over manic symptoms in the course of the illness. When compared to mania, episodes of depression are associated with greater impairment in work, family, and social life. Thus, adequate and prompt treatment is critical in preventing prolonged morbidity and increased risk of suicide.

- When evaluating a patient for a major depressive episode, information may be obtained from the patient’s subjective report, observation of symptoms, or report of reliable family members.
- In order to meet diagnostic criteria, there must have previously been at least one manic episode or mixed episode or hypomanic episode.
- The depressive episode must not be due to schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.

DEFINITIONS

Diagnostic Criteria for a major depressive episode DSM-IV-TR

1. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) or (2).
   1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood
   2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
   3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains
   4. Insomnia or hypersomnia nearly every day
   5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
   6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

2. The symptoms do not meet criteria for a Mixed Episode.

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

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

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

B-2. Complete Assessment; Review Current Medications; Assess Suicide Risk

BACKGROUND

A full psychiatric history, and mental state and physical examinations are necessary to confirm diagnosis, exclude underlying organic conditions (e.g., hypothyroidism), identify physical complications, and ascertain the risk of self-harm.

Bipolar disorder (BD) shares clinical features with major depressive disorder but its episodes of hypomania or mania are distinct. Since the latter may merge into psychosis, patients may remain undiagnosed for years or be incorrectly diagnosed as having schizophrenia or personality disorder. At the same time, patients presenting with depressive symptoms, who deny or neglect to provide information to the provider about their manic or hypomanic episode may be continually treated for major depressive disorder, which may not provide the most effective benefit to a patient with bipolar. Thorough assessment is vital, with diagnostic monitoring when new information emerges and use of collateral sources with attention especially to co-occurring conditions (e.g. substance use disorders or anxiety disorders).

Table B-1. Clinical Status Assessment

<table>
<thead>
<tr>
<th>Areas to be assessed</th>
<th>Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical comorbidity</td>
<td>Comorbid medical problems can contribute to mood dysregulation</td>
</tr>
<tr>
<td>Psychiatric comorbidity</td>
<td>It is important to assess for and treat all psychiatric comorbid conditions</td>
</tr>
<tr>
<td>Psychosocial Stressors</td>
<td>Current stressors can contribute to mood problems and adherence to treatment</td>
</tr>
<tr>
<td>Current medications</td>
<td>Assess the frequency and dosages of all prescribed and over-the-counter medications the patient is taking</td>
</tr>
<tr>
<td>Past medications</td>
<td>Check for previous historical response to mood stabilizers; note reasons for discontinuation, including side effect problems and nonresponse</td>
</tr>
<tr>
<td>Medication compliance</td>
<td>Evaluate whether the patient has been compliant in the past with medication treatment</td>
</tr>
<tr>
<td>Suicide risk</td>
<td>Evaluate risk factors for suicide including family history, previous attempts, and co-occurring substance use</td>
</tr>
<tr>
<td>Substance Use</td>
<td>Substance abuse can contribute to or precipitate a relapse; it can also be a reason for medication nonresponse</td>
</tr>
</tbody>
</table>
ACTION STATEMENT

Patients with a bipolar depressive episode require a thorough evaluation to determine level of risk and appropriate treatment.

RECOMMENDATIONS

1. A complete clinical assessment should be obtained for patients with BD depression episode to include:
   a. Clinical status
   b. Medical comorbidities
   c. Psychiatric comorbidities
   d. Psychosocial status
   e. Current medications
   f. Past medications
   g. Medication compliance
   h. Substance use

See Appendix B: Dangerous to Self or Others.

2. A standardized tool combined with a clinical interview should be used to obtain the necessary information about symptoms, symptom severity, and effects on daily functioning that is required to diagnose BD depression based on DSM-IV-TR criteria.

3. Consider using the same standardized questionnaire to monitor treatment response at 4 to 6 weeks, after each change in treatment, and to periodically assess the patient’s response to treatment until full remission is achieved. (Further information on assessment and screening tools for Bipolar Disorder and suicide- see: http://www.cqaimh.org/stable.html)

DISCUSSION

> Many factors can worsen the course of BD. These can cause general distress, decreases in functioning or relapses. These factors include medical problems that are untreated, other untreated psychiatric disorders, and psychosocial stressors.

> Bipolar disorder with a co-occurring substance use disorder is a common presentation. Substance abuse may precipitate mood episodes or be used by patients to ameliorate the symptoms of such episodes. Co-occurring substance use is typically associated with fewer and slower remissions, greater rates of suicide and suicide attempts, and poorer outcome.

> Suicide completion rates in patients with bipolar I disorder may be as high as 10 - 20%; thus, a careful assessment of the patient’s risk for suicide is critical.

> The adverse effects of medication, the availability of medications, family and community support and the patient’s ambivalence about medications all can affect their adherence to the medication regimen and can affect rates of relapse.

B-3. Is The Patient at High Risk of Harming Self or Others?

BACKGROUND

Unstable conditions, whether psychiatric or physiologic, represent situations that require immediate attention. Whatever the cause, the following situations may serve as warning signs of violence:

> Ideas about, or intent to, harm others
• Verbal escalation or inability to be redirected
• History of violent behavior
• Severe agitation or hostility
• Active psychosis
• Intoxication or withdrawal from alcohol or drugs

Immediate attention and intervention, including referral or consultation with a mental health professional, may be required in order to stave off the potential for escalation of agitation or violent impulses.

ACTION STATEMENT

Identify patients who are at high risk of harm to self or others.

RECOMMENDATIONS

1. Patients with a possible diagnosis of BD depression should be assessed for suicidality, acute or chronic psychosis or other unstable or dangerous conditions.

2. A referral to emergency services and/or a mental health professional is indicated for patients presenting with any of the following unstable conditions:
   a. Delirium
   b. Marked psychotic symptoms
   c. Severe depressive symptoms/depression (e.g., catatonia, malnourishment, severe disability)
   d. Suicidality or homicidality
   e. Potential for violence (e.g., ideas about or intent to harm others; history of violent behavior; severe agitation or hostility; active psychosis)
   f. Substance withdrawal or intoxication.

4. Any patient with suicidal or homicidal ideation or attempts necessitating psychiatric hospitalization should be considered for referral to mental health specialty care. (See Appendix B: Dangerous to Self or Others.)

5. Patients with a possible diagnosis of BD depression who exhibit any of the following characteristics related to psychosis need to be referred for urgent/emergent mental health intervention as these are inappropriate for care in the primary care setting:
   a. Serious delusions (e.g., fixed false beliefs)
   b. Visual or (typically) auditory hallucinations
   c. Confusion (incoherence)
   d. Catatonic behavior (e.g., motor immobility or excessive agitation)
   e. Extreme negativism or mutism
   f. Peculiar voluntary movement
   g. Inappropriate affect of a bizarre or odd quality.

DISCUSSION

Delirium - Delirium (also known as organic brain syndrome, organic psychosis, acute confusional state, acute brain syndrome and various other names) is a very common disorder of cognition and consciousness, with an abrupt onset that is commonly unrecognized. This is especially true in the elderly and chronically ill.
• Marked psychotic symptoms - "Psychosis," in and of itself, is not a disorder. Rather, it is a symptom, which may present in a variety of conditions. Psychotic patients have an impaired sense of reality, which may manifest in several ways (hallucinations, delusions, mental confusion, or disorganization).

• Severe depressive symptoms/depression (e.g., catatonia, malnourishment, severe disability) - The clinical presentation of depressed patients is marked by considerable variation, not only in the expression of various neurovegetative symptoms themselves, but also in the magnitude of severity of these symptoms. While many mild to moderate illnesses may not necessarily present situations requiring immediate attention, the presence of severe depressive symptoms may represent an urgent condition, even in the absence of suicidal ideation.

• Suicidally - Suicidal behavior is best assessed with the following criteria: current suicidal ideas or plans, presence of active mental illness (severe depression or psychosis), presence of substance use disorder, past history of suicidal acts, formulation of plan, availability of means for suicide (firearms, pills, etc.), disruption of important personal relationships, or failure at important personal endeavors.

• Potential for violence - Violence often emerges as a response to a perceived threat or as marked frustration resulting from the inability to meet goals by nonviolent means. Specific factors that contribute to violent behavior include psychiatric, medical, environmental, and situational/social factors.

• Unstable urgent medical conditions - Any condition immediately threatening to life, limb, or eyesight, or requiring emergency medical care. These may include acute myocardial infarction, respiratory failure, hypertensive crisis, diabetic ketoacidosis, crushing radiating chest pain, or other unstable conditions

IS THERE EVIDENCE OF PSYCHOSIS?
Psychosis is defined as a mental state in which the patient is significantly out of touch with reality to the extent that it impairs functioning. Patients with psychotic symptoms may present in an acutely agitated state with a recent onset of disturbed and/or disturbing symptoms.

In particular, paranoid concerns that others wish to harm the patient and voices (especially command hallucinations) telling the patient to hurt him or herself or someone else, are indications for an immediate mental health consultation or referral.

It is important to bear in mind that psychotic symptoms may be the direct result of an underlying medical condition, toxic state, alcohol or substance use disorder, or may be associated with a mental health condition such as schizophrenia or affective illness. (Kaplan & Sadock, 1995).

B-4. Refer for Hospitalization

BACKGROUND

The usual reasons for urgent hospitalization include acute suicide risk; acute violence risk due to mental illness; delirium, and acute unstable medical condition. Specialized treatments only available or often best provided in an inpatient setting include:

• Electro-convulsive therapy (ECT)
• Close monitoring and daily titration of medications with disabling side effects or toxicity
• Constant staff observation as part of an intensive behavioral modification program
• Close monitoring of behavior in an episodic disorder
• Close monitoring of vital signs or need for multiple daily laboratory or electrophysiological testing.
ACTION STATEMENT

Ensure that appropriate care, protocols, and regulatory/policy mandates are followed during diagnosis and stabilization of the patient with an unstable bipolar depressive episode.

RECOMMENDATIONS

1. Local, state and federal regulations/mandates as well as guidelines should be followed when the patient represents a risk to self or other.
2. Patients with urgent, unstable conditions, severe depression or elevated dangerousness should be referred to a higher level of care (hospitalization).

B-5. Is Patient Currently Receiving Clinically Effective Medications for Bipolar Depression?

All patients with BD depression should be treated with medications that have been shown to be effective. Some patients may have been treated in the past with medications that have not been shown to be efficacious in trials. If they continue to have symptoms, patients should be gradually shifted to medications that have been shown as effective.

For recommendation on modifying medication treatment see Annotation B-7

B-6. Pharmacotherapy for Bipolar Depression

BACKGROUND
Pharmacologic treatments that have been studied in bipolar depression include lithium, antiepileptics, antipsychotics, antidepressants, and ECT. The primary goal is remission of symptoms of depression and return to normal levels of psychosocial functioning. Depending on the choice of the medication used for treatment, there may also be concerns about precipitation of a manic or hypomanic episode. Mood stabilizers (e.g., lithium, valproate, carbamazepine, and some of the antipsychotics) are used to prevent acute mood destabilization.

ACTION STATEMENT
Patients with a bipolar depressive episode should be treated with medications that have demonstrated efficacy in treating that depressive episode while minimizing the risk of inducing a manic, hypomanic or mixed manic episode.

RECOMMENDATIONS

General considerations
1. Pharmacotherapy for bipolar depression should start with initiation or optimization of a medication that has been shown to be the most effective in treating bipolar depressive episodes, while minimizing the potential risks. [B] (see Table B - 2)
2. Consider using the agent(s) that have been effective in treating prior episodes of depression. [I]
3. The risk for mood destabilization or switching to mania should be evaluated and the patient should be monitored closely for emergent symptoms after initiation of pharmacotherapy for a depressive episode. [I]
4. For patients with BD depression with psychotic features, an antipsychotic medication should be started. [I]
5. Consider adding one of the evidence-based psychotherapeutic interventions to improve adherence and patient outcome. [B] (See Module D: Psychosocial Interventions)
6. In selecting a drug treatment regimen for patients with bipolar disorder, clinicians should be aware of the patient’s other psychiatric and medical conditions and should try to avoid exacerbating them.

7. In selecting a drug treatment regimen for patients with diabetes or obesity consider the risk and benefit of utilizing medications that are less associated with weight gain.

**Monotherapy**

8. Quetiapine, [A], lamotrigine [B], or lithium [B] monotherapy should be considered as first-line treatment for adult patients with BD depression.

