Clinical Practice Guideline

Management of Bipolar Disorder in Adults (BD)

May, 2010

VA/DoD Evidence Based Practice

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

Department of Veterans Affairs

Department of Defense

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 – 2009

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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 intervnetion 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: 225-55.

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

SR = Strength of recommendation

GRADING RECOMMENDATIONS

If evidence exists, the discussion following the recommendations for each annotation includes an evidence table that indentifies 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.

REFERENCES

American Psychiatric Association (Ed.) (2000) Diagnostic and statistical manual of mental disorders.

Mitchell. et al. The management of bipolar disorder in general practice. Med J Aust 2006; 184(11): 566-70.

Vieta E. Rosa A. Evolving trends in the long-term treatment of bipolar disorder. World J Biol Psychiatry 2007;8(1): 4-11.]

Thase, M. Maintenance therapy for bipolar disorder. J Clin Psychiatry 2008; 69(11): e32.

Bipolar Disorder Guideline Update Working Group

VA	**DoD**
Eileen P. Ahearn, MD, PhD	Aaron Bilow, PharmD
Thomas J. Craig, MD, MPH	**Gary Southwell, PhD LTC, USA**
Jennifer Hoblyn, MD, MPH	**Randon S. Welton MD. LtCol, USAF - Co-Chair**
Amy M. Kilbourne, PhD, MPH	
Todd. P. Semla, PharmD	
Alan C. Swann, MD	
Trisha Suppes, MD, PhD - Co-Chair	
Michael Thase, MD	
Office of Quality and Performance, VHA Carla Cassidy, RN, MSN, NP	**Quality Management Division** **US Army Medical Command** Ernest Degenhardt, RN, MSN, ANP-FNP Joanne Ksionzky BSN, RN, CNOR, RNFA Mary Ramos, PhD, RN
FACILITATOR **Oded Susskind, MPH**	
Research Team – ECRI Vivian H. Coats, MPH Eileen G. Erinoff Karen Schoelles, MD David Snyder, PhD	**Healthcare Quality Informatics** Martha D'Erasmo, MPH Rosalie Fishman, RN, MSN, CPHQ Joanne Marko, MS, SLP

** **Bolded** names are members of the CORE Editorial Panel.*
Additional contributor contact information is available in Appendix E.

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 Guideline includes Appendices:

