

Management of Bipolar Disorder in Adults (BD)

May, 2010



VA/DoD CLINICAL PRACTICE GUIDELINE FOR MANAGEMENT OF BIPOLAR DISORDER IN ADULTS

**Department of Veterans Affairs
Department of Defense**

GUIDELINE SUMMARY

Prepared by:

The Management of Bipolar Disorder Working Group

With support from:

**The Office of Quality and Performance, VA, Washington, DC
&
Quality Management Division, United States Army MEDCOM**

QUALIFYING STATEMENTS

The Department of Veterans Affairs (VA) and The Department of Defense (DoD) guidelines are based on the best information available at the time of publication. They are designed to provide information and assist in decision-making. They are not intended to define a standard of care and should not be construed as one. Also, they should not be interpreted as prescribing an exclusive course of management.

Variations in practice will inevitably and appropriately occur when providers take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in any particular clinical situation.

Version 2.0 – 2010

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For Appendices A, C, F, and G please see the full guideline at: www.healthquality.va.gov

INTRODUCTION

The Clinical Practice Guideline Update for the Management of Bipolar Disorders (BD) was developed under the auspices of the Veterans Health Administration (VHA) and the Department of Defense (DoD) pursuant to directives from the Department of Veterans Affairs (VA). VHA and DoD define clinical practice guidelines as:

“Recommendations for the performance or exclusion of specific procedures or services derived through a rigorous methodological approach that includes:

Determination of appropriate criteria such as effectiveness, efficacy, population benefit, or patient satisfaction; and

Literature review to determine the strength of the evidence in relation to these criteria.”

The VHA published the first Clinical Practice Guideline for the Management of Person with Psychosis in 2001. The original publication was aimed to assist medical care providers in all aspects of mental health care for a cluster of medical conditions characterized as mood disorders. The overall expected outcomes of successful implementation of the guideline were to:

- Formulate an efficient and effective assessment of the patient's complaints
- Optimize the use of therapy to control symptoms
- Minimize preventable complications and morbidity
- Achieve satisfaction and positive attitudes regarding the management of psychosis
- Promote recovery to the fullest extent possible

The current publication aims to update the evidence base of the 2001 Guideline. However, it is focused on management of patients with a specific diagnosis of Bipolar Disorder (BD). Other VA/DoD clinical practice guidelines that have been developed since 2001 address other mental health conditions that were included in the original psychosis guideline. (See www.healthquality.va.gov)

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. VHA has been rapidly moving from an inpatient to an outpatient model for the provision of general and mental health services. Primary care providers also provide continuing general medical care for patients with BD, understand patients' life circumstances and monitor their progress over time. 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. The goal of this 2009 update of VA/DoD guideline is to provide education and guidance to primary care clinicians, researchers and other health professionals as they treat patients with Bipolar Disorder.

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 primary care and 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.

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.
- Individuals with bipolar disorder are currently treated in a range of VHA/DoD settings, including primary-care services, general mental health services and specialist secondary-care mental health services.

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.

TARGET POPULATION:

Adults (18 years of age or older) with a BD diagnosis including:

- Adults who meet the standard (DSM IV-TR) diagnostic criteria of bipolar disorder.
- Adults with bipolar disorder whether they present with mania, hypomania, depression, or mixed episodes, or are in stable condition in maintenance phase.
- Adults with bipolar disorder and significant comorbidities, such as substance misuse or anxiety disorder.
- Consideration will be given to the needs of: pregnant women, older people and those with a range of cognitive impairments.

AUDIENCES

Health care providers and other healthcare professionals working in the clinical settings, who have direct contact with, and make decisions concerning, the care of patients with bipolar disorder.

SCOPE OF THE GUIDELINE

- Offers best practice advice on the care of adults who have a clinical working diagnosis of BD

- Provides a systematic approach to assessment and diagnosis for BD.
- Addresses assessment of suicidal ideation and prevention of suicide
- Covers drug and non drug treatment and management of manic and hypomanic episodes, depressive episodes, mixed affective states and management of prophylaxis in the maintenance phase of the disease
- Specifically addresses medication classes including lithium, antiepileptics, antipsychotics, and antidepressants and builds on the appraisal of new drugs for bipolar disorder
- Includes considerations of shared care between specialty mental health services and primary care
- Examines and incorporates the body of evidence on psychotherapies and psychoeducation
- Includes emerging evidence regarding the application of Chronic Care Models as effective intervention packages for patients with BD
- Specifies key elements in the evaluation of patients with BD including urine drug screening and other standardized assessment/evaluation tools and processes
- Specifies key elements in the evaluation of patients with BD including monitoring of drug serum concentration and other standardized assessment/evaluation tools and processes
- Addresses specific considerations in the treatment of older patients with BD.
- Addresses indications for consultation and referral to specialty care
- Does not cover the management of patients with other physical or psychiatric conditions except in the presence of BD, and does not address children or adolescents

DEVELOPMENT PROCESS

The development process of this guideline follows a systematic approach described in “Guideline-for-Guidelines,” an internal working document of the VA/DoD Evidence-Based Practice Working Group that requires an ongoing review of the work in progress. Appendix A clearly describes the guideline development process followed for this guideline.

In the development of this guideline, the Working Group relied heavily on 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]

National Institute for Health and Clinical Excellence (NHS). Bipolar disorder; The management of bipolar disorder in adults, children and adolescents, in primary and secondary care; London (UK), NICE Clinical Guideline 38; National Collaborating Centre for Mental Health; July 2006 [Referred throughout document as NICE, 2006]

Yatham LN, Kennedy SH, O’Donovan C, et al., Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009, *Bipolar Disorders* 2009; 11: 225-255

Search for additional research published since the previous 2001 VHA/DoD guideline and until May 2009 reveals that considerable progress has been made in BD research over the period separating these two works. The literature was critically analyzed and evidence was graded using a standardized format. The evidence rating system for this document is based on the system used by the U.S. Preventive Services Task Force (USPSTF).

EVIDENCE RATING SYSTEM

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

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. A complete bibliography of the references found in this guideline can be found in [Appendix G](#).

This Guideline is the product of many months of diligent effort and consensus building among knowledgeable individuals from the VA, DoD, academia, and a guideline facilitator from the private sector. An experienced moderator facilitated the multidisciplinary WG. The draft document was discussed in 2 face-to-face group meetings. The content and validity of each section was thoroughly reviewed in a series of conference calls. The final document is the product of those discussions and has been approved by all members of the Working Group.

The list of participants is included in [Appendix F](#) to the guideline.

IMPLEMENTATION

The guideline and algorithms are designed to be adapted by individual facilities in considering needs and resources. The algorithms serve as a guide that providers can use to determine best interventions and

timing of care for their patients to optimize quality of care and clinical outcomes. This should not prevent providers from using their own clinical expertise in the care of an individual patient. Guideline recommendations are intended to support clinical decision-making and should never replace sound clinical judgment.

Although this guideline represents the state of the art practice on the date of its publication, medical practice is evolving and this evolution requires continuous updating of published information. New technology and more research will improve patient care in the future. The clinical practice guideline can assist in identifying priority areas for research and optimal allocation of resources. Future studies examining the results of clinical practice guidelines such as these may lead to the development of new practice-based evidence.

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STRUCTURE OF THE GUIDELINE:

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

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.

Three 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: Pharmacotherapy Interventions

Module F: Specific Recommendations for Management of Older Persons with BD

The Full Guideline includes Appendices:

- A. Guideline Development Process
- B. Assessment of Dangerousness to Self or Others
- C. PICO Questions Guiding the Literature Search
- D. Drug Tables
- E. Acronym List
- F. Participant List
- G. Bibliography