9. Olanzapine/fluoxetine combination (OFC) should be considered for treatment of BD depression, but its adverse effects (weight gain, risk of diabetes, hypertriglyceridemia) places this combination as a second-line treatment. [B]

10. Olanzapine alone may be considered for BD depression, but adverse effects require caution. [C]

11. There is insufficient evidence to recommend for or against the use of valproate, carbamazepine, topiramate, risperidone, ziprasidone, or clozapine for BD depression. [I]

12. Aripiprazole NOT recommended for monotherapy in the treatment of acute bipolar depression, unless there is a history of previous good response during depression without switch to mania or a history of treatment refractory depression. [D]

**Combination Strategies**

13. Combining lithium with lamotrigine can be considered for patients with BD depression who do not respond to monotherapy. [A]

14. When patients do not respond to treatment options that have shown better efficacy, antidepressant augmentation with SSRI, SNRI, buproprion, and MAOI can be considered for short-term treatment monitoring closely for triggering of manic symptoms. [C]

15. Clozapine may be considered for augmentation, using caution regarding metabolic or other adverse effects. [I]

16. There is insufficient evidence to recommend for or against use of augmentation with aripiprazole, olanzapine, risperidone, haloperidol, oxcarbazepine, topiramate, ziprasidone, valproate, or carbamazepine for the treatment of bipolar depression. [I]

17. Gabapentin and the tricyclic antidepressants (TCAs) are NOT recommended for monotherapy or augmentation in the treatment of acute bipolar depression, unless there is a history of previous good response during depression without switch to mania or a history of treatment refractory depression. [D]

**Table B - 2. Effectiveness of Medication in Acute Bipolar Depression**

<table>
<thead>
<tr>
<th>Likely to be Beneficial [SR]</th>
<th>Trade off between Benefit and Harm [SR]</th>
<th>Unknown</th>
<th>Unlikely to Be Beneficial or May be Harmful</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Quetiapine (in BD types I &amp; II) [A]</td>
<td>Olanzapine [C]</td>
<td>- Clozapine</td>
<td>- Gabapentin [D]</td>
</tr>
<tr>
<td>- Lithium with adjunctive lamotrigine [A]</td>
<td>Lamotrigine [B]</td>
<td>- Haloperidol</td>
<td>- Antidepressant monotherapy [D]</td>
</tr>
<tr>
<td>Augmentation with SSRI, SNRI, buproprion, and MAOI [C]</td>
<td>Olanzapine/Fluoxetine [B]</td>
<td>- Oxcarbazepine</td>
<td>- Antidepressant monotherapy [D]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Risperidone</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Topiramate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Valproate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Ziprasidone</td>
<td></td>
</tr>
</tbody>
</table>

*SR = Strength of Recommendation (See Appendix A)*
B-7. Modify Dose or Medication if Indicated, Using Medications Effective for Bipolar Depression

**BACKGROUND**

A significant percentage of patients will not respond to any one medication approach even when the medication is taken regularly in proper dosages. For these patients, the provider will need to try different strategies in order to maximize benefits and obtain remission. Unfortunately, little data exists to guide the provider in the exact sequence of steps. Possible strategies include switching to a different mood stabilizer or combining agents.

For patients with a partial response to treatment, the medication therapy should continue and include monitoring and adjusting the dose to maximize response and minimize adverse events.

**RECOMMENDATIONS**

1. If patient is having intolerable side effects switch to another effective treatment [I]
2. If the patient has switched into mania or hypomania or entered a mixed manic state, go to Module A (Acute Mania) [I]
3. Assess compliance and blood serum concentration to assess if medications are in therapeutic range [I]
   a. The serum trough concentration of lithium should be maintained between 0.8 - 1.2 mEq/L
   b. The serum trough concentration of valproate should be maintained between 50-125 mcg/ml
   c. The serum trough concentration of carbamazepine should be maintained between 4 - 12 mcg/ml.
4. If medication is not in therapeutic range, adjust medication to maximum range [I]
5. Medications without known therapeutic plasma concentrations should be increased until significant improvement is seen, side effects become intolerable or the dose reaches the manufacturer’s suggested upper limits. [I]

**Partial response**

6. Adjust medications if there is no response within 2 - 4 weeks on an adequate dose of medication. Adjustment may include:
   a. Augmenting with additional agents (See Annotation B-6)
   b. Discontinue the current agent and switch to another effective medication (See Annotation B-6)
   c. If multiple trials of switching medications or augmentation strategies have not been effective consider ECT [I]
7. Any discontinuation of medication used to treat bipolar depression should be tapered and the patient should be monitored for antidepressant discontinuation syndrome and mood destabilization [I]
8. Risks and benefits of long term pharmacotherapy should be discussed prior to starting medication and should be a continuing discussion item during treatment. [A]

**RATIONALE**

Most patients with bipolar disorder will have a recurrence of depression or mania after the initial episode. Symptomatic bipolar disorder patients spend, on average, 33% of their time in a depressive phase compared with 11% in a manic/hypomanic phase (Post, 2004). Depressive symptoms tend to occur 3 to 4 times more frequently than manic symptoms (Judd et al., 2002; Post et al., 2003). In addition, impairment in work, social life, and family
life appears to be more significantly impacted by depressive rather than manic symptoms (Calabrese et al., 2004). Yet, the treatment of bipolar depression remains understudied. All current guidelines recommend that depressed bipolar I (and most bipolar II) patients first be optimized on a mood stabilizer to have improved outcomes (APA, 2002; Goodwin, 2003; Suppes et al., 2005).

Rosenbaum et al., (2005) suggests that a treatment trial for acute bipolar depression should be carried out until one of three endpoints is reached:

- Discontinuation due to adverse events, including emergence of manic/hypomanic symptoms
- Discontinuation due to lack of response to maximal trial of treatment, including augmentation strategies
- Improvement of symptoms.

Problems may include treatment intolerance, inadequate dosage, partial response, and nonresponse. It may be useful to obtain medication concentrations for some treatments to ensure adequate dosing and medication adherence. Treatments should be adjusted or replaced as necessary to address these problems until acute symptoms remit (Rosenbaum et al., 2001).

**B-8. Reassess Every One to Two Weeks for Six Weeks**

**BACKGROUND**

Medications for depression may take up to 6 weeks to demonstrate initial effectiveness and up to 8 - 12 weeks to demonstrate their full efficacy. During the first few months of treatment, patients will require consistent monitoring to assess positive and adverse effects of the medications as well as changes in the patient’s symptoms and psychosocial circumstances. This monitoring will also help to identify those who are not improving despite following the treatment recommendations. These patients may require more intensive interventions. If no effectiveness is noted, it is sometimes useful to obtain medication concentration to assure adequate dosing and medication compliance.

**RECOMMENDATIONS**

1. Ongoing assessment of patients starting treatment for acute bipolar depression should include a reassessment for: [I]
   a. Changes in depressive symptoms
   b. Neurovegetative symptoms
   c. Emerging symptoms of mania/hypomania
   d. Psychotic symptoms
   e. Development of suicidal or homicidal ideation
   f. Substance use
   g. Adverse effects of medications
   h. Medication compliance
   i. Medical stability (e.g., blood pressure)
   j. Significant changes in psychosocial circumstances

2. Reassess patient every 1 to 2 weeks for at least 6 weeks. [I]

3. Ongoing assessment of patients starting treatment for acute bipolar depression may include pertinent laboratory studies (e.g., medication plasma concentrations, urine drug screening, CBC, blood glucose, liver panel, lipid panel) and weight. [I]

**RATIONALE**

- Treatment of acute bipolar depression can result in dramatic changes in the patient’s symptoms, including the development of new symptoms. Providers need to monitor these changes until the patient enters full remission. Providers also need to monitor for emergence of manic symptoms,
especially if antidepressant augmentation is used for treatment. The use of standardized rating scales for the monitoring of symptoms is often a helpful way to document progress of therapy.

> Medication compliance, often closely linked to adverse effects of the medications, is one of the chief determinants of patient response and needs to be closely monitored.

> Patients experiencing bipolar depression are at increased risk for substance abuse, which can complicate or confuse the clinical picture. Patients should be assessed for use of alcohol and drugs.

> Many of the medications used in the treatment of bipolar depression can have broad systemic effects and might affect blood pressure, glucose metabolism, weight, and liver function. These will also need to be monitored. Medications such as lithium and carbamazepine have defined meaningful drug plasma concentrations which directly impact the effectiveness of these medications. These concentrations must be monitored closely.

> Patients should also be asked about their current life circumstances. Fluctuations in psychosocial stress, such as changes in employment or support systems, may have a significant impact on their condition or their ability to follow through with treatment recommendations.

**B-9. Provide Psychoeducation, Psychotherapy, and Family Intervention as Indicated**

**BACKGROUND**

Adju|unctive psychotherapy is frequently necessary for bipolar disorder because despite the availability of evidence-based pharmacotherapy, outcomes remain suboptimal for patients with BD. Notably, adherence is consistently low in this group (~50% on average) and poor insight into the illness is a factor. Moreover, psychotherapy addresses other independent determinants of poor outcome, including stressors and comorbidities, poor social functioning and quality of life. The cyclical nature of the illness also warrants additional psychoeducation on symptom management and coping strategies that focus on maintaining and improving medication adherence.

**RECOMMENDATIONS**

1. Providers should give simple educational messages regarding medication therapy (e.g., take daily, understand gradual nature of benefits, continue even when feeling better, do not stop without checking with the provider, and specific instructions on how to address issues or concerns) in order to increase adherence to treatment. [B]

2. Patient, family and/or caregiver should be educated about the risk of switching to mania or hypomania that may occur naturally or as a result of medications. They should be instructed on identifying symptoms and the importance of contacting their provider immediately if they notice these symptoms. [I]


4. Patients who are currently in a depressive episode and are at high risk for non-adherence to medication, should be considered for one of the following evidence-based psychotherapeutic interventions
   a. Cognitive behavioral therapy (CBT) [A]
   b. Family Therapy [B]
   c. Interpersonal and Social Rhythm Therapy (IPSRT) [B]
EVIDENCE STATEMENTS

For a discussion of the supporting evidence used in grading the recommendation see Module D Psychosocial Intervention.

B-10. Is Patient Responding to Treatment?

BACKGROUND

To assess response to treatment, the patient’s symptoms should be carefully assessed at follow-up visits. A standardized, validated questionnaire for self- or interviewer-administered instrument that assesses DSM-IV-TR criterion symptoms, effects on functioning, and suicidal ideation can be used as a continuous measure to assess severity and monitor treatment response.

RECOMMENDATIONS

1. Once the patient has demonstrated a response to treatment, continue to monitor progress every 4 to 8 weeks and after each change in treatment until full remission is achieved. [B]
2. In patients who reach full remission, assessment of symptoms should be continued periodically to monitor for relapse or recurrence. [B]
3. Patients with suicidal ideation should have a careful evaluation of suicide risk. [A]

B-ll. Is Patient in Full Remission?

BACKGROUND

Although many standardized rating scales will give ranges for normal or nonsymptomatic scores, remission is best determined by a thorough clinical evaluation.

Full remission from depression is defined as “a period of at least 2 months in which there are no significant signs or symptoms of depression.” (DSM-IV-TR)

ACTION STATEMENT

Patients with bipolar depression who have been without any significant symptoms of depression for two months should be considered to be in full remission.

RECOMMENDATIONS

1. Following remission of the depressive episode, it is appropriate to consider withdrawing antidepressant treatment after 4-6 months. [C]

RATIONALE

Once a patient's depression symptoms have remitted and this stabilization has continued for a few months it is reasonable to consider if antidepressant treatment is still needed. There continues to be controversy due to lack of definitive data on the relative harm and benefit of continuing or discontinuing antidepressants. Some evidence supports the importance of discontinuing to minimize future cycling, while other data suggests for some patients continuing antidepressants may be important for stability. Counterpoint to this clinical perspective are the acute depression double blind, in some cases placebo-controlled, showing limited value of add-on antidepressant (Sachs et al., 2007; Altshuler et al., 2003, 2009).
EVIDENCE TABLE

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Source</th>
<th>LE</th>
<th>QE</th>
<th>SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Full remission from bipolar depression defined as two months with no significant signs or symptoms of depression</td>
<td>DSM-IV-TR</td>
<td>III</td>
<td>Poor</td>
</tr>
</tbody>
</table>

LE = Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

B-12. Assess Adherence, Side Effects, and Psychosocial Barriers to Therapy; Assess Risk for Suicide

BACKGROUND

Patient adherence to medication is a key factor in obtaining relief from depressive symptoms, as well as avoiding recurrence of mania. Adverse effects from medication can lead to nonadherence. Lack of insight, poor cognition, and poor functional capacity in acute illness can also contribute to nonadherence. Psychosocial barriers to treatment may also impair adherence to treatment. Minimizing medication side effects, providing psychoeducation, and attention to psychosocial barriers to treatment may all be useful in facilitating patient adherence to treatment.

ACTION STATEMENT

Assess adherence to treatment, and other possible causes for partial response or no-response.

RECOMMENDATIONS

1. Patients should be followed by a scheduled visit to the clinic periodically, depending on their response, for a thorough assessment that includes:
   a. Adherence to therapy. Reasons for noncompliance should be explored with the patient. [B]
   b. Assessment of potential adverse effects. [A]
   c. Monitoring of serum concentration for lithium and other appropriate blood work to maintain efficacy and avoid toxicity [B]
   d. For antipsychotics monitor weight (BMI), waist circumference, blood pressure, BMI, plasma glucose and fasting lipids [C].
   e. Assess for co-occurring medical conditions that can mimic or exacerbate bipolar disorder depression. [B]
   f. Assessment of any changes in patient’s family and community support (housing, care givers, employment, income, social networks). [B]

2. Assess for improvement or change of the core symptoms of depression through a clinical interview or the use of a standardized rating scale to determine changes in the severity of depression. [I]

3. Patients with suicidal ideation should have a careful evaluation of suicide risk. [A]

RATIONALE

Treatment nonadherence is very common in bipolar disorder (Colom et al., 2000) and can be associated with rehospitalization and suicide. Though more common in the maintenance phase, treatment nonadherence secondary to disability and poor insight is more likely to be a problem during acute bipolar
depression. Nonadherence rates are reported as high as 18 - 53% (Goodwin & Jamison, 1990) and 30% (Sajatovic et al., 2004), some of the factors influencing treatment adherence include (Jamison et al., 1979; Sajatovic et al., 2004):

- Illness denial
- Psychosis
- Feeling depressed
- Experience of side effects, particularly lethargy and lack of coordination
- Comorbid disorders such as substance abuse

Providers may use the education of patients and families about the disorder, treatment, and treatment side effects as a means to improve adherence. If the patient is being treated on an outpatient basis, knowledge of ability/support for self-medication is important and must be addressed (i.e., the potential use of a mediplanner box). In addition, any psychosocial barriers to adherence to treatment (e.g., transportation, ability to financially obtain medication) must be identified and addressed in order to effectively address the patient’s depression.

Minimizing medication side effects seems especially important in assuring medication adherence.

EVIDENCE STATEMENTS

> “Medication side effects, costs, and other demands of long-term treatment… need to be discussed realistically with the patient and family members. Many side effects can be corrected with careful attention to dosing, scheduling, and preparation” (APA, 2002).

> “Patients with this disorder are frequently ambivalent about treatment. This ambivalence often takes the form of noncompliance with medication and other treatments, which is a major cause of relapse” (APA, 2002).