A. Guideline Development Process

B. Assessment of Dangerousness to Self or Others

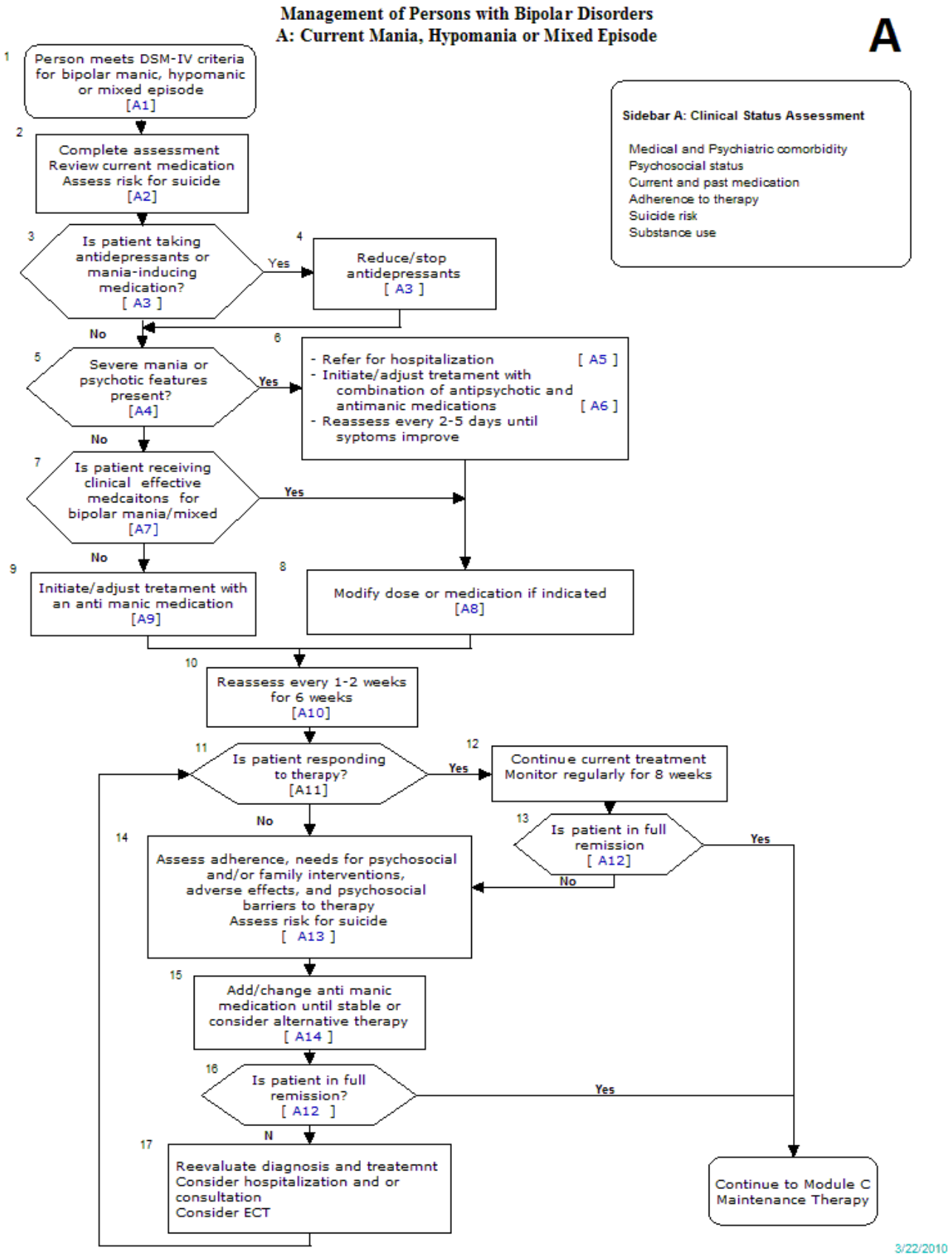
C. PICO Questions Guiding the Literature Search

D. Drug Tables

E. Acronym List

F. Participant List

G. Bibliography


Management of Persons with Bipolar Disorders
A: Current Mania, Hypomania or Mixed Episode
A
1
Person meets DSM-IV criteria for bipolar manic, hypomanic or mixed episode [A1]
2
Complete assessment
Review current medication
Assess risk for suicide
[A2]
3
Is patient taking antidepressants or mania-inducing medication? [A3]
Yes
4
Reduce/stop antidepressants [A3]
No
5
Severe mania or psychotic features present? [A4]
Yes
6
- Refer for hospitalization [A5]
- Initiate/adjust tretament with combination of antipsychotic and antimanic medications [A6]
- Reassess every 2-5 days until syptoms improve
No
7
Is patient receiving clinical effective medcaitons for bipolar mania/mixed [A7]
Yes
No
9
Initiate/adjust tretament with an anti manic medication [A9]
8
Modify dose or medication if indicated [A8]
10
Reassess every 1-2 weeks for 6 weeks [A10]
11
Is patient responding to therapy? [A11]
Yes
12
Continue current treatment
Monitor regularly for 8 weeks
No
13
Is patient in full remission [A12]
Yes
No
14
Assess adherence, needs for psychosocial and/or family interventions, adverse effects, and psychosocial barriers to therapy
Assess risk for suicide
[A13]
15
Add/change anti manic medication until stable or consider alternative therapy [A14]
16
Is patient in full remission? [A12]
Yes
N
17
Reevaluate diagnosis and treatemnt
Consider hospitalization and or consultation
Consider ECT
Continue to Module C Maintenance Therapy
Sidebar A: Clinical Status Assessment
Medical and Psychiatric comorbidity
Psychosocial status
Current and past medication
Adherence to therapy
Suicide risk
Substance use
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.