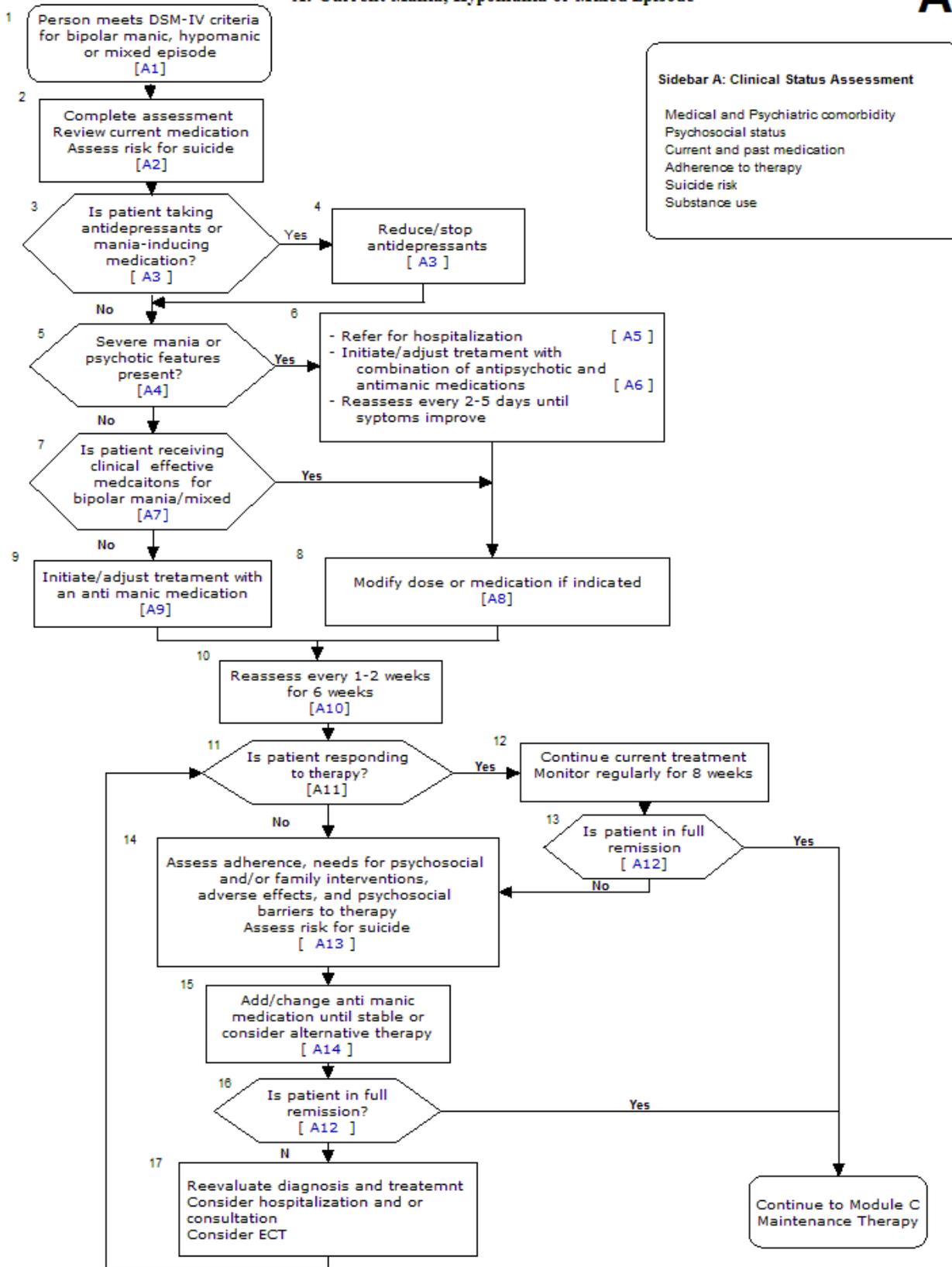
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**Management of Persons with Bipolar Disorders
A: Current Mania, Hypomania or Mixed Episode**

A



3/22/2010

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, hypomanic, 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)^a

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).

^a *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

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

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.

RECOMMENDATIONS

1. Antidepressants or other manic inducing substances should be stopped in patients experiencing a manic, hypomanic, or mixed manic episode. [B]
2. 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.

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
- Confusion (incoherence)
- Catatonic behavior (e.g., motor immobility or excessive agitation)
- Extreme negativism or mutism
- Peculiar voluntary movement

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. (See Appendix B: [Assessment of Dangerous to Self or Others](#).)
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

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]

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 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.

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]

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

	Likely to be Beneficial [SR]	Trade off between Benefit and Harm [SR]	Unknown	Unlikely to Be Beneficial or May be Harmful
Mania	Lithium, valproate, carbamazepine, aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone [A] Combining (lithium or valproate) with aripiprazole, olanzapine, quetiapine, or risperidone [A]	Clozapine [I] Oxcarbazepine [I]		Gabapentin [D] Lamotrigine [D] Topiramate [D] Antidepressant monotherapy [C]
Mixed Episode	Valproate, carbamazepine, aripiprazole, olanzapine, risperidone, or ziprasidone. [A]	Clozapine [I] Lithium [I] Oxcarbazepine [I] Quetiapine [I]		Gabapentin [D] Lamotrigine [D] Topiramate [D]

SR = Strength 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
(See [Table E - 1 Adverse Events – Lithium](#); [Table E - 4 Adverse Events Antiepileptic Medications](#); [Table E - 6 Adverse Events - Antipsychotics](#))
 - 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] ([Table E - 1 Adverse Events – Lithium](#); [Table E - 4 Adverse Events Antiepileptic Medications](#); [Table E - 6 Adverse Events - Antipsychotics](#))
 - 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]. (See [Table E-8 Monitoring Parameters for Metabolic Adverse Effects in Second Generation Antipsychotics.](#))
 - 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]

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

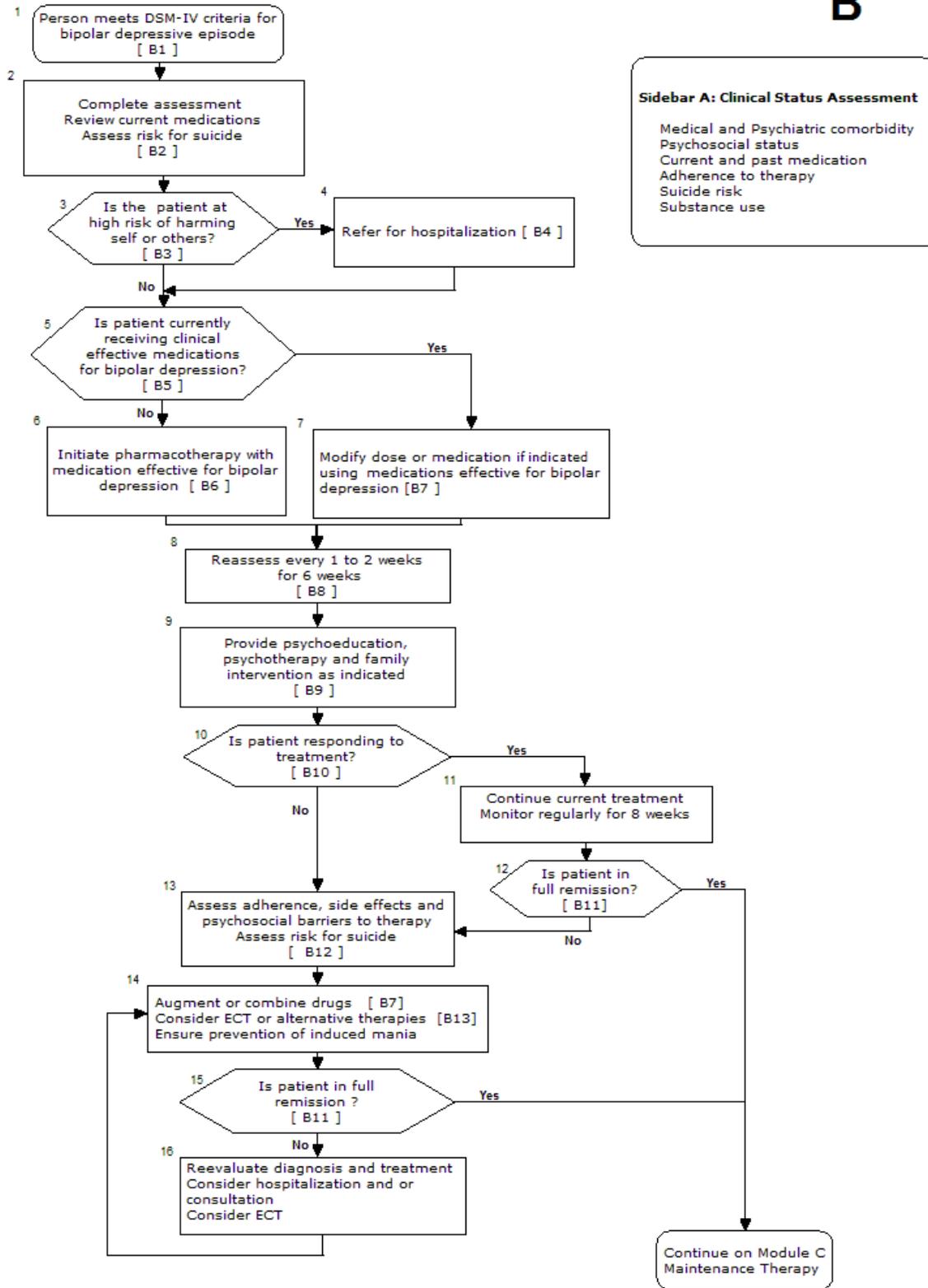
Patients whose mania or mixed episode does not respond to adequate doses of a single medication should be receiving more aggressive medication treatment or hospitalization.

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) [B] 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]
-

**Management of Persons with Bipolar Disorders
B: Current Bipolar Depressive Episode**

B



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

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

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: Assessment of 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>)

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.