> “Patients with bipolar disorder benefit from education and feedback regarding their illness, prognosis, and treatment. Frequently, their ability to understand and retain this information will vary over time. Patients will also vary in their ability to accept and adapt to the idea that they have an illness that requires long-term treatment. Education should therefore be an ongoing process in which the psychiatrist gradually but persistently introduces facts about the illness” (APA, 2002).

> A systematic review by Sajetovic et al., (2004) noted that effective therapies are “patient-focused and include family members or significant others whenever possible.” Promotion of treatment adherence was facilitated through a longitudinal interactional component between patients and care providers and frequently focused on issues of “appropriately taking medications to manage illness.”

The effect of treatment for BD on other medical conditions

- The use of antipsychotic medications for bipolar disorder is associated with higher risk of weight gain, obesity and progression of diabetes. Other medication commonly used in BD may cause hypothyroidism, thyroid disease, polycystic ovarian syndrome, renal disease, and skin disorders.

The effect of medical comorbid conditions on BD illness or treatment of:

> In some situations the medical condition or the treatment of a medical condition can mimic or exacerbate bipolar disorder.

> Co-occurring general medical conditions may also contribute to greater bipolar illness severity and reduced recovery, impaired quality of life and increased/premature mortality (Carney & Jones 2006; McIntyre et al. 2007). Chronic medical disorders are associated with a more severe course of BD, increased burden of disease and psychosocial stressors (employment adjustment, disability reimbursement, and increased frequent utilization of health services). Comorbid medical disorders in bipolar disorder are associated with several indices of harmful dysfunction, decrements in functional outcomes, and increased utilization of medical services. (McIntyre et al. 2006)
Medical condition may exacerbate and increase the severity of bipolar disorder. For example, the use of corticosteroids (e.g., asthma, inflammatory disease) or disorders that leads to abnormal thyroid functioning. Medications such as stimulants and corticosteroids may be associated with secondary mania (Peet & Peters 1995; Arora & Daughton 2007). The treatment of BD may be complicated by conditions such as chronic kidney disease or hypertension that require the use of diuretics, angiotensin-converting enzyme inhibitors. Treatment of conditions that are associated with abnormal cardiac conduction or rhythm or that affect hepatic function may further limit the choice or dosage of effective BD medications. [APA 2002]

**EVIDENCE TABLE**

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Source</th>
<th>LE</th>
<th>QE</th>
<th>SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor and adjust treatment for mediation side effects.</td>
<td>APA, 2002</td>
<td>III</td>
<td>Poor</td>
<td>C</td>
</tr>
<tr>
<td>Psychoeducation to improve adherence.</td>
<td>Colom et al., 2000 Sajatovic et al., 2004 SR</td>
<td>I</td>
<td>Good</td>
<td>B</td>
</tr>
<tr>
<td>Assess for and address cognitive and functional barriers to compliance.</td>
<td>Martinez-Aran, 2004</td>
<td>I</td>
<td>Fair</td>
<td>C</td>
</tr>
</tbody>
</table>

*LE = Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)*

B-13. Consider ECT or Alternative Therapies; Monitor for Risk for Mood Destabilization

**BACKGROUND**

Electro-convulsive therapy (ECT) is a rapid and effective treatment for both mania and bipolar depression, although it is probably underused in severely depressed patients.

**ACTION STATEMENT**

ECT should be utilized for the treatment of severe and refractory bipolar depression in patients who consent and have no absolute medical contraindications.

**RECOMMENDATIONS**

1. Electro-convulsive therapy (ECT) should be initiated in patients with severe or refractory bipolar depression who consent and have no absolute medical contraindications. [B]

2. The risk for mood destabilization or switching to mania should be evaluated and the patient should be monitored closely for emergent symptoms.
C-1. Adult Person with BD in Symptomatic Remission after an Acute Manic/Hypomanic/Mixed or Depressive Episode

BACKGROUND

Use this module to manage patients with history of BD who have achieved remission from an acute episode of depression, hypomania, or mania to develop a long-term prophylaxis treatment plan.

RECOMMENDATIONS

1. A structured approach to maintenance management of the patient with BD who has recently experienced an acute episode and is now in remission is recommended. [A]

2. Patients who have had an acute manic episode should be treated for at least 6 months after the initial episode is controlled and encouraged to continue on life-long prophylactic treatment with medication. [A]

3. Risks and benefits of long term pharmacotherapy should be discussed prior to starting medication and should be a continued discussion item during treatment. [C]

4. Patients who have had more than one manic episode or with one manic and one depressive episode, or three or more depressive episodes, should be encouraged to continue on life-long prophylactic treatment, as the benefits clearly outweigh the risks. [A]

5. If medications are to be discontinued, they should be slowly and gradually tapered over at least a 2 to 4 week period, unless medically contraindicated, in order to prevent an episode of bipolar disorder and/or increase the risk of suicide. [B]

RATIONALE

Most patients with bipolar disorder will have recurrences of manic or depressive episodes following their initial episode. Following remission from an acute episode, patients are at high-risk for relapse in the first 6 months. Long-term prophylaxis will minimize the risk of relapse and suicide.

EVIDENCE STATEMENTS

The APA (2002) Guideline states that following remission of an acute episode, patients may remain at particularly high-risk of relapse for a period of up to 6 months; this phase of treatment, sometimes referred to as continuation treatment, is considered in this guideline to be part of the maintenance phase. Maintenance regimens of medication are recommended following a manic episode. Although few studies involving patients with bipolar II disorder have been conducted, consideration of maintenance treatment for this form of the illness is also strongly warranted.

According to Simon et al., (2005) “A systematic care program for bipolar disorder significantly reduces risk of mania over 12 months. Preliminary results suggest a growing effect on depression over time, but longer follow-up will be needed”.

If a patient and/or physician elect to discontinue mood stabilizer medication, a very slow and gradual taper schedule should be used, since there is some data (Suppes et al., 1991; Faedda et al., 1993) stating that an episode of bipolar disorder may occur sooner, and there is an increase in suicide risk (Baldessarini et al., 1999), in patients who stop mood stabilizers abruptly.

Suppes et al., (1991) compiled data from 124 patients with BD type I in 10 studies who were stable for an average of at least 30 months prior to lithium discontinuation. Fifty percent (50%) of persons relapsed within 5 months of discontinuation, and half of these relapsed within 6 weeks. Among those who relapsed, mania occurred more often than depression, and significantly earlier (2.7 versus 14
months). The time to relapse after discontinuation was shorter than the prior illness pattern would have predicted, suggesting that lithium discontinuation may have caused a physiological "stress" to otherwise stable persons. Suppes et al., (1993) reviewed another 15 studies of 632 persons with mood disorders and determined that relapse rates were almost threefold higher after lithium discontinuation (75 percent versus 27 percent).

> Faedda et al., (1993) compared rapid (< 2 weeks) versus slower (2 to 4 weeks) lithium discontinuation in a prospective naturalistic study of 64 bipolar type I or II persons stable for an average of 3.6 years. Rapid discontinuation resulted in more and earlier relapses.

> Bouman et al., (1986) found earlier and more frequent relapses in bipolar or schizoaffective persons after lithium was discontinued during lithium treatment. Mortality from suicide and from other medical causes (Müller-Oerlinghausen et al., 1992; Nilsson, 1995) appeared to be higher as well.

> Also, up to 20 percent of persons for whom lithium is discontinued respond less well to lithium if it is later reinstituted (Maj et al., 1995). Although there are no data regarding other mood stabilizers, similar concerns apply, and similar procedures should be followed.

EVIDENCE TABLE

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Source</th>
<th>LE</th>
<th>QE</th>
<th>SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  Systematic care program</td>
<td>Simon et al., 2005</td>
<td>I</td>
<td>Good</td>
<td>A</td>
</tr>
<tr>
<td>2  Initiate prophylaxis and consider psychosocial rehabilitation</td>
<td>Goodwin &amp; Jamison, 2007</td>
<td>I</td>
<td>Good</td>
<td>A</td>
</tr>
<tr>
<td>3  Discourage discontinuation of mood stabilizer(s) even in patients with prolonged stability</td>
<td>Goodwin &amp; Jamison, 2007</td>
<td>I</td>
<td>Good</td>
<td>A</td>
</tr>
<tr>
<td>4  If discontinuing taper over more than 2 weeks</td>
<td>Baldessarini, 1999</td>
<td>II</td>
<td>Fair</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Faedda et al., 1993</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Suppes et al., 1991</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5  Earlier and more frequent relapses may be seen with lithium discontinuation</td>
<td>Bouman, 1986</td>
<td>II</td>
<td>Fair</td>
<td>B</td>
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<td></td>
<td>Faedda et al., 1993</td>
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<td>Suppes et al., 1991</td>
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</tbody>
</table>

LE = Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)
C-2. Assess Course of Illness, Treatment History, and Current Clinical Status

BACKGROUND

A psychiatric history, assessment of mental status and physical examinations are important to confirm diagnosis, exclude underlying organic conditions (e.g., hypothyroidism), identify physical complications or comorbidities, and ascertain the risk of self-harm.

Table C-1 Clinical Status Assessment

<table>
<thead>
<tr>
<th>Areas to be assessed</th>
<th>Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical comorbidity</td>
<td>Comorbid medical problems can contribute to mood dysregulation</td>
</tr>
<tr>
<td>Psychiatric comorbidity</td>
<td>It is important to assess for and treat all psychiatric comorbid conditions</td>
</tr>
<tr>
<td>Psychosocial Stressors</td>
<td>Current stressors can contribute to mood problems and adherence to treatment</td>
</tr>
<tr>
<td>Current medications</td>
<td>Assess the frequency and dosages of all prescribed and over-the-counter medications the patient is taking</td>
</tr>
<tr>
<td>Past medications</td>
<td>Check for previous historical response to mood stabilizers; note reasons for discontinuation, including side effect problems and nonresponse</td>
</tr>
<tr>
<td>Medication compliance</td>
<td>Evaluate whether the patient has been compliant in the past with medication treatment</td>
</tr>
<tr>
<td>Suicide risk</td>
<td>Evaluate risk factors for suicide including family history, previous attempts, and co-occurring substance use</td>
</tr>
<tr>
<td>Substance Use</td>
<td>Substance abuse can contribute to or precipitate a relapse; it can also be a reason for medication nonresponse</td>
</tr>
</tbody>
</table>

ACTION STATEMENT

Patients with BD who have achieved remission from an acute episode require a thorough evaluation to determine appropriate maintenance treatment.

RECOMMENDATIONS

1. A complete clinical assessment should be obtained for patients with BD who are entering the maintenance phase following an acute episode, to include:
   a. Clinical status
   b. Medical comorbidities
   c. Psychiatric comorbidities
   d. Psychosocial status
   e. Current medications
   f. Past medications
   g. Medication compliance
   h. Suicide risk
   i. Substance use

DISCUSSION

Many factors can worsen the course of BD. These factors include medical problems that are untreated, other untreated psychiatric disorders, and psychosocial stressors. These can cause general distress, decreases in functioning or relapses.
Bipolar disorder with a co-occurring substance use disorder (SUD) is a very common presentation. Substance abuse may precipitate mood episodes or be used by patients to ameliorate the symptoms of such episodes. Co-occurring substance use is typically associated with fewer and slower remissions, greater rates of suicide and suicide attempts, and poorer outcomes.

Suicide completion rates in patients with bipolar I disorder may be as high as 10 - 20%; thus, a careful assessment of the patient’s risk for suicide is critical.

The adverse effects of medication, the availability of medications, family and community support and the patient’s ambivalence about medications all can affect their adherence to the medication regimen and can affect rates of relapse.

C-3. Is Patient Receiving Tolerable and Clinically Effective Medications for Maintaining Remission?

Patients who are clinically stable and tolerating their medication can be maintained on the agent used in acute treatment.

Patients who continue to experience sub-threshold symptoms or breakthrough mood episodes may require the addition of another maintenance medication. Certain medications have shown stronger evidence for the prevention of mania or depression. (See Annotation C-4)

C-4. Institute Maintenance Medications that Have Demonstrated Clinical Efficacy for At Least 6 Months.

BACKGROUND

Patients with bipolar disorder whose acute symptoms of a manic or depressive episode have been in remission for three to six months should begin long-term maintenance on prophylactic treatment and psychosocial rehabilitation.

ACTION STATEMENT

Pharmacotherapy should optimally consist of a clinically effective medication for the prevention of manic and depressive episodes and should be prescribed to patients with bipolar disorder in the maintenance phase.

RECOMMENDATIONS

1. Consider using the agent(s) that have been effective in the recent acute phase or in past mood episodes. (See Table C-2) [I]

2. Consider reducing to a single medication (monotherapy) that has been shown to be most effective in delaying/preventing relapse while minimizing the potential risks by monitoring the patient closely. [I]

3. Consider the pharmacokinetics, adverse effects, and drug-drug interactions when selecting the specific agent(s). [I]

4. Lithium [A] or olanzapine [B] should be considered as first-line maintenance treatment for adults with BD to delay/prevent the recurrence of mania.

5. Risperidone long-acting IM injection should be considered for patient with frequently relapses. [B]

6. Aripiprazole [B] may be considered as a second line treatment to prevent or delay the recurrence of mania.
7. Lithium, or lamotrigine, should be considered as a first-line treatment to prevent or delay the recurrence of bipolar depression. [B]

8. Olanzapine may be considered as a second line treatment to prevent /delay bipolar depressive episodes. [C]

9. Quetiapine augmentation of valproate or lithium should be considered a first-line maintenance treatment for adults with BP to maintain remission and prevent new episodes of all types. [B]

10. Adding Olanzapine to lithium or valproate may be used in maintenance treatment to delay or prevent symptomatic relapse. [C]

11. In patients with a history of severe or recent mania, lamotrigine should be used in combination with lithium, olanzapine, or aripiprazole. [I]

12. Valproate and carbamazepine may also be considered as alternatives for maintenance medication. [C]

13. There is insufficient evidence to recommend for or against other antipsychotic or anti-epileptic agents in the maintenance treatment of Bipolar Disorder.