RECOMMENDATION

5. Antidepressants or other manic inducing substances should be stopped in patients experiencing a manic, hypomanic, or mixed manic episode. [B]
6. Antidepressant medications known to be associated with discontinuation syndromes may be tapered over 3 to 5 days rather than being abruptly stopped. [C]

The most common discontinuation symptoms include:

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

RATIONALE

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

EVIDENCE STATEMENTS

- Bottlender et al., (2001) studied the development of mania and hypomania in a retrospective review of 158 patients. The 69 patients who were on a tricyclic antidepressant but not on a mood stabilizer had a significantly higher switch rate than did those who were on a tricyclic antidepressant and a mood stabilizer. The differences in patients on selective serotonin reuptake inhibitors (SSRIs) and

monoamine oxidase inhibitors (MAOIs) did not reach statistical significance, possibly because of small sample sizes (total of 25 on SSRI and 12 on MAOI).

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

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

EVIDENCE TABLE

	Evidence	Source	LE	QE	SR
1	Antidepressants may induce or worsen mania, hypomania, or mixed episode	Amsterdam, 1998 Bottlender et al., 2001 Gijsman et al., 2004 Nemeroff, 2004	I I II-2 I	Fair	B
2	Antidepressants may induce or worsen rapid cycling	Altshuler et al., 1995 Bauer et al.,1994 Wehr & Goodwin, 1987	II-3 II-2 III	Fair	B
3	Antidepressants should be discontinued by slow taper to avoid relapse	Faedda et al., 1993 Suppes et al., 1993 Rosenbaum et al., 1998	II	Fair	C

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

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

BACKGROUND

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

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

- Inappropriate affect of a bizarre or odd quality
- Delusions (e.g., fixed false beliefs)
- Visual or (typically) auditory hallucinations

- 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: 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

DISCUSSION

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

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

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

A-5. Refer for Hospitalization

BACKGROUND

Some patients seeking treatment will present with severe mania or mixed episode. Because of the increased impairment experienced by these patients and the increased risk they present to themselves or others, hospitalization should always be considered as perhaps the most appropriate environment for treatment.

Specialized treatments only available, or often best provided, in an inpatient setting include:

- Electro-convulsive therapy (ECT)
- Close monitoring and daily titration of medications with disabling side effects or toxicity

- Constant staff observation as part of an intensive behavioral modification program
- Close monitoring of behavior in an episodic disorder
- Close monitoring of vital signs or need for multiple daily laboratory or electrophysiological testing.

ACTION STATEMENT

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

RECOMMENDATIONS

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

RATIONALE

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

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

BACKGROUND

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

ACTION STATEMENT

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

RECOMMENDATIONS

1. Patients with severe mania should be treated with a combination of antipsychotics and lithium or valproate. These antipsychotics include olanzapine, quetiapine, aripiprazole, or risperidone [B] and may include and ziprasidone. [I]

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

RATIONALE

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

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

EVIDENCE STATEMENTS

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

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

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

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

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

- Sachs et al., (2006) studied 272 patients with mania or mixed episode in a 3-week multicenter trial. One hundred thirty seven were randomly assigned to receive **aripiprazole** 15 – 30 mg per day and 135 were to receive placebo. Only 53% of the patients completed the three week study (55% of

aripiprazole group and 52% of the placebo group). The aripiprazole group experienced greater reduction in YMRS scores as well as a greater response rate as measured by the YMRS (> 50% reduction). They also experienced greater improvement on the Clinical Global Impression – Bipolar Version Severity and Improvement scores.

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

EVIDENCE TABLE - SEVERE MANIA OR MIXED EPISODE

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

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

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

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

For recommended medications see Annotation A-9

A-8. Modify Dose of Medication As Needed

BACKGROUND

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

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

ACTION STATEMENT

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

RECOMMENDATIONS

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

RATIONALE

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

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

EVIDENCE TABLE

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

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

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

BACKGROUND

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

ACTION STATEMENT

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

RECOMMENDATIONS

General considerations

1. Pharmacotherapy for bipolar mania or mixed episode should start with initiation or optimization of a medication that has been shown to be the most effective in treating bipolar manic episodes while minimizing the potential risks. [I] (see **Table A - 2**)
2. Consider using the agent(s) that have been effective in treating prior episodes of mania or mixed episode. [I]
3. Ensure that the patient has stopped taking any antidepressant or mania inducing substances. [B]
4. In selecting a drug treatment regimen for patients with bipolar disorder, clinicians should be aware of the patient's other psychiatric and medical conditions and should try to avoid exacerbating them.
5. In selecting a drug treatment regimen for patients with diabetes or obesity consider the risk and benefit of utilizing medications that are less associated with weight gain.