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, bupropion, 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

Likely to be Beneficial [SR]	Trade off between Benefit and Harm [SR]	Unknown	Unlikely to Be Beneficial or May be Harmful
<ul style="list-style-type: none"> - Lithium [B] - Quetiapine (in BD types I & II) [A] Lithium with adjunctive lamotrigine [A] 	<ul style="list-style-type: none"> - Olanzapine/Fluoxetine [B] - Olanzapine [C] - Lamotrigine [B] Augmentation with SSRI, SNRI, bupropion, and MAOI [C] 	<ul style="list-style-type: none"> - Carbamazepine - Clozapine - Haloperidol - Oxcarbazepine - Risperidone - Topiramate - Valproate - Ziprasidone 	<ul style="list-style-type: none"> - Aripiprazole monotherapy [D] - Gabapentin [D] - Antidepressant monotherapy [D]

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]

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]

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

BACKGROUND

Adjunctive 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]
3. 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]
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]

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-11. 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]

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, 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] (See [Table E - 1 Adverse Events – Lithium](#); [Table E - 4 Adverse Events Antiepileptic Medications](#); [Table E - 6 Adverse Events - Antipsychotics](#))

- c. Monitoring of serum concentration for lithium and other appropriate blood work to maintain efficacy and avoid toxicity [B] (See [Table E - 5 Recommended Pharmacotherapy Monitoring](#))
 - d. For antipsychotics monitor weight (BMI), waist circumference, blood pressure, BMI, plasma glucose and fasting lipids [C]. (See [Table E - 8 Monitoring Parameters and Frequency for Metabolic Adverse Effects Secondary to Second Generation Antipsychotics](#))
 - 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 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]

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

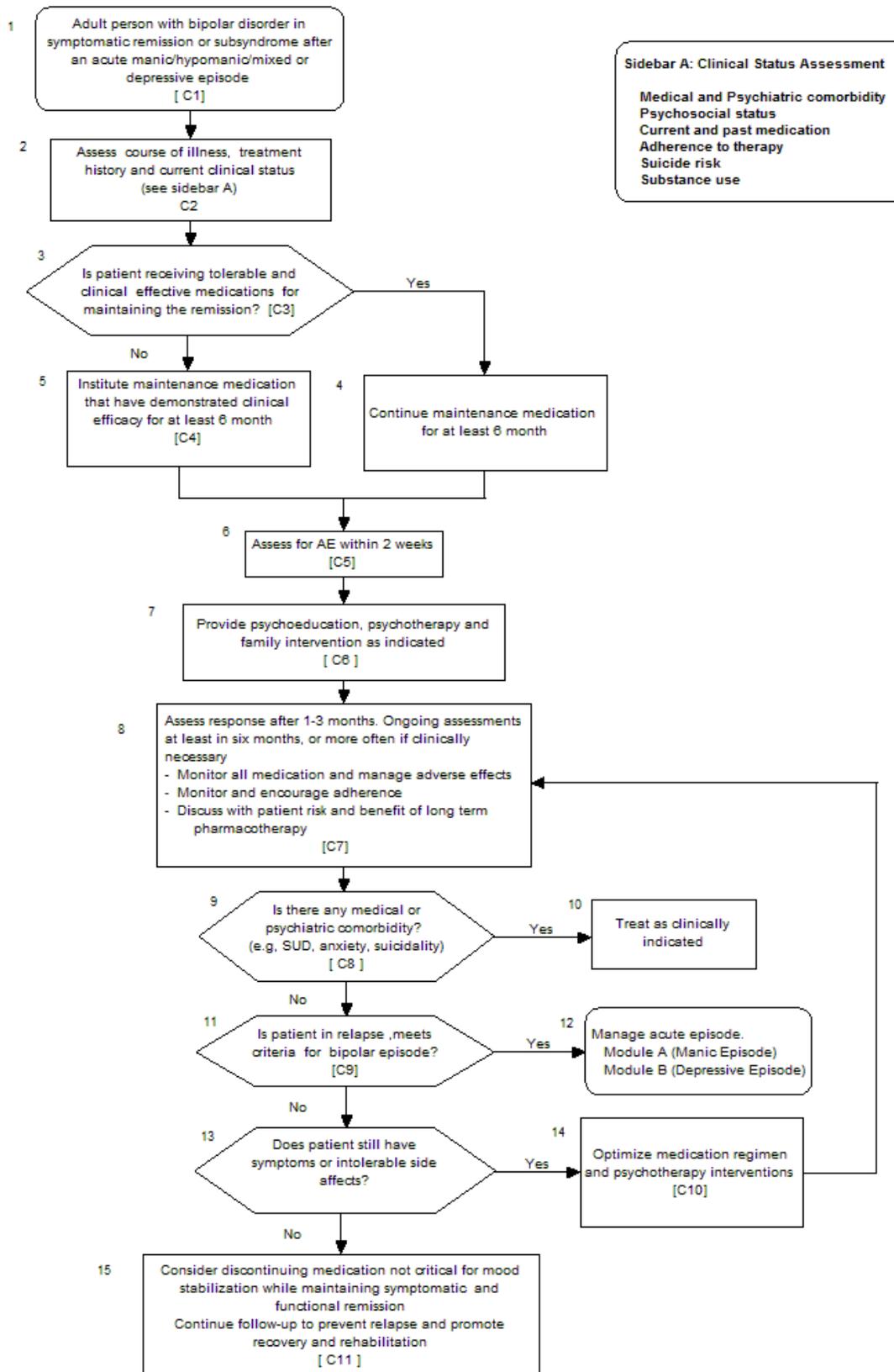
ECT should be utilized for the treatment of severe and refractory bipolar depression in patients who consent and have no absolute medical contraindications.

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.

Management of Persons with Bipolar Disorders [BD]
Module C: Maintenance

C



MODULE C – MAINTENANCE/PROPHYLAXIS PHASE

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]

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.

ACTION STATEMENT

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

Table C - 1 Clinical Status Assessment

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

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

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

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

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

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

See [Table E - 1 Adverse Events – Lithium](#); [Table E - 4 Adverse Events Antiepileptic Medications](#); [Table E - 6 Adverse Events - Antipsychotics](#)

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]

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] (See Module E: [Table E - 1 Adverse Events – Lithium](#); [Table E - 4 Adverse Events Antiepileptic Medications](#); [Table E - 6 Adverse Events - Antipsychotics](#))
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] ([Table E - 5 Recommended Pharmacotherapy Monitoring](#))
3. For antipsychotics monitor weight (BMI), waist circumference, blood pressure, plasma glucose and fasting lipids annually [B]. (See [Table E - 8 Monitoring Parameters and Frequency for Metabolic Adverse Effects Secondary to Second Generation Antipsychotics](#))
4. Adherence to medication therapy should be routinely evaluated at each visit. Reasons for noncompliance should be explored with the patient. [A]
5. Assess any changes in patient’s family and community support (e.g., housing, care givers, employment, income, social networks) [C]

C-8. Is there any Medical or Psychiatric Comorbidity (e.g., SUD, anxiety, suicidality, personality disorders, ADHD)?

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. Manage co-occurring Substance Use Disorders, including nicotine disorders in patients with BD using the VA/DoD guidelines for SUD and for Tobacco Use while continuing to manage the BD according to this guideline. 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.

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-11. 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-focused 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.

Psychochorducation

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]

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]

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.

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.

RECOMMENDATIONS

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.

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. 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.

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]

MODULE E: PHARMACOTHERAPY INTERVENTIONS

LITHIUM

BACKGROUND

Lithium has been used to treat bipolar disorder for 60 years and is the most extensively studied agent for the treatment of bipolar disorder. Lithium has established efficacy in the treatment of acute mania and as preventive maintenance therapy for both mania and depression although it is more effective in preventing mania. Lithium's established therapeutic range and linear pharmacokinetics assist the clinician when making dose adjustments or assessing therapeutic response. Lithium is almost entirely eliminated via glomerular filtration in the kidney, making dose adjustments based on kidney function necessary. Lithium toxicity is related to its serum concentration, with tremor occurring at concentrations within the therapeutic range and more serious CNS effects (confusion, ataxia, seizures and coma) occurring at concentrations above the therapeutic range. Other common adverse effects of lithium are not concentration related such as hypothyroidism, polyuria and polydipsia, leukocytosis, dermatologic disorders. Lithium is also involved in a number of drug and food interactions that can increase or decrease lithium concentrations.