Table C - 2. Effectiveness of Bipolar Medication in Maintaining Remission

<table>
<thead>
<tr>
<th>Likely to be Beneficial [SR]</th>
<th>Trade off between Benefit and Harm [SR]</th>
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<th>Unlikely to Be Beneficial or May be Harmful</th>
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<tbody>
<tr>
<td><strong>Monotherapy:</strong></td>
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</tr>
<tr>
<td>- Lithium [B*/A**]</td>
<td>- Valproate [C]</td>
<td>- Clozapine</td>
<td>- Antidepressant monotherapy [D]</td>
</tr>
<tr>
<td>- Lamotrigine [B*/C**]</td>
<td>- Carbamazepine [C]</td>
<td>- Gabapentin</td>
<td></td>
</tr>
<tr>
<td>- Olanzapine [C*/B**]</td>
<td>- Aripiprazole [B**]</td>
<td>- Haloperidol</td>
<td></td>
</tr>
<tr>
<td><strong>Combination:</strong></td>
<td></td>
<td>- Olanzapine/Fluoxetine</td>
<td></td>
</tr>
<tr>
<td>- Quetiapine as adjunct to lithium or valproate [B]</td>
<td>- Oxcarbazepine</td>
<td>- Risperidone ***</td>
<td></td>
</tr>
<tr>
<td>- Olanzapine as adjunct to lithium or valproate [C]</td>
<td>- Topiramate</td>
<td>- Ziprasidone</td>
<td></td>
</tr>
</tbody>
</table>

* Prevention of depression episode ** Prevention of Mania/hypomania episode ***
Consider Risperidone long-acting IM injection for patient with frequent recurrences

SR = Strength of Recommendation (See Appendix A)

EVIDENCE STATEMENTS

- There is good evidence to demonstrate that specific medication treatments delay/prevent the time to relapse in bipolar disorder. Therefore, long term maintenance medication is generally recommended. The choice of medication depends on the balance between effectiveness of the medication in maintaining euthymia and the tolerability of adverse effects (possible harm). It is general clinic practice to continue the medication that led to remission. In patients who are not currently on medications or who are not tolerating their current medications, providers should consider those medications which have the strongest evidence as a Maintenance Treatment.

- Data suggests that some medications are more effective in preventing the depressed phase while others are more effective in preventing the manic phase. The choice of a maintenance treatment needs to consider the individual’s course of illness. As an example, if the individual has had a greater number of manic episodes, it may be logical to use agents that have been shown to be better in preventing
manic episodes (e.g. lithium, valproate, an antipsychotic). Clearly, both phases should be prevented, and all patients with recurrent bipolar disorder should be receiving prophylaxis medication therapy.

- Because of the prominent psychosocial issues which accompany bipolar disorder, psychotherapy can play a pivotal role in treating these patients and should be considered as complementing the medication treatment. (See Module D Psychosocial Interventions)

C-5. **Assess for Adverse Events within 2 Weeks**

**BACKGROUND**

Medications commonly have adverse effects that may interfere with adherence and successful treatment.

**ACTION STATEMENT**

Assess for adverse effects and tolerability after any change of treatment strategy.

**RECOMMENDATIONS**

1. Using a standardized clinical tool in addition to a clinical interview, assess for response to treatment, adherence to treatment and adverse effects of treatment after initiating or changing treatment.

2. Identified side effects should be managed to minimize or alleviate if possible.

C-6. **Provide Psychoeducation, Psychotherapy, and Family Intervention as Indicated**

**BACKGROUND**

Adjunctive psychotherapy is recommended for bipolar disorder. Despite the availability of evidence-based pharmacotherapy, outcomes remain suboptimal for many patients with BD who are treated with medications alone. Notably, adherence is consistently low in this group (~50% on average) and poor insight into the illness is a factor. Moreover, psychotherapy addresses other independent determinants of poor outcome, including stressors and comorbidities, poor social functioning and quality of life. The cyclical nature of the illness also warrants additional psychoeducation on symptom management and coping strategies that focus on maintaining and improving medication adherence. (See Module D for additional recommendations)

**RECOMMENDATIONS**

1. Providers should give simple educational messages regarding medication therapy (e.g., take daily, understand gradual nature of benefits, continue even when feeling better, do not stop without checking with the provider, and specific instructions on how to address issues or concerns) in order to increase adherence to treatment. [C]

2. Consider psychoeducation and care management for patients with BD. [B] For best effect consider offering in a structured group setting with ongoing care/disease management. [A]

3. Patients on prophylactic medications, who are recovering or have recovered from a manic or hypomanic episode, as well as those currently in a depressive episode and who are at high risk for non-adherence to medication; should be considered for one of the following evidence-based psychotherapeutic interventions:
a. Cognitive behavioral therapy (CBT) [A]
b. Family Therapy [B]
c. Interpersonal and Social Rhythm Therapy (IPSRT) [B]

EVIDENCE STATEMENTS
For a discussion of the supporting evidence used in grading the recommendation see Module D: Psychosocial Interventions.

C-7. **Assess Response after 1-3 months; Monitor All Medications and Manage Adverse Effects. Monitor and Encourage Adherence. Discuss with Patient Risks and Benefits of Long-Term Pharmacotherapy.**

BACKGROUND
Patient adherence to medication is a key factor in maintaining a remission from bipolar disorder. Adverse effects from medications or simply feeling better can lead to nonadherence. Lack of insight, poor cognition, and poor functional capacity in acute illness can also contribute to nonadherence. Psychosocial barriers to treatment may also impair adherence to treatment. Patients fear the potentially abrupt loss of control and its embarrassing consequences. They may resist accepting the diagnosis and need for treatment despite experiencing several episodes.

Minimizing medication side effects, providing psychoeducation, and attending to psychosocial barriers to treatment may all be useful in facilitating patient adherence to treatment. As non-compliance is the most common factor in relapse of bipolar disorder, providers should attempt to improve compliance by strategies such as educating patients and families about the disorder and its treatment, as well as about side effects. Excluding noncompliance should be the first step in assessing failure to respond to prophylaxis therapy.

Other strategies include:
- Active bipolar support groups are widespread and may contribute usefully to a treatment program. Written material about bipolar disorder and its treatment is helpful to enhance patient knowledge.
- An under-acknowledged aspect of long-term care of bipolar disorder is provider continuity, relevant to both patient and provider. Contact with the same provider enhances early identification of recurrence and facilitates joint awareness of the continuing impact of the illness.

ACTION STATEMENTS
Patients’ adherence to treatment should be assessed. Barriers to adherence should be addressed.

RECOMMENDATIONS
1. Patients whose BD is in remission should be followed by a scheduled visit to the clinic every 1 to 3 months with a thorough assessment of current and recent symptoms. [I]
2. All patients on medication should be monitored for potential adverse effects. [B]
3. Monitor serum concentration for lithium, carbamazepine, or valproate and other appropriate blood work every 3 to 6 months to maintain efficacy and avoid toxicity. [A/B]
4. For antipsychotics monitor weight (BMI), waist circumference, blood pressure, BMI, plasma glucose and fasting lipids [C].
5. Adherence to medication therapy should be routinely evaluated at each visit. Reasons for noncompliance should be explored with the patient. [A]

6. Assess any changes in patient’s family and community support (e.g., housing, care givers, employment, income, social networks). [C]

EVIDENCE STATEMENTS

> Treatment nonadherence is very common in bipolar disorder (Colom et al., 2000) and can be associated with rehospitalization and suicide. Treatment non-adherence secondary to disability and poor insight is a common problem during maintenance treatment. With nonadherence rates cited as 18 - 53% (Goodwin & Jamison, 2007) and 30% (Sajatovic et al., 2004), some of the factors influencing treatment adherence include illness denial, psychosis, feeling depressed, side effects, and comorbid disorders, (Jamison et al., 1979; Sajatovic et al., 2004). Minimizing medication side effects seems especially important in assuring medication adherence.

> One consequence of non-compliance is that rapid discontinuation of lithium leads to a high rate of relapse, greater than the ‘natural’ pattern; 50% of patients relapse within 5 months (mostly with mania) (Suppes et al., 1991).

> “Medication side effects, costs, and other demands of long-term treatment… need to be discussed realistically with the patient and family members. Many side effects can be corrected with careful attention to dosing, scheduling, and preparation” (APA Guidelines, 2002).

> “Patients with this disorder are frequently ambivalent about treatment. This ambivalence often takes the form of noncompliance with medication and other treatments, which is a major cause of relapse” (APA Guidelines, 2002).

> “Patients with bipolar disorder benefit from education and feedback regarding their illness, prognosis, and treatment. Frequently, their ability to understand and retain this information will vary over time. Patients will also vary in their ability to accept and adapt to the idea that they have an illness that requires long-term treatment. Education should therefore be an ongoing process in which the psychiatrist gradually but persistently introduces facts about the illness” (APA Guidelines, 2002).

> A systematic review by Sajetovic et al. (2004) noted that effective therapies are “patient-focused and include family members or significant others whenever possible.” Promotion of treatment adherence was facilitated through a longitudinal interactional component between patients and care providers and frequently focused on issues of “appropriately taking medications to manage illness.”
C-8. Is there any Medical or Psychiatric Comorbidity

BACKGROUND

The majority of patients with a bipolar disorder have at least one comorbid psychiatric or medical disorder, and many have more than one.

Comprehensive management of persons with bipolar disorder (BD) should take into consideration the complex inter-relationships between BD, medical comorbid conditions, lifestyle risk factors and pharmacotherapy interventions. Optimized treatment of the mood disorder should include continuing vigilance and assessment for co-occurring conditions along with individualized treatment planning addressing all of their co-occurring disorders. Pharmacotherapy for BD should maximize therapeutic benefit while minimizing the risk of creating or exacerbating a co-occurring condition.

Common medical comorbidities associated with BD include cardiovascular, metabolic, pulmonary, hematological, neurological, infectious and endocrine disorders accompanied by addictions (including nicotine) and other life style risk factors that occur in patients with BD in higher rates than national norms and at significantly younger ages.

Comorbid psychiatric conditions (e.g., SUD, anxiety, suicidality, personality disorders, ADHD) may impact response to therapy. In all patients and in cases of failure to respond in particular, other comorbidities need to be thoroughly assessed. Substance abuse comorbidity is higher than in any other psychiatric condition.

ACTION STATEMENT

Identify any medical or psychiatric comorbidity in patients receiving maintenance treatment for bipolar disorder.

RECOMMENDATIONS

1. Addiction focused treatment should be coordinated with the treatment of BD. [I]
2. Refer patients with other co-occurring major psychiatric illnesses to specialty care. [I]
3. Refer patients who have had significant suicidality or homicidality to specialty care. [I]
4. Because of possibility of adverse drug-drug interactions, the provider should consider all current medications including OTC medication and nutritional supplements whenever new medications are prescribed.
5. In selecting a drug treatment regimen for patients with bipolar disorder, clinicians should be aware of the patient’s other psychiatric and medical conditions and should try to avoid exacerbating them.
6. In selecting a drug treatment regimen for patients with diabetes or obesity consider the risk and benefit of utilizing medications that are less associated with weight gain.
7. Primary care providers should continue follow patients who are referred to specialty care, and should coordinate the management of all of their health conditions.
RATIONALE

Medical problems can cause mood episodes as well as exacerbate the course of bipolar disorder and complicate treatment. Patients with bipolar disorder are at higher risk for other psychiatric disorders such as anxiety disorders or substance abuse. In addition, patients with co-morbid personality disorders may have a worse course of illness and lower compliance, necessitating concurrent treatment for these disorders in order to optimize outcome. Patients with bipolar disorder are a high-risk for suicide that should be routinely assessed.
DISCUSSION

Epidemiology of Medical Comorbidity and Bipolar Disorder

Patients with BD have high rates of comorbid medical conditions. This finding is especially remarkable when considering the relatively young age of patients (average 38.8 years) with bipolar disorder when they develop these co-occurring medical conditions. (Carney et al., 2006). Kilbourne et al., (2004) report that more than a third of patients with BD who responded to a survey were given a diagnosis of 3 or more chronic medical conditions and the risk for medical comorbidity was significantly higher in the BD group at an earlier age (compared with the reference group).

Common medical conditions in patients with bipolar disorder include cardiovascular conditions, ischemic heart disease, stroke, neurological disorders, epilepsy and multiple sclerosis, endocrine and metabolic conditions, respiratory disorders such as asthma, hematological conditions including some types of cancer, and infectious diseases (hepatitis-C and HIV/AIDS) (Krishnan 2005; Carney & Jones 2006; McIntyre et al. 2007).

In the Canadian Community Health Survey (n = 36,984), rates of medical comorbidities, including chronic fatigue syndrome, migraine, asthma, chronic bronchitis, multiple chemical sensitivities, hypertension, and gastric ulcer were significantly higher in patients with BD compared to matched controls. (McIntyre et al. 2006)

An elevated cancer risk in patients with BD has been reported in both men and women. Fibromyalgia has also been highly associated with BD, suggesting these conditions may share underlying pathophysiological links (BarChana et al., 2008)

Organic conditions, such as thyroid disease, multiple sclerosis or any lesion(s) involving right-sided subcortical or cortical areas may be associated with secondary mania (Cummings and Mendez, 1984; Strakowski et al., 1994; Mendez, 2000)

A study of persons (90% men) seeking health care through the Veterans Affairs Healthcare System found that hepatitis C, diabetes, low back pain, and pulmonary conditions were more common among subjects with bipolar disorder (Kilbourne et al., 2004)

Individuals with bipolar disorder may have higher rates of sexually transmitted diseases and substance misuse. They tend to underutilize preventative health care services, which further predisposes them to develop medical conditions (McIntyre et al. 2005b).