Mania

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

Mixed episode

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

Mania or Mixed episode

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

RATIONALE

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

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

	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]		Lamotrigine [D] Topiramate [D] Gabapentin [D] Antidepressant monotherapy [C]
Mixed Episode	Valproate, carbamazepine, aripiprazole, olanzapine, risperidone, or ziprasidone. [A]	Clozapine [I] Oxcarbazepine [I] Quetiapine [I] Lithium [I]		Lamotrigine [D] Topiramate [D] Gabapentin [D]

SR = Strength of Recommendation (See Appendix A)

EVIDENCE STATEMENT

For discussion of the evidence and grading of recommendations see Module E: Pharmacotherapy Interventions

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]

RATIONALE

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

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

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

BACKGROUND

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

ACTION STATEMENT

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

RECOMMENDATIONS

1. Patients whose mania does not respond to monotherapy should be considered for consultation/referral with specialty care. For patient with severe mania or mixed episode – see Annotation A-6

2. Reassess for co-occurring medical conditions that may also contribute to greater bipolar illness severity and reduced recovery. [C]
3. Escalating pharmacotherapy may be considered for patients whose mania/mixed episode or hypomania does not respond to monotherapy. The possible options for escalating pharmacotherapy include:
    a. Switching to another monotherapy may be considered if the patient did not respond to the first medication. [I]
    b. In patients with mania/hypomania who do not respond to monotherapy, consider combining a non-antipsychotic mood stabilizer (lithium or valproate) with a second generation antipsychotic such as aripiprazole, olanzapine, quetiapine, or risperidone [A] or ziprasidone. [I]
    c. In patients with mixed episode who do not respond to monotherapy, consider a combination of non-antipsychotics mood stabilizer (lithium or valproate) and a second generation antipsychotic such as aripiprazole, olanzapine, or risperidone [B] or quetiapine or ziprasidone. [I]
4. Clozapine, with its more serious side effect profile, may be combined with valproate or lithium as a treatment of severe mania or mixed episode, if it has been successful in the past or if other antipsychotics have failed. [I]
5. Adjust medications if there is no response within 2 – 4 weeks on an adequate dose of medication.
6. Electroconvulsive therapy (ECT) may be considered for patients with severe mania patients or whose mania is treatment resistant, those patients who express a preference for ECT, and patients with severe mania during pregnancy. [C]
7. Risks and benefits of long-term pharmacotherapy should be discussed prior to starting medication and should be a continued discussion item during treatment. [A]