ADVERSE EVENTS

Table E - 1. Adverse Events – Lithium

<p>Many of lithium's adverse effects are dose or serum concentration related.</p> <ul style="list-style-type: none">• Acne• Alopecia• Cognitive or memory impairment• Dermatologic (macular popular eruptions, exfoliative dermatitis, follicular eruptions)• Polyuria/dypsia• Diabetes Insipidus• Drug interactions• Encephalopathy• GI complaints, e.g., nausea, vomiting, diarrhea, anorexia• Hypothyroidism• Increased parathyroid hormone• Leukocytosis• Muscle weakness (transient)• QRS widening• Renal complications (tubular acidosis, decreased glomerular filtration rate, nephritic syndrome, and possibly interstitial fibrosis, tubular atrophy or glomerular sclerosis with long term exposure• Teratogenic (Pregnancy Category D)• Thrombocytosis• Toxicity• Tremor• T-wave changes• Weight gain

Table E - 2. Signs, Symptoms and Management of Lithium Toxicity

Lithium Concentration (12-hours post dose unless specified)	Interpretation Signs & Symptoms of Toxicity	Management
1.2 – 1.5 mEq/L	Warning of potential serious toxicity New onset or worsening of tremor, nausea, vomiting, diarrhea, drowsiness, sluggishness	Hold lithium until concentration returns to therapeutic range. Identify causes of toxicity: drug-drug & drug-diet interactions, dosing errors. If a cause cannot be identified, then evaluate the patient’s kidney function
1.6 – 2.5 mEq/L	Serious, but not considered life-threatening Coarse, irregular tremor, apathy, sluggishness, drowsiness, sleepiness, speech difficulty, smaller myoclonic twitching, muscular weakness, ataxia, and small increase in serum creatinine	Hold lithium; determine when last dose taken; repeat lithium concentration ≤ 3 hours (if dose not taken in the past 12 hours); assess fluid status, electrolytes, and renal function. Assess for drug-drug & drug-diet interactions. Admission may be necessary to manage fluid and electrolytes.
>2.5 mEq/L	Severe toxicity; >3.5 mEq/L is a medical emergency. Nausea, vomiting, diarrhea, renal failure, hyperreflexia, myoclonic and choreoathetoid movements, ataxia, dysarthria, coarse tremor, confusion, delirium, hallucinations, seizures, stupor, and coma.	Admit patient for management and assessment.

Table E - 3. Lithium Drug Interactions

↑ Li Concentration	↓ Li Concentration	Other Interactions
Thiazide diuretics	Increased sodium intake	Neurotoxicity
Furosemide	Sodium bicarbonate antacids	Antipsychotics
Caffeine via diuresis	Theophylline	Carbamazepine
Desmopressin	Verapamil	Methyldopa
Angiotensin converting enzyme inhibitors (ACEIs)	Osmotic diuretics	SSRIs
Angiotensin receptor blockers (ARBs)		MAOIs
Nonsteroidal anti-inflammatory drugs (except sulindac)		Diltiazem
Reduced sodium intake		Verapamil
		Lithium effect on:
		Amphetamines – decreased stimulatory effects
		Chlorpromazine – reduced concentrations
		Neuromuscular blocking agents – enhanced
		Potassium iodide – enhance lithium’s thyroid toxicity

Other drugs and diet can interact with lithium by affecting lithium clearance or through non-pharmacokinetic mechanisms.

ANTIEPILEPTIC MEDICATIONS

SUMMARY - EFFECTIVENESS OF ANTI-EPILEPTIC DRUGS (AED)

In this class of medications most of the studies compared carbamazepine, valproate, gabapentin, and lamotrigine with either placebo or lithium used as the standard treatment. No evidence of even fair quality was found on the other anti-epileptic drugs. There was insufficient evidence to compare these different AEDs in terms of medications efficacy and dangerousness. Prospective, randomized head-to-head trials are needed to assess these comparisons.

ADVERSE EVENTS OF ANTI ANTIEPILEPTICS

Table E - 4. Adverse Events Antiepileptic Medications

Intervention	Significant Adverse Events or may affect adherence	Serious or Life Threatening Adverse Events
Valproate	Alopecia Drug interactions Tremor Weight gain	Hepatotoxicity Hyperammonemia Pancreatitis Pregnancy Category D Stephens-Johnson syndrome Thrombocytopenia
Lamotrigine	Cognitive impairment Drug interactions Headache Peripheral edema Rash Vision changes	Pregnancy Category C Stephens-Johnson syndrome
Topiramate	Cognitive impairment Weight loss Anorexia Nystagmus Vision changes Paresthesia	Decreased serum bicarbonate Leukopenia Nephrolithiasis Purpura Thrombocytopenia
Gabapentin	Peripheral edema Requires dose adjustment based on renal function	----
Oxcarbazepine	Ataxia Drug interactions Rash	Agranulocytosis Aplastic anemia AV block/bradycardia Pregnancy Category D SIADH/hyponatremia Stephens-Johnson syndrome Thrombocytopenia
Carbamazepine	Ataxia Drug interactions Rash	Agranulocytosis Aplastic anemia AV block/bradycardia Pregnancy Category D SIADH/hyponatremia Stephens-Johnson syndrome Thrombocytopenia

Table E - 5. Recommended Pharmacotherapy Monitoring: Lithium, Antiepileptics

Medication	Starting Therapy		Follow-up during Ongoing Therapy (Stable Outpatient)
	Baseline	During Titration	
Lithium 0.6 to 1.2 mEq/L	sCr, eCrCl, Electrolytes, Thyroid profile Pregnancy test ***	Lithium serum concentration every 4-14 days	- Every 6 months serum concentration - Annual sCr, eCrCl, * - Annual Thyroid profile ** - Annual CBC w/diff
Carbamazepine 4 to 12 mcg/ml	CBC w/diff, LFTs	CBZ concentration every 2 weeks for 3 months CBC w/dif LFTs at 1 and 3 months	- Annual serum concentration - Annual CBC w/diff - Annual LFTs - Annual Electrolytes
Valproate 50 to 125 mcg/ml	CBC w/diff LFTs	Valproate serum concentration no sooner than 5-7 days after a change in dose. CBC w/dif LFTs at 1 and 3 months	- Annual serum concentration - Annual CBC w/diff - Annual LFTs - Annual Electrolytes

CBC w/ diff = complete blood count with differential, sCr = serum creatinine, eCrCl = estimated/calculated creatinine clearance, LFTs= liver function tests

* If sCr is elevated, even after a repeat check, then a 24-hour creatinine clearance should be obtained every 6 months (q3-9 months) if sCr < 2 mg/dL and if >2 mg/dL then a 24-hour creatinine should be obtained and the patients primary care provider notified. Defer to the patient's nephrologist if the patients under the care of nephrology.

** Obtain annually (e.g., 9 – 15 months) for 5-years while on lithium. If after 5-years and no abnormalities, a thyroid profile should be ordered when a patient's clinical presentation warrants it.

*** For women of child-bearing potential

ANTIPSYCHOTIC MEDICATIONS

SUMMARY

General Caution Statements

First generation (typical) antipsychotics (FGAs) have traditionally been considered a first-line treatment for acute mania. FGAs, mostly haloperidol, have been used for decades and are generally regarded as acting faster than mood stabilizers. The data supporting the use of FGA's in mania, however, is limited. Additionally many psychiatrists have shared their anecdotal clinical impression that FGAs induce depression.

Unlike FGAs, second generation (atypical) antipsychotics (SGAs) do not induce depression and typically are not associated with extrapyramidal symptoms (EPS). Moreover, several recent studies support their usefulness in all phases of bipolar illness, either as monotherapy or as an adjunct to conventional mood stabilizers. Improvement is reported to be similar among different antipsychotic agents, regardless of whether the antipsychotic was utilized as monotherapy or adjunctive therapy. Olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole have already been approved by the FDA for the treatment of acute mania.

During the guideline development, asenapine, an atypical antipsychotic, was approved by the FDA with label indications for the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults. Published trials were not available during the panel's deliberations to allow the inclusion of asenapine in the guideline.

The use of adjunct SGAs plus antiepileptics or lithium produces a response rate increase of about 20% relative to the use of placebo with anticonvulsant or lithium alone,

Although antipsychotic medications have a number of valid uses, they can be associated with severe side effects. These side effects include a potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS). Individuals on antipsychotic medications for any reason may also experience a syndrome of potentially irreversible, involuntary, dyskinetic movements called Tardive Dyskinesia. These adverse effects are more common in first-generation antipsychotics such as haloperidol and chlorpromazine but are occasionally found after using second generation antipsychotics. (See [Table E - 6 Adverse Events - Antipsychotics](#)).

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with second generation antipsychotics. There have been few reports of hyperglycemia in patients treated with aripiprazole. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.

An elevation in cholesterol and triglyceride concentrations is possible with second generation antipsychotic medication. In a 26 week trial of aripiprazole, there were no changes in patients' cholesterol values. Nonetheless, cholesterol should be monitored in patients on atypical antipsychotics.

Antipsychotics have also been associated with an increase in mortality rates when used in geriatric patients with dementia.