The rates of metabolic syndrome and diabetes are elevated in patients with BD. These conditions worsen impairment and functioning. In patients with BD, comorbid diabetes almost doubled the overall health care costs compared to patients without diabetes. Patients with psychiatric disorders and comorbid diabetes reported greater impairment in both physical and mental health, lower quality of life, and less satisfaction with health compared to those without diabetes (180).

The effect of treatment for BD on other medical conditions

The use of antipsychotic medications for bipolar disorder is associated with higher risk of weight gain, obesity and progression of diabetes. Other medication commonly used in BD may cause hypothyroidism, thyroid disease, polycystic ovarian syndrome, renal disease, and skin disorders.

The effect of medical comorbid conditions on BD illness or treatment of:

In some situations the medical condition or the treatment of a medical condition can mimic or exacerbate bipolar disorder.

Co-occurring general medical conditions may also contribute to greater bipolar illness severity and reduced recovery, impaired quality of life and increased/premature mortality (Carney & Jones 2006; McIntyre et al. 2007). Chronic medical disorders are associated with a more severe course of BD, increased burden of
disease and psychosocial stressors (employment adjustment, disability reimbursement, and increased frequent utilization of health services). Comorbid medical disorders in bipolar disorder are associated with several indices of harmful dysfunction, decrements in functional outcomes, and increased utilization of medical services. (McIntyre et al. 2006)

Medical condition may exacerbate and increase the severity of bipolar disorder. For example, the use of corticosteroids (e.g., asthma, inflammatory disease) or disorders that leads to abnormal thyroid functioning. Medications such as stimulants and corticosteroids may be associated with secondary mania (Peet & Peters 1995; Arora & Daughton 2007). The treatment of BD may be complicated by conditions such as chronic kidney disease or hypertension that require the use of diuretics, angiotensin-converting enzyme inhibitors.

Treatment of conditions that are associated with abnormal cardiac conduction or rhythm or that affect hepatic function may further limit the choice or dosage of effective BD medications. [APA 2002]

Psychiatric comorbidity

> Medical conditions can lead to mood change episodes or can exacerbate the course of bipolar illness and complicate recovery.

> Patients with bipolar disorder are at greater risk for comorbid anxiety disorders, especially panic disorder and obsessive-compulsive disorder. Comorbid anxiety disorders may lead to longer recovery times from mood episodes.

> Co-occurring alcohol abuse or dependence is found in 46% of patients with a bipolar disorder. The prevalence of drug abuse or dependence is 41% in the bipolar population.

> The course of bipolar illness for comorbid personality disorders is frequently worse with lower recovery rates, greater impairment, and a higher risk for relapse.

> Patients with bipolar disorder are at high-risk for suicide. The completed suicide rate in bipolar I disorder is estimated to be 10-20%.

> There is insufficient evidence to indicate whether patients with a co-occurring SUD should be managed differently than other patients with BD. There is also insufficient evidence to indicate the order of treating BD and co-occurring SUD (Vornik 2006). Generally, practitioners treat the mood instability and address any immediate needs or detoxification for a given patient. Once stabilized, the substance abuse or dependence takes on a more primary focus of the treatment plan.

C-9. Is Patient in Recurrence and Meets DSM-IV-TR Criteria for Bipolar Episode?

BACKGROUND

Patients with BD will inevitably have variations in their symptoms. When their symptoms worsen to the point of once again meeting full DSM-IV-TR criteria for a manic, hypomanic or depressed episode, then they are experiencing a recurrence. Recurrence is common in bipolar disorder.

ACTION STATEMENT

For patients who experience a recurrence, manage their care according to the respective module.

RECOMMENDATIONS

See Module A - For management of Bipolar Acute Manic/Hypomania/Mixed episode.

See Module B - For management of Bipolar Acute Depressive Episode.
C-10. Optimize Medication Regimen and Psychotherapy Interventions

BACKGROUND

Patients with BD may continue to experience significant symptoms in the maintenance phase even if they do not experience a complete recurrence. The symptoms may be due to a lack of compliance stemming from severe side effects or other issues. The residual symptoms may also result from inadequate treatment. Addressing these residual symptoms should be a priority for the provider. The evidence on addressing residual symptoms is very limited. Because of the lack of evidence for a specific approach to modify therapy, the provider should use the options that have been shown to be effective in treating BD while maximizing the potential benefit and harm.

RECOMMENDATIONS

1. If patient is having intolerable side effects switch to another effective treatment. [I]
2. If symptoms of mania, hypomania, or depression re-occur but do not meet criteria for a relapse adjust current treatment as follows:
   • Assess compliance and if medications are in therapeutic range [I]
   • Assess for other factors that may cause the symptoms (i.e., medical condition or substance use) [I]
   • If medication is not in therapeutic range adjust medication to maximum range [I]
   • Consider adding one of the evidence based psychotherapeutic interventions [B] (See Module D-Psychosocial Interventions)
   • Consider adding an augmenting agent (quetiapine or olanzapine) [A]
   • Consider switching to another treatment that is effective for maintenance treatment. [I]
3. Risks and benefits of long-term pharmacotherapy should be discussed prior to starting medication and during treatment. [A]

C-II. Consider Discontinuing Medications that Are Not Critical for Mood Stabilization While Maintaining Symptomatic and Functional Remission. Continue Follow-Up to Prevent Recurrence and Promote Recovery and Rehabilitation.

BACKGROUND

Most patients with BD would do best to continue their medication indefinitely. Occasionally patients or providers will want to consider optimizing the patient’s medication in order to minimize the side effect burden or other potential harm caused by medications. This may be especially true in patients who are elderly or have significant medical co-morbidities.

RECOMMENDATIONS

1. Medications that are believed not to be critical for mood stabilization are recommended to be gradually tapered one at a time.
2. In all of these cases the taper should be done gradually with close observation by the provider, patient, and if possible, other objective sources of information (e.g. spouses).
3. If symptoms re-occur, alternative medications with lower side effects burden or using somewhat lower doses should be considered.
MODULE D: PSYCHOSOCIAL INTERVENTIONS

BACKGROUND

Adjunctive psychosocial interventions have long been recommended for bipolar disorder but have only recently received serious research interest. The major modalities with empirical support appear to be individual cognitive and interpersonal therapy, family-focusing therapy and other forms of patient and family psychoeducation and structured group psychoeducation, with and without chronic disease/care management. The majority of the benefits have been observed during maintenance treatment, although the acute impact of these interventions deserves further study.

Adjunctive psychotherapy is recommended for BD because, despite the availability of evidence-based pharmacotherapy, outcomes remain suboptimal for patients with BD. Notably, adherence is consistently low in this group (~50% on average) and poor insight into the illness is a factor. Moreover, psychotherapy addresses other independent determinants of poor outcome, including stressors and comorbidities, poor social functioning and quality of life. The cyclical nature of the illness also warrants additional psychoeducation on symptom management and coping strategies that focus on maintaining and improving medication adherence.

Recent studies have examined the value of combining structured forms of psychotherapy with medication maintenance for patients with BD. These studies have been influenced by the growing literature on stress in the elicitation of manic and depressive episodes. Randomized trials published within the past 5 years indicate positive benefits of cognitive-behavioral therapy, interpersonal and social rhythm therapy, family-focused treatment, and group psychoeducation, especially coupled with systematic chronic care management (CCM) as adjuncts to mood stabilizers in delaying recurrences, stabilizing symptoms, and improving medication adherence.

Questions remain about the relative advantages of one psychosocial approach over the others, whether there are subgroups of patients who respond to each type of intervention, the impact of psychotherapy on role functioning, mediators of treatment effects, and the potential utility of early intervention as a preventative agent.
PSYCHOEDUCATION

BACKGROUND
Because of the emotional distress and severe dysfunction associated with BD, it is important that patients with BD understand the nature of their illness and the most effective ways of treating acute symptoms and preventing recurrence.

This involves a thorough understanding of behavioral and biological factors that may worsen the course of the illness and increase the risk of recurrence. Psychoeducation should be an integral part of the team approach for treatment of patients with BD.

Given the expense of psychotherapy approaches in real-world settings, several investigators have undertaken structured, group-based models that involve treating several patients at once. Recently group psychoeducation has been combined with more systematic chronic care/disease management (CCM) approaches as a means to provide additional support and to promote maintenance of lessons learned from group psychoeducation.

RECOMMENDATIONS
1. Patient should receive psychoeducation that emphasizes: [B]
   a. The importance of active involvement in their treatment
   b. The nature and course of their bipolar illness
   c. The potential benefit and adverse effects of treatment options
   d. The recognition of early signs of relapse
   e. Behavioral interventions that can lessen the likelihood of relapse including careful attention to sleep regulation and avoidance of substance misuse.

2. With the patient’s permission, family members or significant other should be involved in the psychoeducation process. [C]

3. A structured group format in providing psychoeducation and care management for patients with clinically significant mood symptoms should be considered. [A]

RATIONALE
It appears that patients receiving structured psychoeducation in groups, or integrated into a chronic care model program, experience longer intervals prior to recurrences of BD episodes than patients in unstructured support groups. In addition, researchers have found that patients in the care management program had lower levels of manic symptoms and less time in manic episodes. No effects were found on depressive symptoms. Importantly, the program could be implemented with only modest increases in the costs of care, and in the VA, with no differences in cost.

EVIDENCE STATEMENTS
Johnson et al., (1997) found that negative life events were associated with slow recovery from bipolar depressive episodes. However, life events that were positive and involved goal attainment (e.g., getting promoted) were associated with an increase in manic symptoms (Johnson et al., 2000). A retrospective study found that bipolar patients often experienced events that disrupted their sleep/wake rhythms in the months preceding manic onset, although not prior to depressive onset (Malkoff, et al., 2000; Malkoff et al., 1998). These studies underlined the role of stress in mediating the relations between biological vulnerability and relapse, and paved the way for studies of psychosocial treatment as adjunctive to medication.
These interventions have many commonalities, as discussed by Scott and Gutierrez, (2004); they all include psychoeducation about BD, encouragement of medication adherence, recurrence prevention strategies, mood monitoring, and illness management skills.

- Patients with bipolar disorder benefit from education and feedback regarding their illness, prognosis, and treatment. Patients may experience considerable difficulty performing at the level for which their education has prepared them. Patients will also vary in their ability to accept and adapt to the idea that they have an illness that requires long-term treatment (APA, 2002). Education should therefore be an ongoing process and the goals of education need to be sustained and incremental. (APA, 2002).

- A systematic review by Sajetovic et al., (2004) noted that effective therapies are “patient-focused and include family members or significant others whenever possible.” Promotion of treatment adherence was facilitated through a longitudinal interactional component between patients and care providers and frequently focused on issues of “appropriately taking medications to manage illness.”

- Colom, et al., (2003) found that patients in a 21 week structured psychoeducation group had longer intervals prior to recurrences (relapse prevention) than patients in an unstructured support group. Colom, et al., (2005) found that during the Colom et al., (2003) 2-year study, relapses occurred earlier and more often among patients in the unstructured group (92%) than in the structured group (67%). Patients in the structured group had higher and more stable lithium concentration as well. However, the structured group had a higher drop-out rate (27%) than the unstructured groups (12%).

### EVIDENCE TABLE

<table>
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<tr>
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<th>Source</th>
<th>LE</th>
<th>QE</th>
<th>SR</th>
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<td>Psychoeducation to improve adherence.</td>
<td>Colom et al., 2000</td>
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<td></td>
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<td>Sajatovic et al., 2004</td>
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<td>2</td>
<td>Assess for and address cognitive and functional barriers to compliance.</td>
<td>Martinez-Aran, 2004</td>
<td>I</td>
<td>Fair</td>
</tr>
<tr>
<td>3</td>
<td>Structured psychoeducation approach leads to longer intervals prior to recurrences</td>
<td>Colom et al., 2003</td>
<td>I</td>
<td>Fair</td>
</tr>
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<td>Colom et al., 2005</td>
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<td>4</td>
<td>Structured group psychoeducation with systematic chronic care/disease models (CCM) leads to fewer weeks of mood episodes and fewer manic episodes</td>
<td>Bauer et al., 2006 a,b</td>
<td>I</td>
<td>Good</td>
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*LE = Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)*
PSYCHOTHERAPY STRATEGIES

COGNITIVE BEHAVIORAL (CBT)

BACKGROUND

The assumption behind CBT approaches is that BD patients have distorted cognitions and assumptions that lead to negative or dysfunctional mood states and that modifying the cognitive distortion will lead to reduction in mood symptoms.

RECOMMENDATIONS

1. Cognitive Behavioral Treatment (CBT) may be considered as an adjunct to pharmacotherapy for patients with BD who have achieved remission from an acute manic episode and who have had fewer than 12 previous BD acute episodes [A]

2. Implementation of CBT should include components of:
   a. Education regarding symptoms, course and treatment of BD,
   b. Scheduling of pleasurable events to alleviate inactivity,
   c. Teaching the skill of cognitive re-structuring,
   d. Learning to identify maladaptive thoughts and challenge them on logical grounds,
   e. Learning to replace maladaptive thoughts with balanced or adaptive thinking,
   f. Problem solving, and
   g. Learning to detect the earliest signs of recurrence and implement early intervention plans.

3. In considering patients for CBT it is recommended that careful screening for hypomanic episodes be conducted (dynamism, persuasiveness, productiveness) as there is some evidence to support that CBT is less effective with these patients.

4. CBT can be considered as an approach to reduce and prevent depressive symptoms in BD rather than manic symptoms as it has been found to be most effective in depression. [B]

RATIONALE

There is evidence to support the use of CBT as an adjunct to pharmacotherapy in BD patients who have achieved remission. It appears that this intervention is most effective in patients with fewer than 12 previous episodes and those booster sessions after 18 months may help to maintain the benefits over time.