RATIONALE

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

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

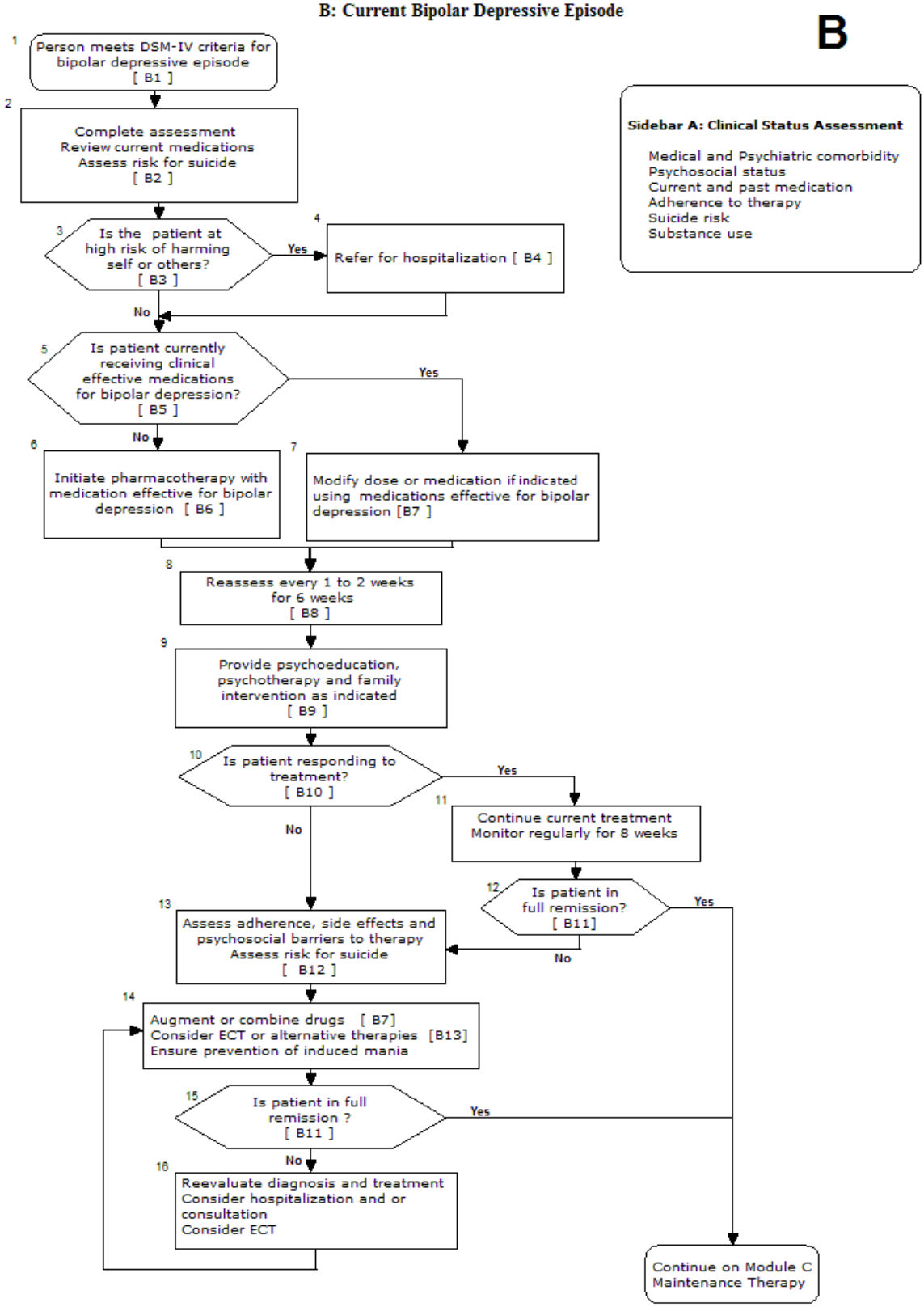
Medical condition may exacerbate and increase the severity of bipolar disorder. For example, the use of corticosteroids (e.g., asthma, inflammatory disease) or disorders that leads to abnormal thyroid functioning. Medications such as stimulants and corticosteroids may be associated with secondary mania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

Many patients with BD will not respond to the first medication they receive. If they do not adequately respond to usual therapeutic doses of an effective medication, then switching from one single medication to another medication is a logical step, although there is little evidence to direct what medication should be tried next. Randomized trials have consistently found that second generation antipsychotics (SGAs) combined with lithium or valproate are more effective than lithium or valproate alone. Most of these studies were conducted in a general population of patients and did not focus solely on patients who failed monotherapy. Despite this limitation, however, combination strategies are also a logical choice for patients who have failed monotherapy. Although this may be a class effect among all of the second generation

antipsychotics, we specifically reviewed the evidence showing the increased efficacy of augmentation with aripiprazole, olanzapine, quetiapine, and risperidone for manic episodes and aripiprazole, olanzapine, or risperidone for a mixed episode.

For discussion of the evidence and grading of recommendations see Module E: Pharmacotherapy Interventions.

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



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: Dangerous to Self or Others.