ADVERSE EVENTS OF ANTIPSYCHOTICS

Table E - 6. Adverse Events - Antipsychotics

Intervention	Significant Adverse Events, or may affect adherence	Serious Adverse Events or Life Threatening
Aripiprazole	Akathisia Anxiety	Neuroleptic Malignant Syndrome
Clozapine	Anticholinergic effects Diabetes Hyperlipidemia Hypersalivation Sedation Urinary incontinence Weight gain	Agranulocytosis Neuroleptic Malignant Syndrome
Haloperidol	EPS	Neuroleptic Malignant Syndrome Tardive dyskinesia
Olanzapine	Anticholinergic effects Diabetes Hyperlipidemia Sedation Weight gain	Neuroleptic Malignant Syndrome
Symbiax (Olanzapine & Fluoxetine)	Anticholinergic effects Diabetes Hyperlipidemia Sedation Weight gain Drug interactions	Neuroleptic Malignant Syndrome
Quetiapine	Diabetes Hyperlipidemia Sedation Weight gain	Neuroleptic Malignant Syndrome
Risperidone	EPS Diabetes Hyperlipidemia Increased prolactin Weight gain	Neuroleptic Malignant Syndrome
Ziprasidone	Drug interactions Diabetes Hyperlipidemia	QRS prolongation Neuroleptic Malignant Syndrome

Table E - 7. Comparison of Relative Adverse Effects of the Second Generation Antipsychotics

Adverse Event	Aripiprazole	Clozapine	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Anticholinergic effects	+	++++	+++	+	+	+
Extrapyramidal effects	+	0	+	0	++	+
Hyperglycemia	+	++++	+++	++	+	0
Hyperlipidemia	+	++++	+++	++	+	0
Hyperprolactinemia	+	+	+	+	+++	+
Neuroleptic Malignant Syndrome	+	+	+	+	+	+
Orthostatic hypotension	+	++++	+	+++	++	+
QTc prolongation	0	++	+	++	++	+++
Sedation	+	++++	+++	+++	++	+
Tardive dyskinesia	0	0	+	0	+	+
Weight gain	0	++++	+++	++	++	0

Extrapyramidal effects include dystonia, akathisia, and pseudoparkinsonism

Incidence: 0 = Zero-unlikely; + = unlikely-low, possible; ++ = low-moderate; +++ = moderate-high, probable; +++++ = high, likely

Table E - 8. Monitoring Parameters and Frequency for Metabolic Adverse Effects Secondary to Second Generation Antipsychotics

Monitoring Parameter	ADA/APA ¹	Mt. Sinai Conference ²
Personal Family History	Baseline	Baseline
Weight and BMI	Baseline, at 2, 8 and 12 weeks, then quarterly, annually	Baseline, then every visit for 6 months, then quarterly if stable. If weight gain results in a ≥ 1 unit increase in BMI, an intervention is recommended.
Waist Circumference	Baseline, annually	Recommended as a supplemental measure to weight and BMI. A circumference ≥ 35 inches in women or ≥ 40 inches in men warrants intervention.
Blood Pressure	Baseline, at 12 weeks, then annually	Not addressed
Fasting Plasma Glucose	Baseline, at 12 weeks, then annually	Baseline, 4 months, then annually if no symptoms of diabetes mellitus or any weight gain does not cause a ≥ 1 unit increase in BMI. If significant weight gain, then every 4 months. Refer to primary care provider if fasting glucose >126 mg/dL or nonfasting glucose >200 mg/dL Diabetics should be followed by a health care provider knowledgeable in diabetes.
Fasting Lipid Profile	Baseline, at 12 weeks, then every 5 years if levels are normal and there is no weight gain	Baseline, then every 2 years when LDL is normal and every 6 months if >130 mg/dL. For all others, follow routine care and the NCEP and USPSTF guidelines.
Pregnancy test <i>For women of childbearing potential</i>	Baseline	

BMI – Body Mass Index (kg/m^2); LDL – Low Density Lipoprotein

NCEP – National Cholesterol Education Program (<http://www.nhlbi.nih.gov/about/ncep/>)

USPSTF – U.S. Preventative Services Task Force (<http://www.ahrp.gov/clinic/ajpmsuppl/lipidrr.htm>)

ANTIDEPRESSANT MEDICATIONS

BACKGROUND

Antidepressants (AD) are commonly used to treat depressive episodes in bipolar disorder (BPD), but the benefits of this class of therapeutics have not been firmly established. There continue to be concerns about the magnitude of the risks of treatment emergent affective switches when using antidepressants (Ghaemi et al., 2008). For this discussion we looked at two systematic reviews (one focusing on acute phase therapy and one pertaining to maintenance therapy) and 5 recent randomized studies of acute phase therapy. There are not enough data from controlled studies of treatment of bipolar depression to yield specific information on individual antidepressants.

ADVERSE EVENTS OF ANTIDEPRESSANTS

Table E - 9. Adverse Events – Antidepressants

Drug Class	Adverse Events	
	Significant or may affect adherence	Serious or Life Threatening
SSRI	GI complaints Drug interactions Headache	
MAO	Pyridoxine deficiency Sedation	Drug/Food interactions Hypotension
TCA	Anticholinergic effects Drug interactions Orthostatic hypotension Sedation	Cardiovascular Overdose (lethal) Risk of switching

ELECTROCONVULSIVE THERAPY (ECT)

BACKGROUND

Electro-convulsive therapy (ECT) is a rapid and effective treatment for both mania and bipolar depression, although it is probably underused in severe depression patients. ECT should be utilized for the treatment of severe and refractory bipolar depression in patients who consent and have no absolute medical contraindications. ECT is generally a safe procedure with predictable hemodynamic responses. There are no absolute contraindications. Pertinent preexisting medical conditions that put patients at higher risk include hypertension, CAD, CHF, aortic stenosis, implanted cardiac devices, atrial fibrillation, obstructive lung disease, and asthma.

Recommendations

1. Electroconvulsive therapy (ECT) may be considered for manic patients who are severely ill and/or whose mania is treatment resistant, those patients who express a preference for ECT and patients with severe mania during pregnancy. [C]
2. Electroconvulsive therapy (ECT) should be used only to achieve rapid and short-term improvement of severe symptoms after an adequate trial of other treatment options has proven ineffective and/or when the condition is considered to be potentially life-threatening,
3. ECT for bipolar disorder is indicated as the primary therapy in the following [A]:
 - a. Psychotic symptoms
 - b. Catatonia
 - c. Severe suicidality
 - d. Food refusal leading to nutritional compromise
 - e. History of prior positive response to ECT
4. ECT is considered as first line therapy for the following conditions [B]:
 - a. Need for rapid, definitive treatment response on either medical or psychiatric grounds
 - b. Risks of other treatments outweigh the risks of ECT
 - c. Adequate trial of other treatment options (including drugs) has proven ineffective
 - d. Patient preference
5. ECT may be considered as augmented therapy in the following [B]:
 - a. Treatment failure
 - b. Unavoidable adverse effects using alternative treatments
 - c. Deterioration of patient's condition such that the first criterion is met.

MODULE F: 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.

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.

APPENDICES

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For Appendices A, C, F, and G please see the full guideline at: www.healthquality.va.gov

APPENDIX B: DANGEROUS TO SELF OR OTHERS

Risk for Suicide or Violence

A. Is Patient a Threat to Self?

BACKGROUND

Suicidality is an important topic for all health care providers. Suicide is highly prevalent, representing one of the leading causes of mortality in the United States. It is the leading cause of violent death in this country. Up to one-third of people in the general population report having had suicidal ideation at some point in their lifetime.

Patients with bipolar disorder have a lifetime risk for completed suicide of 10-20% and a risk for attempted suicide of 20-56%. This risk for completed suicide is over 20 times that of the general population. Suicide risks in these patients is highest during depressive (about 80%) and mixed (11%) episodes but up to 10% of such suicides occur during a manic state, thus indicating the need for screening of all patients with bipolar disorder.

Direct and nonjudgmental questioning regarding suicidal and/or homicidal ideation/intent is indicated in all cases where depression is suspected. A significant number of patients who contemplate suicide are seen by a physician within a month prior to their attempt. Medical providers often express concern regarding this line of questioning in the fear that it may actually stimulate the thought in the patient. However, evidence shows that direct assessment of suicidal ideation and intent does not increase the risk of suicide. The clinician should consider gathering collateral information from a third party, if possible. Homicidal ideation and suicidal ideation may co-occur. Risk of violence towards others should be assessed by asking directly whether the patient has thoughts of harming anyone.

ACTION STATEMENT

Perform a screening to identify patients who pose a threat to self or others and initiate appropriate intervention.

RECOMMENDATIONS

1. Patients with a diagnosis of an acute BD depressive episode should be assessed for suicidality by using a direct line of questioning.
2. Assess static and dynamic risk factors for suicide in patients with mania, hypomania, or mixed episode. [B]
3. Manage suicide risk by implanting interventions appropriate to the suicide risk. [B]
4. Patients with a diagnosis of an acute BD mania/hypomania should be assessed for suicidality, acute or chronic psychosis or other unstable or dangerous conditions.
5. Any patient with suicidal ideation or attempts necessitating psychiatric hospitalization should be considered for referral to mental health specialty care.
6. After resolution of the acute episode of suicidality, and for patients with ongoing high suicidal risk, the institution of long term lithium maintenance should be considered.
7. Educational and psychotherapeutic interventions found to be useful in preventing recurrent suicidal behavior should be considered.

DISCUSSION

The primary challenge to the provider is the prediction of suicide and therefore the assessment of the degree of intent. While there have been numerous epidemiological studies of risk factors in suicide, the translation of these into clinical practice has met with varying degrees of success. Expression of suicidal ideation warrants aggressive assessment and, when coupled with intent, assertive intervention.

The evaluation of the potentially suicidal person consists of three main parts: (1) eliciting suicidal ideation or intent; (2) gathering data on the risk factors for suicide based on the study of completed suicide; and (3) weighing these items along with mitigating factors to assess safety.