EVIDENCE STATEMENTS

The most comprehensive study of CBT was performed by Lam and Associates, (2003, & 2005) who compared a 6-month CBT intervention (12-18 sessions, plus two booster sessions) with pharmacotherapy versus treatment-as-usual with pharmacotherapy (N = 103). The patients had experienced at least three illness episodes in the past five years but had been in remission for at least six months. In the first study year, patients in CBT had lower rates of relapse than those in treatment as usual (44% versus 75%) and spent less time ill. In the 12-30 months following CBT, no differences were found between the CBT and usual treatment groups, although CBT continued to positively influence mood ratings and days spent in episodes.

CBT was evaluated in a five-site U.K. multicenter “effectiveness” trial for 253 bipolar patients treated at community mental health centers (Scott et al., 2006). Like the study by Lam et al., (2003), this study compared CBT (22 sessions) and medications with usual care and medications, but unlike the prior study,
patients could enter in any clinical state (recovered, subsyndromal, or syndromal). There were no differential effects of CBT and pharmacotherapy on time to recurrence over an 18-month follow-up. Patients with fewer than 12 prior illness episodes had fewer recurrences in CBT than in treatment-as-usual, but patients with 12 or more episodes had fewer recurrences in treatment-as-usual than CBT. Possibly, CBT is most appropriate for patients in the early stages of their disorder or those who are less recurrent.

- Lam and colleagues, (2003) found that CBT was less effective among patients who experienced a “sense of hyperpositive self,” marked by dynamism, persuasiveness, and productiveness.

- Scott et al., (2006) found that patients responded best to CBT if they had had fewer than 12 previous episodes.

- In the 1980’s a single randomized trial (Cochran, 1984) of cognitive behavioral therapy (CBT) as an adjunct to lithium found beneficial effects on risk for hospitalization and adherence to medications.

- Ball et al., (2006) found that CBT was effective for treating depressive symptoms for 6 and 12 months but effect decreased with time. Mania symptoms did not improve with treatment.

- Zaretsky et al., (2007, 2008) found that CBT plus psychoeducation was better than just psychoeducation, with a 50% reduction in depressive symptoms over the year of the study. No benefit was found in manic symptoms.

- Miklowitz et al., (2008) found that CBT was better than psychoeducation in reducing symptoms, but not as effective as Family Focused therapy.

### EVIDENCE TABLE

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Source</th>
<th>LE</th>
<th>QE</th>
<th>SR</th>
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<tbody>
<tr>
<td>1 CBT has positive influence on mood ratings and days spent in episodes</td>
<td>Lam et al., 2003, 2005</td>
<td>I</td>
<td>Good</td>
<td>A</td>
</tr>
<tr>
<td>2 CBT is most appropriate for patients in the early stages of their disorder or those who had fewer recurrent (less than 12) episodes of illness</td>
<td>Scott et al., 2006</td>
<td>I</td>
<td>Good</td>
<td>A</td>
</tr>
<tr>
<td>3 Hyperpomonic episodes</td>
<td>Lam, et al., 2003</td>
<td>I</td>
<td>Fair</td>
<td>B</td>
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<td>4 CBT as an adjunct to lithium</td>
<td>Cochran, 1984</td>
<td>I</td>
<td>Fair</td>
<td>B</td>
</tr>
<tr>
<td>5 CBT benefits the maintenance phase</td>
<td>Ball et al., 2006</td>
<td>I</td>
<td>Fair</td>
<td>B</td>
</tr>
<tr>
<td>6 Reduction in depressive symptoms</td>
<td>Zaretsky et al., 2007, 2008</td>
<td>I</td>
<td>Fair</td>
<td>B</td>
</tr>
<tr>
<td>7 CBT better than case management in reducing symptoms</td>
<td>Miklowitz et al., 2007</td>
<td>I</td>
<td>Fair</td>
<td>B</td>
</tr>
</tbody>
</table>

LE = Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)
INTERPERSONAL AND SOCIAL RHYTHM THERAPY (IPSRT)

BACKGROUND

IPSRT like its forerunner, the interpersonal psychotherapy of depression, focuses on the interpersonal context of episodes of depression and mania. Initially, clinicians conduct an illness history and identify a recent problem area on which to focus (i.e., grief, role disputes, role transitions, or interpersonal deficits). In the IPSRT of bipolar disorder, there is an additional focus on regulating and stabilizing sleep/wake rhythms, along with patterns of social routine and stimulation. Patients fill out a self-report instrument (the Social Rhythm Metric) for tracking and quantifying daily and nightly routines, along with ratings of mood.

As treatment ensues, clinicians assist patients in keeping regular routines (e.g., bed times, wake times, exercise) and minimizing the impact of events that could disrupt their moods and daily/nightly stability. The interpersonal focus concerns the resolution of the patient’s current problems (e.g., how to communicate better with one’s spouse) and developing strategies for preventing the same problems from recurring in the future.

RECOMMENDATIONS

1. Interpersonal and Social Rhythm Therapy (IPSRT) may be considered for patients with BD who have achieved remission from an acute manic episode and are maintained on prophylactic medication. [B]

2. Interpersonal and Social Rhythm Therapy (IPSRT) should contain the following components:
   a. Patients should complete the Social Rhythm Metric questionnaire which is a self-report instrument for tracking and quantifying daily and nightly routines, along with ratings of mood
   b. Providers need to assist patients in keeping regular routines (e.g., bed times, wake times, exercise) and minimizing the impact of events that could disrupt their moods and daily/nightly stability
   c. Providers need to maintain an interpersonal focus that concerns the resolution of the patient’s current problems (e.g., how to communicate better with one’s spouse) and developing strategies for preventing the same problems from recurring in the future.

RATONALE

IPSRT is a promising individual approach to BD patients following an acute episode. The mechanisms of action of IPSRT appear to include social rhythm stabilization, but it is not clear whether other mechanisms (e.g., interpersonal problem resolution, enhancing medication adherence) operate as well.

EVIDENCE STATEMENTS

Frank and colleagues, (2005) tested IPSRT in a large-scale maintenance trial at the University of Pittsburgh. In this study, bipolar I patients (N = 175) were randomly assigned following a mood disorder episode (acute treatment) to IPSRT plus protocol pharmacotherapy or an active comparison treatment group receiving intensive clinical management plus protocol pharmacotherapy. Although patients who received IPSRT during the acute treatment phase stabilized at the same rate as patients in intensive clinical management, those in IPSRT had longer survival times (without recurrence) during the maintenance phase of the study, regardless of whether they received IPSRT during the maintenance period. Moreover, patients who showed an ability to regulate their social routines and sleep-wake cycles during the acute phase, which was more likely to occur in IPSRT than intensive clinical management, were less likely to have recurrences during maintenance treatment. Thus, IPSRT was an effective preventative agent and, consistent with its hypothesized mechanisms, appeared to operate through the stabilization of social rhythms.

Frank and colleagues, (2005) also found that IPSRT was less effective among patients with medical co-morbidities.
Weismann et al., (2000) discusses the interpersonal psychotherapy of depression.

Monk et al., (1990) discusses the social rhythm metric - an instrument to quantify daily rhythms of life.

Miklowitz et al. (2003) in an open trial with an “historical comparison” group examined the effects of IPSRT in combination with family-focused treatment (FFT; mean 29 individual and family sessions over one year) for bipolar I and II patients (N = 30). All patients began in an acute illness episode and received standard medication management by study-affiliated psychiatrists. The involvement of family members was hypothesized to have a positive impact on patients’ willingness and ability to regulate their social routines and sleep/wake rhythms. Patients in the combined treatment were compared with 70 bipolar I and II patients who had received medication, two sessions of family education, and crisis management in the context of an earlier study. Over one year, patients in the integrated family and individual therapy group had longer delays prior to recurrence and experienced less severe depressive symptoms than patients in the historical comparison group. The effects were not attributable to differences in medication regimens or compliance.

Miklowitz et al., (2007b) randomly assigned 84 patients to intensive psychosocial intervention (30 sessions over 9 months of IPSRT, CBT, or FFT), and 68 patients were randomly assigned to collaborative care (a 3-session psychoeducational [PE] treatment). Recovery from bipolar depression after 1 year occurred in 50% of those in the 3 PE session group, versus 64% in any of the other modalities (CBT, IPSRT, FFT), and individually, 77% from FFT, 64% IPSRT, and 60% CBT. No statistically significant differences were observed in the outcomes of the 3 intensive psychotherapies. The authors concluded that intensive psychosocial treatment, as an adjunct to pharmacotherapy was more beneficial than brief treatment in enhancing stabilization from bipolar depression. However, the study excluded those with substance use disorders, those with medical contraindications to paroxetine or buproprion, or those requiring antipsychotics, thereby potentially limiting the generalizability of these studies.

EVIDENCE TABLE

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<tr>
<th>Evidence</th>
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<tbody>
<tr>
<td>1 IPSRT in BD I is an effective preventative strategy</td>
<td>Frank et al., 2005</td>
<td>I</td>
<td>Fair</td>
<td>B</td>
</tr>
<tr>
<td>2 Interpersonal psychotherapy of depression</td>
<td>Weisman, et al., 2000</td>
<td>II</td>
<td>Fair</td>
<td>C</td>
</tr>
<tr>
<td>3 Use of Social Rhythm Metric as standardized measure</td>
<td>Monk et al., 1990</td>
<td>II</td>
<td>Fair</td>
<td>C</td>
</tr>
<tr>
<td>4 IPSRT in combination with family focused treatment (FFT) is effective</td>
<td>Miklowitz et al., 2003</td>
<td>II</td>
<td>Fair</td>
<td>B</td>
</tr>
<tr>
<td>5 Effects of IPSRT, FFT, CBT is better than 3 sessions of PE</td>
<td>Miklowitz et al., 2007</td>
<td>I</td>
<td>Fair</td>
<td>B</td>
</tr>
</tbody>
</table>

LE = Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)
FAMILY THERAPY

BACKGROUND

Family therapy approaches to bipolar disorder have a long history. Fitzgerald, (1972) discussed family therapy as a way of augmenting response to lithium, and Davenport and colleagues, (1977) described the benefits of a psychoanalytic couples’ group. Only recently have approaches to family intervention become empirical. Two studies conducted in the late 1980s demonstrated the utility of psychoeducation for couples and families coping with bipolar disorder, either done on an inpatient or outpatient basis.

More recently, Miklowitz and Goldstein, (1990) developed a manual-based, 21 session intervention called family-focused treatment (FFT), which is given to patients who are stabilizing from an acute episode. The treatment consists of four components: (1) an initial assessment phase; (2) psychoeducation about the nature, course, and treatment of bipolar disorder, including the importance of medication consistency, identifying early warning signs of relapse, and implementing relapse prevention strategies; (3) communication enhancement skills, notably role-playing and rehearsal of tools for active listening and expressing positive or negative feelings; and (4) problem-solving skills.

Miklowitz and colleagues (2003) also found differential effects of FFT as a function of whether families were initially high or low in expressed emotion.

RECOMMENDATION

1. Couples and families who are coping with BD should be considered for family therapy either on an inpatient or outpatient basis. [C]
2. Family focused therapy should contain the following four components:
   a. Initial assessment,
   b. Psychoeducation about the nature, course, and treatment of BD, including the importance of medication consistency, identifying early warning signs of relapse, and implementing relapse prevention strategies,
   c. Communication and enhancement skills, notably role playing and rehearsal of tools for active listening and expressing positive or negative feelings, and,
   d. Problem solving skills.

RATIONALE

In two recently completed randomized trials, FFT and pharmacotherapy were found to delay recurrences above and beyond pharmacotherapy alone or pharmacotherapy with individual therapy.

Family interventions may prove to be cost-effective if they have a positive impact on the emotional stability of caregivers as well as patients.

EVIDENCE STATEMENTS

Fitzgerald, (1972) discussed family therapy as a way of augmenting response to lithium
Davenport et al., (1977) described the benefits of a psychoanalytic couples’ group.
Clarkin et al., (1990) in a study conducted in the late 1980s; demonstrated the utility of psychoeducation for couples and families coping with bipolar disorder, either done on an inpatient or outpatient basis
Van Gent & Zwart (1991) in a study conducted in the late 1980s, demonstrated the utility of psychoeducation for couples and families coping with bipolar disorder, conducted on either an inpatient or outpatient basis
Miklowitz and Goldstein, (1990) developed a manual based family-focused treatment (FFT).
Simoneau et al., (1999) studied 101 patients who were randomly assigned to FFT and pharmacotherapy or an active crisis management comparison treatment consisting of two sessions of family education, crisis intervention sessions as needed, and pharmacotherapy. Patients in FFT were more likely to survive the two-year follow-up without recurrence (52%) than patients in active case management (17%). Patients in FFT also had less severe depressive and manic symptoms over the two year study.


Rea et al., (2003) examined the relative effectiveness of FFT compared to individual therapy in hospitalized BD, manic patients. Both therapies included concurrent treatment with mood-stabilizing medications. The individual therapy had many of the same components as the FFT (psychoeducation, monitoring of moods, and encouragement of medication adherence) but family members were not involved. Patients in the two groups did not differ in relapse rates during the first year of treatment, but during a 2-year post-treatment follow-up, patients in FFT had fewer rehospitalizations (12%) and recurrences (28%) than patients in individual therapy (60% and 60%, respectively). Moreover, patients in FFT were less likely to require hospitalization when they did have a recurrence than patients in individual therapy. Possibly, relatives learned to identify patients’ relapses before they escalated and implemented early intervention plans (e.g., calling physicians to arrange emergency medication adjustments) before hospitalization was necessary.

Miller et al., (2004) conducted a trial on family intervention in which the results were negative. In this study, they randomly assigned 92 BD patients to pharmacotherapy with individualized family therapy, multi-family psychoeducation groups, or pharmacotherapy alone. Unlike the previous trials, the primary outcome variable was time to recovery from the acute illness episode at intake. The impact of these interventions on time to recurrence or symptom severity over time was not reported. The groups did not differ in the proportion recovered nor in the time to recovery, suggesting that certain types of family intervention may be less effective for acute stabilization than for maintenance of stability over longer intervals.