2. A standardized tool combined with a clinical interview should be used to obtain the necessary information about symptoms, symptom severity, and effects on daily functioning that is required to diagnose BD depression based on DSM-IV-TR criteria.
3. Consider using the same standardized questionnaire to monitor treatment response at 4 to 6 weeks, after each change in treatment, and to periodically assess the patient's response to treatment until full remission is achieved. (Further information on assessment and screening tools for Bipolar Disorder and suicide– see: http://www.cqaimh.org/stable.html)

DISCUSSION

- Many factors can worsen the course of BD. These can cause general distress, decreases in functioning or relapses. These factors include medical problems that are untreated, other untreated psychiatric disorders, and psychosocial stressors.
- Bipolar disorder with a co-occurring substance use disorder is a common presentation. Substance abuse may precipitate mood episodes or be used by patients to ameliorate the symptoms of such episodes. Co-occurring substance use is typically associated with fewer and slower remissions, greater rates of suicide and suicide attempts, and poorer outcome. Co-occurring substance use disorders should be managed according to the VA/DoD Guideline for Substance Use Disorder.
- Suicide completion rates in patients with bipolar I disorder may be as high as 10 – 20%; thus, a careful assessment of the patient's risk for suicide is critical.
- The adverse effects of medication, the availability of medications, family and community support and the patient's ambivalence about medications all can affect their adherence to the medication regimen and can affect rates of relapse.

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

BACKGROUND

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

- Ideas about, or intent to, harm others

- Verbal escalation or inability to be redirected
- History of violent behavior
- Severe agitation or hostility
- Active psychosis
- Intoxication or withdrawal from alcohol or drugs

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

ACTION STATEMENT

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

RECOMMENDATIONS

1. Patients with a possible diagnosis of BD depression should be assessed for suicidality, acute or chronic psychosis or other unstable or dangerous conditions.
2. A referral to emergency services and/or a mental health professional is indicated for patients presenting with any of the following unstable conditions:
    a. Delirium
    b. Marked psychotic symptoms
    c. Severe depressive symptoms/depression (e.g., catatonia, malnourishment, severe disability)
    d. Suicidality or homicidality
    e. Potential for violence (e.g., ideas about or intent to harm others; history of violent behavior; severe agitation or hostility; active psychosis)
    f. Substance withdrawal or intoxication.
4. Any patient with suicidal or homicidal ideation or attempts necessitating psychiatric hospitalization should be considered for referral to mental health specialty care. (See Appendix B: Dangerous to Self or Others.)
5. Patients with a possible diagnosis of BD depression who exhibit any of the following characteristics related to psychosis need to be referred for urgent/emergent mental health intervention as these are inappropriate for care in the primary care setting:
    a. Serious delusions (e.g., fixed false beliefs)
    b. Visual or (typically) auditory hallucinations
    c. Confusion (incoherence)
    d. Catatonic behavior (e.g., motor immobility or excessive agitation)
    e. Extreme negativism or mutism
    f. Peculiar voluntary movement
    g. Inappropriate affect of a bizarre or odd quality.

DISCUSSION

- **Delirium** – Delirium (also known as organic brain syndrome, organic psychosis, acute confusional state, acute brain syndrome and various other names) is a very common disorder of cognition and consciousness, with an abrupt onset that is commonly unrecognized. This is especially true in the elderly and chronically ill.

- **Marked psychotic symptoms** – "Psychosis," in and of itself, is not a disorder. Rather, it is a symptom, which may present in a variety of conditions. Psychotic patients have an impaired sense of reality, which may manifest in several ways (hallucinations, delusions, mental confusion, or disorganization).
- **Severe depressive symptoms/depression** (e.g., catatonia, malnourishment, severe disability) – The clinical presentation of depressed patients is marked by considerable variation, not only in the expression of various neurovegetative symptoms themselves, but also in the magnitude of severity of these symptoms. While many mild to moderate illnesses may not necessarily present situations requiring immediate attention, the presence of severe depressive symptoms may represent an urgent condition, even in the absence of suicidal ideation.
- **Suicidality** – Suicidal behavior is best assessed with the following criteria: current suicidal ideas or plans, presence of active mental illness (severe depression or psychosis), presence of substance use disorder, past history of suicidal acts, formulation of plan, availability of means for suicide (firearms, pills, etc.), disruption of important personal relationships, or failure at important personal endeavors.
- **Potential for violence** – Violence often emerges as a response to a perceived threat or as marked frustration resulting from the inability to meet goals by nonviolent means. Specific factors that contribute to violent behavior include psychiatric, medical, environmental, and situational/social factors.
- **Unstable urgent medical conditions** – Any condition immediately threatening to life, limb, or eye sight, or requiring emergency medical care. These may include acute myocardial infarction, respiratory failure, hypertensive crisis, diabetic ketoacidosis, crushing radiating chest pain, or other unstable conditions