1. ELICITING SUICIDAL IDEATION OR INTENT

Ideally, eliciting suicidal ideation or intent involves a free and honest exchange of information between the person and the clinician. Unfortunately, this is not always the case. Familiarity with existing epidemiological and demographic data concerning suicide is useful in generating an index of suspicion. Direct questioning regarding suicidal ideation/intent may be initiated. There is no evidence that direct questioning about suicide leads to an increased risk of suicide.

Despite the lack of reliable measures of suicide risk among individuals, (Goldberg, 1987; Mann, Waternaux et al., 1999) a basic assessment should:

- Determine presence/absence of delirium, psychosis, or depression
- Elicit person's statements about his/her suicidality
- Elicit person's ideas concerning what would help attenuate or eliminate suicidal ideation/intent
- Identify a third party contact wherever possible
- Elicit suicide risk with the following suggested sequence of questions:
 - Are you discouraged about your condition, situation, life, or other concerns?
 - Are there times when you think about your situation that you feel like crying?
 - During those times, what sorts of thoughts go through your head?
 - Have you ever felt that if the situation did not change, your life would not be worth living?
 - Have you thought of ending your life?
 - Have you reached a point where you've devised a specific plan to end your life?
 - Do you have the necessary items available to complete that plan?
 - How strong is your intent to do this?
 - Can you resist the impulse to do this?
 - Do you tend to be impulsive?
 - Have you ever rehearsed how you would kill yourself?

2. ASSESS RISK FACTORS FOR COMPLETED SUICIDE

Suicidal behavior is associated with many different types of events, illnesses, and life circumstances.

The endorsement of suicidal ideation and intent are obvious risk factors for suicide attempt or completion. An active plan represents a further risk. All current models of suicide are multifactorial, with the risk increasing with the accumulation of risk factors in a given individual. The strongest predictor of suicide is one or more previous attempts; however, most people who die by suicide die on their first attempt. There are many factors that increase risk for suicide.

Static risk factors for suicide include:

- **Presence of psychiatric illness:** greater than 90 percent of adults who successfully complete suicide have some form of psychiatric illness. A symptom triad of mood symptoms, aggressiveness and impulsivity has been described as a major contributor to suicide completion. The presence of hopelessness has been similarly classified.
- **Serious medical illness:** while particularly true of disorders marked by a debilitating course, suicide rarely occurs in the absence of psychiatric illness.
- **History of previous suicide attempt:** one percent of suicide attempters go on to completion each year, and 10 to 20 percent will eventually succeed at some point in their lives.
- **Impulsivity:** highly impulsive individuals are at higher risk. This includes people with histories of substance abuse, smoking, gambling and other impulse control disorders, as well as those with a history of aggressive behavior and/or head injury.
- **History of poor adaptation to life stress,** including history of trauma or abuse.
- **Male gender:** females attempt suicide three times as frequently as males, but males represent 75 percent of completed suicides.
- **Advanced age:** higher rates of suicide attempts and completion are reported in persons greater than age 60. Age generally becomes an increasing risk factor at age 45. This is a very gross generalization, as there are other age populations with increased clinical risks.
- **Caucasian race.**
- **Family history of suicide.**

Dynamic risk factors for suicide include:

- **Active substance abuse** (including nicotine).
- **Means for suicide completion readily available**-Particularly firearms or other highly lethal modality.
- **Psychosocial disruption**-Includes recent separation, divorce, loss of job, retirement, bereavement or other perceived negative life event (including living alone). Events that seem on the surface to be positive (e.g., birth of a child) can also lead to psychosocial disruption.

Social/Environmental Risk Factors

- Lack of social support and increasing isolation
- Easy access to/familiarity with lethal means (e.g., guns, illicit drugs, medications)
- Local clusters of suicide that have a contagious influence
- Legal difficulties/contact with law enforcement/incarceration
- Barriers to accessing health care, especially mental health and substance abuse treatment

- Certain cultural and religious beliefs (for instance, the belief that suicide is a noble resolution of a personal dilemma)
- Exposure to, including through the media, and influence of others who have died by suicide

Protective Factors:

While protective factors provide a poor counterbalance to individuals who are at high risk for attempting suicide (i.e., someone with strong ideation, intent, a plan, preparatory behaviors, and impaired judgment), protective factors can mitigate risk in a person with moderate to low suicide risk.

- Sense of responsibility to family
- Life satisfaction, social support, belongingness
- Coping skills and problem-solving skills
- Strong therapeutic relationship
- Religious faith that affirms life

3. EVALUATE THE AVAILABLE DATA

Formulate an acute and chronic management plan. Include the following information in your assessment:

- Epidemiological risk factors present (inquire about each one individually if necessary)
- Other psychiatric conditions present (aside from ones mentioned above, and in particular Axis II, and substance abuse disorders)
- Recent completion of a will
- Plans for the future
- Level of hopelessness and helplessness of the person
- Makeup and condition of the person's social support system

4. INTERVENTION

If suicide risk is present, the following system is useful in formulating a strategy for intervention:

Imminent risk (48 hours): suspect if the person endorses suicidal intent, an organized plan is present, lethal means are available, extreme pessimism is expressed (e.g., hopelessness, despair), and signs of psychosis are present along with additional risk factors.

Management suggestions include:

- Immediate action. Hospitalize or commit. **Do not leave the person alone.**

Short-term risk (days to weeks): suspect if there are several risk factors for suicide, but no overt behaviors are present.

Management suggestions include:

- With the person's permission, involve family member or other person close to the person and advise them of the situation.

- Initiate steps to sanitize the environment of potentially lethal means of suicide completion.
- Stay in contact (phone calls, more frequent visits, etc.). Frequently re-evaluate risk.
- Treat psychiatric conditions as appropriate, including substance abuse/dependence.
- Consider hospitalization as appropriate.

Long-term risk: the therapeutic goal is to eliminate or improve modifiable suicide risk factors. This may involve treatment of psychiatric illness (through biological means and/or psychotherapy), substance abuse, environmental modification or manipulation, or attention to other identified risk factors. Frequent reassessment is still essential, as acute situations may arise which could destabilize the situation. Thus, all management suggestions considered at shorter levels of risk are brought to bear here as well.

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

B. Assess Risk for Violence

BACKGROUND

A person at high risk for violence is someone who has expressed thoughts of potential harm to self or others, has demonstrated violent acts or feelings, is paranoid, or has expressed great hostility toward political or prominent figures. Persons with definite intent (suicidal/homicidal ideation, intent, and/or plan) to harm self or others require voluntary or involuntary emergency psychiatric treatment (Department of Health and Human Services pub. no. 95-3061, 1995; American Psychiatric Association, 1993).

DISCUSSION

The challenge in evaluating the violent person parallels that of the suicidal person, requiring the careful eliciting of homicidal ideation, gathering data on risk factors for violent acts, assessing the data and the potential for danger and safety. This is complicated by the fact that an aggressive person, particularly at initial contacts with the mental health professional, or in the midst of an aggressive state, may be uncooperative.

In eliciting homicidal ideation, one must ascertain if there is intent, a plan, the means to carry out the act and the reasons for wanting to do so. The following factors have been identified as significant in assessing violence:

- **History of Previous Violence**—This is the single most significant predictor of violence.
- **Targeted Individual in the Community**—This is particularly a factor with Delusions of Jealousy, Erotomanic Delusions, and Paranoid Idea.
- **Serious psychiatric illness**—In different psychiatric illnesses there is an increase in violence. This can be multifactorial. In psychotic illness it has been related to the threat control override symptoms (Link, 1999). The feeling that thoughts or impulses are being put into one's body accounts for much of the increased risk of violence in psychotic illness. Command hallucinations can be a significant risk factor, especially when they are a manifestation of control override symptoms.
- **Psychosocial disruption**—Includes recent separation, divorce, loss of job, retirement, bereavement or other perceived negative life event (including living alone). Events that seem on

the surface to be positive (e.g. birth of a child) can also lead to psychosocial disruption.

- **History of previous violent suicide attempt**—Firearms, stabbing, hanging and jumping are viewed as violent suicide attempts.
- **Active substance abuse.**
- **Impulsivity**—Highly impulsive individuals are at higher risk. This includes people with histories of substance abuse, smoking, gambling and other impulse control disorders, as well as those with history of self destructive behavior and/or head injury.
- **Verbal abuse and hostility.**
- **History of poor adaptation to life stress.**
- **Male gender.**

SUD and BIPOLAR

Comorbid substance use and mental illness is prevalent and often results in serious consequences. However, little is known about the efficacy of treatments for patients with dual diagnosis. Limited number of studies, especially RCTs, have been conducted within each comorbid category.

There is insufficient evidence to recommend any treatments that had been replicated and consistently showed clear advantages over comparison condition for both substance-related and other psychiatric outcomes.