Miller et al., (2008) analyzed the results of a previous study (Miller et al., 2004) and reported that fewer depressive episodes were evident among those with high family impairment. There was a substantial proportion of drop-outs (>60%) especially among the low-impairment group. As with other family-based treatments, generalizability of the study is limited to patients who have family members willing to participate. Moreover, it is unclear whether the metric used to identify high versus low impairment is operational outside the research setting.

Justo et al., in a Cochrane review (2007) concluded that the evidence regarding FFT for bipolar disorder was inclusive given the heterogeneity of the samples.

Miklowitz et al., (2007b) randomly assigned 84 patients to intensive psychosocial intervention (30 sessions over 9 months of IPSRT, CBT, or FFT), and 68 patients were randomly assigned to collaborative care (a 3-session psychoeducational (PE) treatment). Recovery from bipolar depression after 1 year occurred in 50% of the 3 PE session group, versus 64% in any of the other modalities (CBT, IPSRT, FFT), and individually, 77% from FFT, 64% IPSRT, and 60% CBT. No statistically significant differences were observed in the outcomes of the 3 intensive psychotherapies. The authors concluded that intensive psychosocial treatment, as an adjunct to pharmacotherapy was more beneficial than brief treatment in enhancing stabilization from bipolar depression. However, the study excluded those with substance use disorders, those with medical contraindications to paroxetine or buproprion, or those requiring antipsychotics, thereby potentially limiting the generalizability of these studies.
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<tr>
<td>1</td>
<td>Development of manual-based, 21 session family focused treatment (FFT) model</td>
<td>Miklowitz &amp; Goldstein, 1990</td>
<td>II-3</td>
<td>Fair</td>
</tr>
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<td>2</td>
<td>FFT adjunct to maintenance pharmacotherapy is effective</td>
<td>Simoneau et al., 1999 Miklowitz et al., 2003 Rea et al., 2003</td>
<td>II</td>
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<tr>
<td>3</td>
<td>Family intervention does not improve recovery compared to pharmacotherapy alone.</td>
<td>Miller et al., 2004 &amp; 2008</td>
<td>I</td>
<td>Fair</td>
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<td>4</td>
<td>Positive effect among those from high impairment families</td>
<td>Miller et al., 2008</td>
<td>I</td>
<td>Fair</td>
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<tr>
<td>5</td>
<td>Intensive psychosocial treatment, as an adjunct to pharmacotherapy improved remission from BD depression</td>
<td>Miklowitz et al., 2007</td>
<td>I</td>
<td>Good</td>
</tr>
</tbody>
</table>

*LE = Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)*
CHRONIC CARE MODELS INTERVENTIONS

BACKGROUND
Over 70 reports of randomized controlled trials of collaborative chronic care models (CCMs) for mental health conditions have been published; the vast majority of these address depression in primary care, though a growing literature also supports their effectiveness for bipolar disorder and anxiety disorders. CCMs integrate well into both the primary care and mental health sectors, and as manualized interventions can be incorporated across a broad spectrum of providers and existing practice.

Unlike psychotherapies, CCMs are multi-modal interventions that include, in addition to psychotherapy, core components that support ongoing access and continuity of care for patients as well as linkages to providers and community resources and outcomes monitoring (Wagner, 1996; Bodenheimer, 2002; Badamgarav, 2003). CCMs are defined as interventions having at least 3 of 6 core CCM components as established by Wagner and colleagues, (1996). These include patient self-management support or psychotherapy, clinical information systems, delivery system redesign, decision support, health care organization support, or linkage to community resources, but do not incorporate mobile community outreach components (Badamgarav, 2003).

The CCM for bipolar disorder has been shown in three randomized controlled trials totaling more than 750 patients to improve quality of life, reduce overall affective symptoms, and improve overall functioning, and in at least one of the trials, was cost-neutral when compared to usual care (Simon, 2006; Bauer, 2006; Kilbourne, 2008). CCMs for bipolar disorder have also been shown to be effective in reducing affective symptoms and improving quality of life in more complex patients who were recently hospitalized for manic or affective symptoms (Bauer, 2006) as well as for those with co-occurring substance use (Kilbourne, 2009) and medical comorbidities (Kilbourne, 2008). Hence, CCMs likely have a role in optimizing outcomes for individuals with bipolar disorder including those with severe illness. CCMs should also be implemented in conjunction with psychotherapies, as stand-alone psychotherapies have not been shown to be effective in improving outcomes for more severely ill patients (Sajatovic, 2009; Scott, 2006). Notably, Sajatovic (2009) evaluated a stand-alone psychoeducation program without the CCM model, which was shown to not be as effective in improving outcomes compared to usual care in a more psychiatrically symptomatic patient population from community mental health programs. Scott (2006) found that CBT is most appropriate for patients in the early stages of their disorder or those who had fewer recurrent (less than 12) episodes of illness. Therefore, CCMs provide a care-organization platform (e.g., ongoing care management, outcomes assessment), through which medications and psychotherapies may be more effectively delivered.

RECOMMENDATIONS
1. Patients, who have BD, should be offered chronic care model-based interventions [B], especially when patients are more symptomatic or were recently hospitalized. [A]

DISCUSSION
The CCM for bipolar disorder has been shown in randomized controlled trials to improve quality of life, reduce overall affective symptoms, and improve overall functioning among outpatients as well as those who were recently hospitalized for manic or other affective episodes.

Simon et al., (2005) and Simon et al., (2006) in a large psychotherapy study (N=441), evaluated group psychoeducation in the context of a multicomponent intervention delivered within a managed care network. They randomly assigned bipolar patients to pharmacotherapy alone or a care-management program consisting of pharmacotherapy, structured group psychoeducation following the Life Goals model of Bauer and McBride, (1996) that was also used in Bauer et al., (2006a). This large-scale study of group psychoeducation and care management demonstrated reduction in the frequency and severity of mania in bipolar disorder; however, the effects were only observed among patients who entered with clinically significant mood symptoms.

Bauer et al., (2006a, b) randomized 330 patients from 11 VA sites around the U.S. to group-based psychoeducation combined with systematic chronic care management (CCM) or usual care. Group-based psychoeducation consisted of 5 weekly sessions based on the Life Goals program (Bauer and McBride, 1996) led by a nurse, who also followed up with patients via twice-monthly contacts and continuity procedures based on the chronic care model
The patient sample included older individuals who had been recently hospitalized and had co-occurring substance use and medical disorders. The CCM combined patient structured group psychoeducation (Life Goals) with ongoing care management that provided access and continuity of care support along with guideline dissemination and outcomes monitoring. Compared to usual VA care, PE+CCM led to 6.2 fewer weeks of mood episodes (p=0.041), and 4.5 fewer weeks of manic episodes, improved overall function (+30%; p=0.003), improved mental health-related quality of life (37.6 vs. 34.1; p=0.01), as well as treatment satisfaction. There were no effects on depressive symptoms over time. Fidelity to PE-SSM exceeded 80% in the study sample.

Other structured interventions for bipolar disorder based on the CCM include the Texas Medication Algorithm Project (Suppes, 2003).

Miklowitz, (2008) in a systematic review of 14 randomized trials that indicated the benefits of various psychotherapy approaches for BD, concluded that group PE coupled with systematic CCM led to maintained reductions in manic episodes, while treatments that focus on cognitive or interpersonal strategies (FFT, CBT, IPT) were more effective against depressive episodes.

**EVIDENCE TABLE**

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<tr>
<th>Evidence</th>
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<th>LE</th>
<th>QE</th>
<th>SR</th>
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<tbody>
<tr>
<td>1 CCMs reduce manic symptoms and improve overall quality of life</td>
<td>Lam et al., 2003, 2005</td>
<td>I</td>
<td>Good</td>
<td>A</td>
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<tr>
<td></td>
<td>Bauer et al., 2006b</td>
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<td>Simon et al., 2006</td>
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<td></td>
<td>Kilbourne 2008</td>
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<tr>
<td>2 CCMs should be offered in addition to stand-alone psychotherapies in the management of patients with bipolar disorder</td>
<td>Scott et al., 2006</td>
<td>I</td>
<td>Fair</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Sajatovic et al., 2009</td>
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*LE = Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)*
MODULE E: BIPOLAR DISORDER IN OLDER ADULTS

BACKGROUND

Bipolar disorder (BD) in later life is a chronic psychiatric disorder characterized by at least one manic or hypomanic episode and depression during a person’s lifetime. Older adults with bipolar disorder have increased psychiatric co-morbidities, such as substance abuse, PTSD, other anxiety disorders and dementia (Sajatovic, Blow & Ignacio, 2006). Later onset BD may be associated with longer episodes and be more debilitating (Young & Klerman, 1992) and it may be more difficult to achieve complete remission (Young, 2005). Older adults with bipolar disorder are reported to have higher mortality rates compared with those with major depressive disorders (Gildengers et al., 2008).

BDs are heterogeneous in origin but may be 1) Primary: a) Early onset or b) Late Onset, beginning after 50 years of age or 2) Secondary to General Medical Conditions, Substances or Medications. New onset mania in older adults also calls for neuroimaging studies to rule out tumor and stroke as causes (Hoblyn, 2004).

Large community-based epidemiologic studies are few in number, so the overall incidence and prevalence of BD in older persons is difficult to estimate. It may account for up to approximately 20% of the mood disorders seen in older persons (Sajatovic et al., 2002). Approximately more than 2.3 million or 1% of the adult population in US (0.65% of men and 0.88% of women) have experienced acute BD. Overall, 69% of older adults with bipolar disorder are female (Depp &Jeste, 2004). Between 5-19% of all geriatric patients presenting for treatment of a mood disorder are manic (Dunn & Rabins, 1996; Van Gerpen et al., 1999; Young, 1992; Young & Klerman, 1992; Aziz et al., 2006).

New onset mania in later life is rarer, with a reported prevalence rate of less than 1%, (Young & Klerman, 1992; Van Gerpen et al., 1999). Men appear to be at higher risk for mania in later life than women (McDonald & Wermager, 2002). It is estimated that older adults will represent 1/3 of the bipolar population in a few years (Sajatovic, Blow, Ignacio & Kales, 2004).

Family and Caregiver Effects

Burden experienced by caregivers of patients with BD has been associated with increased caregiver depression (Ogilvie et al., 2005), anxiety, and mental health service use. Caregiver burden is also associated with poor patient outcome. A review of published caregiver studies reported that the presence of psychiatric symptoms has led to 46% of caregivers reporting depression and 32.4% reporting mental health service use (Steele et al., 2009).

Pharmacotherapy

Prescribing medications in older adults requires careful consideration. Metabolic changes that influence pharmacokinetics include decreased absorption, decreased hepatic and renal function, decreased protein binding, and increased volumes of distribution. These changes are combined with increased risks of medical co-morbidities, concurrent medications and increased sensitivity to side effects (e.g. to anticholinergic agents). The aim of this section is to review the evidence for approved treatments for older adults with bipolar disorder. It is beyond the scope of this project to review all medications possibly used in these circumstances.

ACTION STATEMENT

Older Adults with BD who are receiving psychopharmacological treatments should be monitored closely for evidence of efficacy, side effects, toxicity and interactions with other medications. They should also be considered for evidence-based psychotherapeutic interventions and caregiver supports.

RECOMMENDATIONS

1. The likelihood of possible benefits with all medications used to treat BD in older adults needs to be balanced against potential risks.
2. Polypharmacy in older adults should be avoided.

3. Lithium can be used in older adults to treat acute mania, as maintenance, and also to treat bipolar depression.

4. Overall, valproate appears to be better tolerated than lithium in older adult patients with BD.

5. Carbamazepine is an alternative treatment to lithium for older patients with severe cardiovascular or renal disease.

6. Generally, benzodiazepines should be used with caution. However, they may be needed to treat extreme agitation. Care should be taken in the presence of comorbid medical conditions or possible drug-drug interactions. Older adults may be more sensitive than younger adults to central effects of benzodiazepines leading to ataxia, confusion, disinhibition, and delirium. If needed, a shorter-acting benzodiazepine which is metabolized by conjugation could be used, e.g., lorazepam.

7. The role of antidepressants in the management of BD is complex and sometimes controversial. Older adults are more likely than younger adults to develop initial manic episodes during antidepressant therapy. The provider should use tricyclics with caution in the older populations as these have been shown to cause an increased risk of treatment-emergent affective switches in this age group. It has been reported that the first line treatments for bipolar depression are mood stabilizers, and that adjunctive antidepressants should be used with caution. However, older adults with BD treated with a mood stabilizer and an antidepressant may be less likely to attempt suicide.

8. The treatment of secondary mania in older adults is relatively similar to the treatment of primary mania and typically does not usually require prophylaxis unlike primary mania. However, there may be increased sensitivity to side effects of medications, so dosages should be modified. Mania associated with structural central nervous system disease may respond better to carbamazepine or valproate. Newer anticonvulsant agents, such as topiramate and lamotrigine, have not been specifically studied yet in this patient population. Secondary

9. The preferred treatment for older adults with acute mania is an atypical antipsychotic (e.g. risperidone, quetiapine, olanzapine, and aripiprazole) combined with a mood stabilizer. Comorbid medical conditions such as diabetes, constipation, hypotension, weight may influence medication choice.

10. The provider needs to consider that mood stabilizers may impact cognitive functioning in older adults. Adverse effects were reported to be least likely in those taking lamotrigine or oxcarbazepine, intermediate with lithium, and greatest with valproate, carbamazepine, and topiramate. In a study of older adults with BD, lithium was no more likely to impair cognition than other therapies, but this study was limited by low statistical power.

11. There is growing concern regarding metabolic issues related to second-generation antipsychotics. The risk is greatest with clozapine and olanzapine, followed by quetiapine and risperidone, and then followed by aripiprazole and ziprasidone. If an older individual is to be maintained on a second-generation antipsychotic, baseline measures of weight, waist circumference, fasting blood glucose, and HbA1c should be obtained. Weight or waist circumference can be monitored every two months and fasting blood glucose checked every six months or sooner if there is significant weight gain.