IS THERE EVIDENCE OF PSYCHOSIS?

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

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

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

B-4. Refer for Hospitalization

BACKGROUND

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

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

ACTION STATEMENT

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

RECOMMENDATIONS

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

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

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

For recommendation on modifying medication treatmnent see Annotation B-7

B-6. Pharmacotherapy for Bipolar Depression

BACKGROUND

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

ACTION STATEMENT

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

RECOMMENDATIONS

General considerations

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

6. In selecting a drug treatment regimen for patients with bipolar disorder, clinicians should be aware of the patient's other psychiatric and medical conditions and should try to avoid exacerbating them.
7. In selecting a drug treatment regimen for patients with diabetes or obesity consider the risk and benefit of utilizing medications that are less associated with weight gain.

Monotherapy

8. Quetiapine, [A], lamotrigine [B], or lithium [B] monotherapy should be considered as first-line treatment for adult patients with BD depression.
9. Olanzapine/fluoxetine combination (OFC) should be considered for treatment of BD depression, but its adverse effects (weight gain, risk of diabetes, hypertriglyceridemia) places this combination as a second-line treatment. [B]
10. Olanzapine alone may be considered for BD depression, but adverse effects require caution. [C]
11. There is insufficient evidence to recommend for or against the use of valproate, carbamazepine, topiramate, risperidone, ziprasidone, or clozapine for BD depression. [I]
12. Aripiprazole NOT recommended for monotherapy in the treatment of acute bipolar depression, unless there is a history of previous good response during depression without switch to mania or a history of treatment refractory depression. [D]

Combination Strategies

13. Combining lithium with lamotrigine can be considered for patients with BD depression who do not respond to monotherapy. [A]
14. When patients do not respond to treatment options that have shown better efficacy, antidepressant augmentation with SSRI, SNRI, buproprion, and MAOI can be considered for short-term treatment monitoring closely for triggering of manic symptoms. [C]
15. Clozapine may be considered for augmentation, using caution regarding metabolic or other adverse effects. [I]
16. There is insufficient evidence to recommend for or against use of augmentation with aripiprazole, olanzapine, risperidone, haloperidol, oxcarbazepine, topiramate, ziprasidone, valproate, or carbamazepine for the treatment of bipolar depression. [I]
17. Gabapentin and the tricyclic antidepressants (TCAs) are NOT recommended for monotherapy or augmentation in the treatment of acute bipolar depression, unless there is a history of previous good response during depression without switch to mania or a history of treatment refractory depression. [D]

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

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

SR = Strength of Recommendation (See Appendix A)

EVIDENCE STATEMENT

For a discussion of the supporting evidence used in grading the recommendation see Module E: Pharmacotherapy Interventions.

B-7. Modify Dose or Medication if Indicated, Using Medications Effective for Bipolar Depression

BACKGROUND

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

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

RECOMMENDATIONS

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

Partial response

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

RATIONALE

Most patients with bipolar disorder will have a recurrence of depression or mania after the initial episode. Symptomatic bipolar disorder patients spend, on average, 33% of their time in a depressive phase compared with 11% in a manic/hypomanic phase (Post, 2004). Depressive symptoms tend to occur 3 to 4 times more frequently than manic symptoms (Judd et al., 2002; Post et al., 2003). In addition, impairment in work, social life, and family

life appears to be more significantly impacted by depressive rather than manic symptoms (Calabrese et al., 2004). Yet, the treatment of bipolar depression remains understudied. All current guidelines recommend that depressed bipolar I (and most bipolar II) patients first be optimized on a mood stabilizer to have improved outcomes (APA, 2002; Goodwin, 2003; Suppes et al., 2005).