Although no treatment was identified as efficacious for both psychiatric disorders and substance-related disorder, the following have been demonstrated in several studies:

- (1) **Existing efficacious treatments for reducing psychiatric symptoms also tend to work in dual-diagnosis patients,**
- (2) **Existing efficacious treatments for reducing substance use also decrease substance use in dual-diagnosis patients, and**
- (3) **The efficacy of integrated treatment is still unclear.**

APPENDIX D: BIPOLAR DRUG TABLES

Table D - 1. Dosing Parameters for Medications for Bipolar Medications

Medication Formulations and Strengths	Initial Oral Dose and Titration	Days Between Dose Adjustment	Therapeutic Range or Target Daily Dose	Maximum Dose	Initial Dose Adjustment/ Guidance in Special Populations		
					Renal Impairment	Hepatic Impairment	Geriatric
Lithium							
Lithium Carbonate Cap: 150, 300, 600 mEq Tab: 300 mEq Tab CR: 450 mEq Syrup (citrate): 8mEq/5mL	150 – 900 mg/day Single (bedtime) or divided two or three times a day. Increase dose by \leq 150 mEq per day no sooner than every 5 days.	\geq 5	Acute mania: 0.8-1.2 mEq/L Maintenance: 0.6 – 1.0 Eq/L	Serum lithium concentrations should not exceed 1.2 mEq/mL	Adjust dose: CrCl 10-50: 50% - 75% of normal dose CrCl <10: 25% - 50% of normal dose. Best to avoid in moderate to severe impairment.	None	See renal impairment; Initial dose no greater than 600 mg /day
Antiepileptics							
Carbamazepine Cap ER: 100 mg, 200 mg, 300 mg Tab: 200 mg Tab chewable: 100 mg Tablet ER: 100 mg, 200 mg, 400 mg Suspension, oral: 100 mg/5 mL	Initial: 100 –200 mg as a single dose. Increase by 100 mg/day weekly. Dosing should be two or three times a day based on formulation.	3 – 7	4 – 12 mcg/mL	1600 mg	Adjust dose based on response and serum concentration.	Adjust dose based on response and serum concentration.	Adjust dose based on response and serum concentration.

Medication Formulations and Strengths	Initial Oral Dose and Titration	Days Between Dose Adjustment	Therapeutic Range or Target Daily Dose	Maximum Dose	Initial Dose Adjustment/ Guidance in Special Populations		
					Renal Impairment	Hepatic Impairment	Geriatric
Valproate as Divalproex Delayed release: 125, 250, 500 mg Extended release: 250, 500 mg Liq:250/5mL Inject.	Delayed release: Inpatient: 20 mg/kg as a loading dose in two or three divided doses; 750 mg twice a day. Outpatient: 250 – 500 mg divided every 12 hours. Increase by 250 – 500 mg/day no sooner than every 5 days. Maintenance: 20/mg/kg/day in two divided doses Extended release: Inpatient: 25 mg/kg/day as a single daily dose. Outpatient: 250 – 500 mg as a single daily dose. Increase by 250 – 500 mg/day no sooner than every 5 days.	≥5	50 – 125 mcg/mL	60 mg/kg/d	None required. Increased unbound drug may make total valproate concentration misleading	Required in mild-moderate impairment; Avoid if severe.	Lower doses may be required due to increased unbound drug; Sedation more problematic
Lamotrigine Tab: 25, 100, 150, 200 mg	Not taking divalproex or CBZ: 25 mg once a day for 2 weeks, then 50 mg/day for 2 weeks, then 100 mg/day for 1 week	7 -14	200 mg	400 mg	Has not been studied, decreased dosing may be advised.	Moderate to severe impairment without ascites decrease dose by 25%; with ascites decrease dose by 50%. Titrate based on clinical response.	No specific age adjustment required.
	Taking divalproex: 25 mg every other day for 2 weeks, then 25 mg/day for 2 weeks, then 50 mg/day for 1 week, then 100 mg/day	7 -14	100 mg	200 mg			
	Taking enzyme inducing drug (e.g., CBZ): 50 mg/day for 2 weeks, then 100 mg/day for 2 weeks, then 200 mg/day for 1 week, then 300 mg/day for 1 week	7-14	300 – 400 mg	400 mg			

Medication Formulations and Strengths	Initial Oral Dose and Titration	Days Between Dose Adjustment	Therapeutic Range or Target Daily Dose	Maximum Dose	Initial Dose Adjustment/ Guidance in Special Populations		
					Renal Impairment	Hepatic Impairment	Geriatric
Antipsychotics							
Aripiprazole Tab: 5, 10, 15, 20,30 mg Soln: 1 mg/mL	30 mg (may reduce to 15 mg if needed)	14	30 mg	30 mg	No adjustment required	No adjustment required	No specific recommendations
Clozapine Tab: 12.5, 25, 100 mg	12.5 mg	1 - 4	300 – 450 mg	900 mg	No adjustment required	No adjustment required	No specific recommendations
Olanzapine Tab: 2.5, 5, 7.5, 10, 15, 20 mg Inj: IM	Acute Mania: 10 – 15 mg	≥1	5 – 20 mg	20 mg	No adjustment required	Adjustment may be necessary; no specific recommendations	Lower initial doses and slower titration, 2.5 – 5 mg, may be better tolerated.
Quetiapine Tab: 25, 100, 200, 300 mg	Acute Mania: 50 mg twice a day on Day 1, increase by 100 mg/day to 200 mg twice a day on Day 4.	≥1	400 – 600 mg	800 mg	No adjustment required	Adjustment may be necessary; 25 mg/day, increase by 25-50 mg per day to effective dose based on response.	Reduced clearance; lower doses may be needed.
	Acute Depression: 300 mg		300 or 600 mg	600 mg			
Risperidone Tab: 0.25, 0.5, 1, 2, 3, 4 mg Soln: 1 mg/mL Long-acting inj.	Oral: 2-3 mg	>1	1 – 6 mg	6 mg	Reduced clearance of active metabolite with moderate to severe impairment; Starting dose 0.5 mg twice a day	Reduced clearance; Starting dose 0.5 mg twice a day	Initial dose 0.5 mg twice a day; increase no greater than 0.5 mg twice a day and no sooner than once a week at doses >1.5 mg/day
	Maintenance: IM: 25 mg every 2 weeks	>4 weeks	25 – 50 mg every 2 weeks	50 mg every 2 weeks			
Ziprasidone Cap: 20, 40 , 60, 80 mg	Acute Mania: 40 mg twice a day	≥1	120 – 160 mg	160 mg	No adjustment recommended	No adjustment recommended	No adjustment; lower doses may be sufficient

Medication Formulations and Strengths	Initial Oral Dose and Titration	Days Between Dose Adjustment	Therapeutic Range or Target Daily Dose	Maximum Dose	Initial Dose Adjustment/ Guidance in Special Populations		
					Renal Impairment	Hepatic Impairment	Geriatric
Olanz/Fluoxetine Cap: 6/25, 6/50, 12/25, 12/50 mg	Olanz 6 mg/Fluox. 25 mg		Olanz 6-12 mg/ Fluox. 25-50 mg	Olanz. 18 mg/ Fluox. 75 mg	See individual agents		
Antidepressants							
Citalopram	20 mg once a day	≥1	10-60 mg/day	60 mg	Avoid: CrCl < 20	↓ dose	10-20 mg
Escitalopram	10 mg once a day	≥1	10-20 mg	40 mg	Avoid: CrCl < 20	10 mg	5-10 mg
Fluoxetine	20 mg once a day	≥2	20-80 mg	80 mg	No change	↓dose 50%	10 mg
Fluoxetine weekly	90 mg once a week	NA	90 mg	90 mg	Avoid	Avoid	90 mg
Paroxetine	20 mg once a day	≥1	20-50 mg	50 mg	10 mg	10 mg	10 mg
Paroxetine CR	25 mg once a day	≥1	25 mg	62.5 mg	12.5mg	12.5 mg	12.5 mg
Sertraline	50 mg once a day	≥1	50-200mg	200 mg	25 mg	↓ dose	25 mg
Duloxetine	20-30 mg twice a day	≥1	20-60	60 mg	Avoid if CrCl < 30	Avoid	20 – 40mg
Venlafaxine IR	37.5 mg twice a day	≥1	37.5-225 mg	225-375 mg	CrCl 10-70, ↓ 50%	↓ dose 50%	25-50 mg
Venlafaxine XR	75 mg once a day	≥1	75-225 mg	225 mg	CrCl 10-70, ↓ 50%	↓ dose 50%	37.5-75 mg
Bupropion IR	100 mg twice a day	≥1	75-450 mg	450 mg	Has not been studied	Severe: 75 mg/day	37.5mg BID
Bupropion SR	150 mg once a day	≥1	100-150 mg	400 mg		100 mg / day	100 mg QD
Bupropion XR	150 mg once a day	≥1	150-300 mg	450 mg		150 mg /other day	150 mg QD
Trazodone	50 mg three times a day	≥1	75-600 mg	600 mg	No change	Unknown	25- 50 mg
Nefazodone	100 mg twice a day	≥1	300-600 mg/day	600 mg	No change	Avoid	50 mg BID
Mirtazapine	15 mg QHS	≥1	15-45 mg/day	45 mg	CrCl <40 mL/min	Cl ↓ 30%	7.5 mg QHS
Amitriptyline	50 mg QD – TID	≥1	75 mg QD	300 mg	No change	Lower dose and slower titration recommended	10–25 mg HS
Impramine	25 mg QD – QID	≥1	50-150 mg/day	300 mg	No change		10-25 mg HS
Nortriptyline	25 mg TID – QID	>1	25 mg, 3-4/ day	150 mg	No change		10-25 mg HS
Desipramine	25 mg TID – 75 mg QD	≥1	100-200 mg/day	300 mg	No change		10-25 mg QD
Doxepin	25-75 mg QHS or BID	≥1	75 -150 mg/day	300 mg	No change		1-25 mg QHS
Isocarboxazid	10 mg BID-TID	≥1	10-60 mg	60 mg	No change	No change	10 mg BID
Phenelzine	15 mg TID	≥1	60-90 mg	90 mg			7.5 mg QD
Selegiline patch	6mg/24h	≥2	6 mg/24 hours	12 mg/24h			6 mg/24h
Tranlycypromine	10 mg BID	≥1	30 mg/day	60 mg/day			10 mg BID