12. All pharmacological interventions for older adults with BD should be combined with cognitive, behavioral, family, interpersonal and social rhythm therapies in conjunction with psychoeducation and chronic disease management.

RATIONALE
Although there is a distinct paucity of research in this area, it is important to understand how older adults with BD may present, and respond, to currently available approved treatment options. Consideration must be given to pharmacokinetic changes commonly seen in older adults, which in turn may impact medication absorption, distribution, metabolism and excretion.

Unfortunately, as of late 2009, there have been no large, randomized controlled trials to provide
definitive evidence based therapies in older adults with BD. Hopefully, in the future, large, randomized controlled trials will provide evidence to better inform clinicians treating this population.

EVIDENCE STATEMENTS

LITHIUM

Previously considered the first choice treatment for older adults with BD (Oshima & Higuchi, 1999), new prescriptions for lithium have decreased while those for valproate have increased (Shulman et al., 2003). This may be related to a lack of efficacy of lithium in mood states more commonly seen in older adults (e.g. mixed episodes, dysphoric mania, rapid cycling and secondary mania). Lithium is approved for the treatment of acute mania in Bipolar I disorder as well as maintenance treatment. After assessing the individual’s baseline medical condition; electrolytes, renal and thyroid function, and an electrocardiogram should be obtained. No systematic studies in older adults with BD have been conducted.

There are a few uncontrolled retrospective studies (Chen et al., 1999; Hewick et al., 1977; Himmelhoch et al., 1980; Sanderson, 1998; Stone, 1989; Van der Velde, 1970) and a few prospective studies that have suggested efficacy and tolerability of lithium in older adults with BD (Abou-Saleh and Coppen, 1983; Murray et al., 1983; Sajatovic et al., 2005). The latter study included 98 Bipolar I Disorder subjects aged 55 years or older. Lithium (mean dose 750 mg/day) significantly delayed time to intervention for mania. Lamotrigine (mean dose 240 mg/day) significantly delayed time to intervention for any mood episode and for depressive episodes vs. placebo (Sajatovic et al., 2005).

VALPROATE

Valproic acid (or valproate) is increasingly used in older patients with BD. This may be related to some of the efficacy and tolerability issues seen with lithium in this age group. It is approved for the treatment of acute mania in Bipolar I disorder. Valproate may be used as an augmentation strategy in lower doses. Valproate prescribing information includes black box warnings regarding the risks of hepatotoxicity, teratogenicity, and pancreatitis. However, the risks of hepatotoxicity and pancreatitis appear to decrease with age. Overall, valproate would be a reasonable choice for treatment when using a mood stabilizer with response rates of 50-65%, unless the patient has hepatic failure. No systematic studies in older adults with BD have been conducted.

There are limited case reports and case series data regarding the use of valproate in BD. In these reports, mean valproate doses were approximately 750 to 1500 mg/day, with mean valproate serum concentrations of 50 to 75 mg/mL.

CARBAMAZEPINE

Carbamazepine is occasionally used in both younger and older patients with BD, but its adverse effects and drug interaction profile limits its use in older adults who are more prone to experience these problems. However, carbamazepine may be a good choice in older patients who have BD and chronic nerve pain. No systematic studies in older adults with BD have been conducted.

There are very limited case reports and case series data regarding the use of carbamazepine in older adult BD patients (Cullen et al., 1991; Kellner & Neher, 1991; Sanderson, 1998; Schneier & Kahn, 1990).

LAMOTRIGINE

The FDA, for maintenance treatment in adults with BD, approved Lamotrigine in 2003. Its tolerability, efficacy for the depressive symptoms, and relatively limited drug interactions make it particularly useful
in older adults.
No systematic studies in older adults with BD have been conducted. Limited case report data in older adults suggests that lamotrigine may help delay relapse or recurrence of bipolar depression (Robillard & Conn, 2002).
In a post-hoc analysis, controlled data suggested lamotrigine maintenance delayed overall and depressive episodes and was well tolerated in older adults with Bipolar I Disorder (Sajatovic et al., 2005). See section above on lithium for further details. Both treatments were generally well tolerated, with the most common adverse events with lamotrigine being back pain and headache. No serious rash was reported.
The possible benefits of lamotrigine need to be weighed against potential risks in older adults. Prescribing information includes a boxed warning regarding the risk of serious rashes, including Stevens-Johnson syndrome. The risk of rash may be higher when given in combination with valproate, or if the recommended initial dose or dose escalation of lamotrigine are exceeded. However, lamotrigine is generally very well tolerated in older adults (Bowden et al., 2004; Brodie et al., 1999).

ANTIPSYCHOTICS

Previously, first-generation antipsychotics were often prescribed for psychotic symptoms associated with depression or mania, but adverse events such as emotional blunting, and neurological side effects have limited their use.
The use of second-generation antipsychotics in the acute treatment and maintenance of adults with BD has expanded. As a class, the second-generation antipsychotic medications are associated with increased risk of stroke and death in those with dementia. There is currently no data to suggest that this is also the case for older adults with BD (Brooks et al., 2009).

Both first-generation and second-generation antipsychotics carry class warnings for neuroleptic malignant syndrome and tardive-dyskinesia (TD). Prescribing information for both first- generation and second-generation antipsychotics includes a boxed warning that these agents may increase mortality (mostly due to cardiac and infectious causes) in older adults with dementia- related psychosis. Their use remains controversial with a report of lower mortality in older adults with second-generation compared to first-generation antipsychotics (Nasrallah, White, & Nasrallah, 2004). Thus, even if used for short periods of time, the choice of antipsychotics may impact the health and functioning of older patients with BD.

FIRST-GENERATION ANTIPSYCHOTICS

The FDA approved chlorpromazine in 1973, for use in acute mania.
There are limited data case reports on the use of first-generation antipsychotics in older adults with BD (Chen et al., 1999; Stone, 1989).
The incidence of TD is higher in older adults (26%, 52%, and 60%, after 1, 2, and 3 years, respectively (Jeste et al., 1995) than in younger adults (5% per year) (Kane, Woerner, & Lieberman, 1988). Higher potency antipsychotics (e.g., haloperidol, fluphenazine) have a higher incidence of extrapyramidal symptoms, which may increase agitation. Older patients experience extrapyramidal symptoms more often than younger patients (Lancot et al., 1998). First-generation antipsychotics (particularly higher potency agents) may also exacerbate the depressive component of BD (Ahlfors et al., 1981; Sachs & Thase, 2000).
The lower potency first-generation antipsychotics chlorpromazine and thioridazine have greater anticholinergic effects. In older adults, these side effects are associated with confusion, cognitive impairment and even delirium. Sedation and orthostatic hypotension are also more common among low-potency compared to high-potency first-generation antipsychotics.
Cardiac arrhythmias may also occur: Thioridazine has been associated with abnormal QT intervals and ventricular arrhythmias (Timell, 2000). Haloperidol has been associated with torsade de pointes and increased risk of sudden death, but the greatest risk may be with thioridazine (Glassman & Bigger, 2001). Therefore, baseline EKG’s are needed and histories reviewed for any syncopal episodes.
SECOND-GENERATION ANTIPSYCHOTICS

Second-generation antipsychotics are now prescribed more often than first-generation antipsychotics in the treatment of older adults (Jeste, Rockwell, Harris, Lohr, & Lacro, 1999). They have enhanced tolerability, and show efficacy in treatment of mood disorders and for the negative symptoms of psychosis. Aripiprazole, olanzapine, risperidone, quetiapine and ziprasidone are approved for use in acute mania; aripiprazole and olanzapine for use in maintenance and the combination of olanzapine and fluoxetine for the treatment of acute depression in BD.

There are limited data on the use of second-generation antipsychotics in older adult BD patients (Gareri et al., 2006; Madhusoodanan, Brenner, Araujo, & Abaza, 1995; Sajatovic et al., 2008; Shulman, Singh, & Shulman, 1997).

A vital safety concern with second-generation antipsychotics in older adults is the increase in mortality with these agents observed in older adults with dementia. In 2005, the FDA noted that in 17 controlled trials including 5,106 older adult demented patients with behavioral disorders; olanzapine, risperidone, quetiapine, and aripiprazole yielded an approximately 1.7 fold (typically increased from 2.6% to 4.5% with 10 weeks exposure) increase in mortality, primarily due to cardiovascular related events (e.g., heart failure, sudden death) or infections (mostly pneumonia) (Brooks et al., 2009). The FDA has also mandated prescribing information warnings of the increased risk of developing hyperglycemia and diabetes mellitus from all second-generation antipsychotics. The greatest risk appears to be with clozapine and olanzapine, followed by risperidone, quetiapine, ziprasidone and aripiprazole in that order.

OLANZAPINE

Olanzapine is approved as monotherapy for the treatment of acute mania/mixed episode in Bipolar I disorder. Combination treatment with lithium or valproate as well as maintenance treatment in bipolar disorder is also approved. The olanzapine/fluoxetine combination has been approved for bipolar depression. A rapid-acting intramuscular formulation of olanzapine has been approved for the treatment of agitation associated with bipolar I mania in adults. However, olanzapine’s use has been limited by safety and tolerability concerns including sedation, weight gain, metabolic problems, and risks of increased mortality and cerebrovascular accidents in dementia patients. There are very limited data regarding the use of olanzapine in older adults with BD (Nicolato, Romano-Silva, et al., 2006; Samuels & Fang, 2004).

RISPERIDONE

Risperidone is approved as monotherapy for the treatment of acute manic or mixed episodes in Bipolar disorder I. It is also approved for combination treatment with lithium or valproate. No systematic studies in older adults with BD have been conducted.

There are very limited data regarding the use of risperidone in older adults with BD (Madhusoodanan et al., 1995). There are few studies regarding the use of long-acting injectable risperidone in older adults with BD (Hudson-Jessop, Hughes, & Brinkley, 2007; Kissling, Glue, Medori, & Simpson, 2007; Lasser et al., 2004; Yumru, Eren Ozen, Savas, & Selek, 2006).

QUETIAPINE

Quetiapine is approved for the treatment of acute mania in bipolar I disorder as monotherapy or in combination with either lithium or valproate. Quetiapine’s use has been limited by safety and tolerability concerns including sedation, weight gain, metabolic problems, and postural hypotension. As a second-generation antipsychotic, it also poses an increased risk of mortality in dementia patients.

No systematic prospective studies in older adults with bipolar disorder have been conducted.

There are very limited data regarding the efficacy of quetiapine in older adults with BD (Madhusoodanan, Brenner, & Alcantra, 2000; Tariot, Salzman et al., 2000).

In a post hoc analysis of two double blinded randomized parallel groups controlled, safety and
efficacy trials, 28 older adults aged 55 and above taking quetiapine were compared to 31 taking placebo. Significant improvement was reported in YMRS scores with an effect size of 0.92. Side effects reported were dry mouth, somnolence, insomnia, weight gain and dizziness compared to placebo (Sajatovic et al., 2008).

**ARIPIPRAZOLE**

Aripiprazole is approved for the treatment of acute mania as monotherapy and adjunctive therapy (added to lithium or valproate), for bipolar maintenance as monotherapy, and for schizophrenia. A rapid-acting intramuscular formulation of aripiprazole is approved for the treatment of agitation associated with BD, manic or mixed episodes.

No systematic studies in older adults with bipolar disorder have been conducted.

There are limited data regarding the use of aripiprazole in older adults with BD. In an open-label, 12-week prospective trial in 20 older adults with Bipolar I Disorder, adjunctive aripiprazole (starting with 5 mg/day and gradually increasing, mean final dose 10.3 mg/day) found significant reductions in mean depression and mania scores compared to baseline (Sajatovic et al., 2008).

One case report described improvement in symptoms of mania as well as Parkinson’s disease in an older adult woman, when olanzapine 5 mg/day was replaced by aripiprazole, starting at 7.5 mg/day and gradually titrating up to 40 mg/day (Gupta, Chohan, & Madhusoodanan, 2004).

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**PSYCHOSOCIAL INTERVENTIONS IN OLDER ADULTS**

There is an increasing body of evidence supporting the use of psychosocial interventions for individuals with BD. However, to date there remains limited data regarding the efficacy of such interventions in older adults with BD. Thus, clinicians are left to extrapolate from studies of younger
adults with BD or older adults with depressive disorders. Psychotherapeutic interventions are useful in older adults with depression, particularly cognitive behavioral therapy (CBT). A recent meta-analysis reviewed five randomized controlled trials (153 participants) that suggested CBT was more effective than a waiting list control condition. (Wilson, Mottram & Vassilas, 2008)

Integrated appropriate psychosocial interventions for older adults with depression include psychoeducation, family counseling, and visiting nurse services as part of a treatment program and are recommended by an expert consensus guideline (Alexopoulos et al., 2001). This expert consensus guideline also suggested that the preferred psychotherapy techniques for treating depression in older patients were CBT, supportive psychotherapy, problem-solving psychotherapy, and interpersonal psychotherapy (Alexopoulos et al., 2001).

Integrated psychosocial interventions may also benefit older patients with BD, however currently the data remains limited. In one report of 441 mixed-age (mean age 44.2 years) BD patients, a systematic care management plan (structured group psychoeducation; monthly telephone monitoring; and feedback to, and coordination with, a mental health treatment team) was provided by nurse care managers and yielded lower mean mania ratings over 24 months (Simon, Ludman, Bauer, Unutzer & Operskalski, 2006). In another randomized controlled trial of 306 mixed-age (mean age 46.6 years) veterans with BD, a collaborative model for chronic care (group psychoeducation; nurse care coordinators to improve information flow, access to care, and continuity of care; and clinician decision support with simplified practice guidelines) reduced weeks in (primarily manic) mood episodes, and improved social role function, mental quality of life, and treatment satisfaction over 36 months (Bauer et al., 2006a).

Taken together, the above suggest the potential utility of psychotherapy and psychosocial interventions in older adults with BD, and the need for studies of these interventions in this population.
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