Bipolar Medications in Pregnancy and Breastfeeding

Information on medications used to treat bipolar disorder during pregnancy and most of what is known comes from other patient populations, e.g., seizure disorder and schizophrenia. Lithium, valproate, and carbamazepine are to be avoided in the first trimester whenever possible (American Psychiatry Association). Additional fetal monitoring is advised when exposure to lithium or valproate cannot be avoided. Referral to a specialist in treating with psychiatric disorders during pregnancy is advised.

Information on the excretion of medications used to treat bipolar disorder into breast milk, concentrations in infant serum, and effects on the infant is limited and generally taken from other patient populations. LactMed an internet data base (<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>) maintained and updated monthly by the National Library of Medicine is a searchable and useful resource.

Table D - 2. Bipolar Medications in Pregnancy and Breastfeeding

Drugs Class Drug	*FDA Pregnancy Category	Teratogenic & Neonatal Effects	Breastfeeding	Recommendations
Lithium	D	First trimester: spina bifida, craniofacial and cardiac abnormalities. Neonatal bleeding	According to the American Academy of Pediatrics, lithium is contraindicated during breastfeeding due to concerns of infant lithium toxicity. Lithium serum concentrations in breastfed infants are one-third to one-half of those of the mother.	Lithium is to be avoided in the first trimester due to the risk of fetal Ebstein's anomaly with a risk that is 10 to 20 times greater than the general population. High-resolution ultrasonography and fetal echocardiography should be performed at 16 – 18 weeks gestation to screen for cardiac anomalies in fetuses exposed to lithium in the first trimester. Lithium can be restarted in the second trimester. Due to the increases in glomerular filtration rate and volume of distribution during pregnancy, lower serum concentrations are expected and the lithium concentration are to be monitored every 2-4 weeks during pregnancy and weekly in the last month, then every few days just prior to delivery. Dose adjustments to maintain the concentration in the therapeutic range may be necessary. Lithium should be discontinued or its dose reduced just prior to delivery to avoid lithium toxicity in the infant. Lithium should be restarted after delivery at a lower dose. Adequate hydration and electrolyte management should be maintained during pregnancy and delivery to avoid lithium toxicity.

Drugs Class Drug	*FDA Pregnancy Category	Teratogenic & Neonatal Effects	Breastfeeding	Recommendations
Antiepileptics				
Carbamazepine	D	First trimester: spina bifida, craniofacial and cardiac abnormalities. Neonatal bleeding	Excreted into breast milk in high concentrations; measurable in infant serum. Usually without adverse effects in the infant but poor sucking, withdrawal reactions and hepatic dysfunction reported. Monitor infant if breastfeeding.	Avoid in 1st trimester; Vitamin K supplementation and IV vitamin K for infant has been suggested as a precaution
Lamotrigine	C	First trimester: cleft lip and palate; rate of major defects increased when combined with valproate	Infants achieve a serum concentration of 30-35% of maternal concentrations.	Avoid in combination with valproate; avoid doses >200 mg/day which are believed to increase risk. Rash can develop in breast fed infants.
Oxcarbazepine	C	First trimester: spina bifida. Neonatal bleeding	Limited information. Monitor infant for drowsiness, normal weight gain and development	Avoid in 1st trimester; Vitamin K supplementation and i.v. vitamin K for infant has been suggested as a precaution
Valproate	D	First trimester: neural tube deficits and craniofacial abnormalities. Fetal valproate syndrome (facial characteristics, cardiovascular and limb abnormalities) and developmental delay, autism.	Low concentrations in breast milk and infant. Theoretical risk for hepatotoxicity or thrombocytopenia. Monitor for jaundice, liver damage, bleeding.	Avoid in first trimester. If 1st trimester exposure, a high-resolution fetal ultrasound and fetal echocardiogram at week 16-18 of gestation plus serum alpha protein or amniocentesis is advised. Dose should be <1000 mg/day and in divided doses to keep serum conc. <70 mcg/mL.

Drugs Class Drug	*FDA Pregnancy Category	Teratogenic & Neonatal Effects	Breastfeeding	Recommendations
Second Generation Antipsychotics				
Aripiprazole Clozapine Olanzapine Paliperidone Quetiapine Risperidone	C B C C C C	Insufficient data for the class.	Not recommended unless indicated otherwise; all excreted into breast milk Use with caution.	Monitoring for gestational diabetes and excess weight gain may be warranted with clozapine and olanzapine. Perinatal syndromes, although rare, may be minimized by discontinuing prior to delivery; however, there is concern about maternal decompensation.
Ziprasidone	C	Increased EPS and muscle tone	Parent and active metabolite excreted into breast milk. Do not BF for 12-weeks post last IM injection	
Typical Antipsychotics				
Haloperidol	C			
Antidepressants				
SSRIs: Citalopram Escitalopram Fluoxetine Paroxetine Sertraline	C C C D C	The SSRIs have been associated with persistent pulmonary hypertension with maternal use after 20 weeks of gestation, a slight decrease in gestational age, lower birth weight, and neonatal withdrawal or adaptation syndrome. Paroxetine has been associated with first-trimester cardiovascular malformations (ventricular and atrial septal defects).	For women planning to breast feed, consider an antidepressant with the lowest excretion into breast milk resulting in the lowest infant serum concentrations and fewer adverse reactions, these include: paroxetine, sertraline, and nortriptyline. Citalopram and fluoxetine have the highest concentrations in breast milk and more reports of infant adverse effects. A 40% decrease in breast milk concentration can be achieved by switching to escitalopram at 25% of the citalopram dose.	For treatment of depression in pregnancy, TCAs and SSRIs (particularly fluoxetine) are generally the agents of choice. Avoid the use of paroxetine during the first trimester.
SNRIs: Duloxetine Venlafaxine	C C		Venlafaxine is detectable in the serum and associated with less weight gain in breast-fed infants.	

Drugs Class Drug	*FDA Pregnancy Category	Teratogenic & Neonatal Effects	Breastfeeding	Recommendations
TCAs Amitriptyline Imipramine Desipramine Nortriptyline	C D C D	TCAs have been associated with neonatal withdrawal symptoms and anticholinergic adverse effects.	TCAs are nearly undetectable in infant plasma concentrations and low concentrations are found in breast milk.	
Others: Bupropion Mirtazepine	B C	There are insufficient data about other newer antidepressants; there may be a link between bupropion and spontaneous abortion.	Less information is available about bupropion, mirtazepine and trazodone, although the concentrations in breast milk infant serum are low.	

A – Controlled studies in pregnant women fail to demonstrate a risk to the fetus in the first trimester with no evidence of risk in later trimesters. The possibility of fetal harm appears remote.

B – Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, OR animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester and there is no evidence of a risk in later trimesters.

C – Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal effects or other) and there are no controlled studies in women, OR studies in women and animals are not available. Drugs should be given only if the potential benefits justify the potential risk to the fetus.

D – There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

X– Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.FDA Pregnancy Category.

APPENDIX E: ACRONYM LIST

AAP	Atypical Anti Psychotics
BD	Bipolar Depression
BDI	Beck Depression Inventory
BT	Behavioral Therapy
CBC	Complete Blood Count
CBT	Cognitive Behavioral Therapy
CCBT	Computer-Based Cognitive Behavioral Therapy
CCM	Chronic Care/disease Management
CFT	Couples/Marital-Focused Therapy
ECT	Electro-Convulsive Therapy
FFT	Family Focused Treatment
ISPRT	Interpersonal & Social Rhythm Therapy
MAOI	Monoamine Oxidase Inhibitor Medication
MDD	Major Depressive Disorder
MMSE	Mini-Mental State Examination
MAOIs	Monoamine Oxidase Inhibitors
MSE	Mental Status Examination
NOS	Not Otherwise Specified
OTC	Over-the-Counter
QE	Quality of Evidence
RCT	Randomized Controlled Trials
SNRI	Serotonin Norepinephrine Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
TCAs	Tricyclic & Tetracyclic Antidepressants
TMS	Transcranial Magnetic Stimulation
USPSTF	U.S Preventive Services Task Force
VNS	Vagus Nerve Stimulation