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

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

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

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

BACKGROUND

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

RECOMMENDATIONS

1. Ongoing assessment of patients starting treatment for acute bipolar depression should include a reassessment for: [I]
    a. Changes in depressive symptoms
    b. Neurovegetative symptoms
    c. Emerging symptoms of mania/hypomania
    d. Psychotic symptoms
    e. Development of suicidal or homicidal ideation
    f. Substance use
    g. Adverse effects of medications
    h. Medication compliance
    i. Medical stability (e.g., blood pressure)
    j. Significant changes in psychosocial circumstances
2. Reassess patient every 1 to 2 weeks for at least 6 weeks. [I]
3. Ongoing assessment of patients starting treatment for acute bipolar depression may include pertinent laboratory studies (e.g., medication plasma concentrations, urine drug screening, CBC, blood glucose, liver panel, lipid panel) and weight. [I]

RATIONALE

- Treatment of acute bipolar depression can result in dramatic changes in the patient's symptoms, including the development of new symptoms. Providers need to monitor these changes until the patient enters full remission. Providers also need to monitor for emergence of manic symptoms,

especially if antidepressant augmentation is used for treatment. The use of standardized rating scales for the monitoring of symptoms is often a helpful way to document progress of therapy.

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

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

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

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

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

BACKGROUND

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]

EVIDENCE STATEMENTS

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

B-10. Is Patient Responding to Treatment?

BACKGROUND

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

RECOMMENDATIONS

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

B-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]

RATIONALE

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

EVIDENCE TABLE

	Evidence	Source	LE	QE	SR
1	Full remission from bipolar depression is defined as two months with no significant signs or symptoms of depression	DSM-IV-TR	III	Poor	I

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

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

BACKGROUND

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

ACTION STATEMENT

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

RECOMMENDATIONS

1. Patients should be followed by a scheduled visit to the clinic periodically, depending on their response, for a thorough assessment that includes:
    a. Adherence to therapy. Reasons for noncompliance should be explored with the patient. [B]
    b. Assessment of potential adverse effects. [A] (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. Assess for co-occurring medical conditions that can mimic or exacerbate bipolar disorder depression. [B]
    f. Assessment of any changes in patient's family and community support (housing, care givers, employment, income, social networks). [B]
2. Assess for improvement or change of the core symptoms of depression through a clinical interview or the use of a standardized rating scale to determine changes in the severity of depression. [I]
3. Patients with suicidal ideation should have a careful evaluation of suicide risk. [A]

RATIONALE

Treatment nonadherence is very common in bipolar disorder (Colom et al., 2000) and can be associated with rehospitalization and suicide. Though more common in the maintenance phase, treatment nonadherence secondary to disability and poor insight is more likely to be a problem during acute bipolar

depression. Nonadherence rates are reported as high as 18 – 53% (Goodwin & Jamison, 1990) and 30% (Sajatovic et al., 2004), some of the factors influencing treatment adherence include (Jamison et al., 1979; Sajatovic et al., 2004):

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

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

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

EVIDENCE STATEMENTS

- "Medication side effects, costs, and other demands of long-term treatment…need to be discussed realistically with the patient and family members. Many side effects can be corrected with careful attention to dosing, scheduling, and preparation" (APA, 2002).
- "Patients with this disorder are frequently ambivalent about treatment. This ambivalence often takes the form of noncompliance with medication and other treatments, which is a major cause of relapse" (APA, 2002).
- "Patients with bipolar disorder benefit from education and feedback regarding their illness, prognosis, and treatment. Frequently, their ability to understand and retain this information will vary over time. Patients will also vary in their ability to accept and adapt to the idea that they have an illness that requires long-term treatment. Education should therefore be an ongoing process in which the psychiatrist gradually but persistently introduces facts about the illness" (APA, 2002).
- A systematic review by Sajetovic et al., (2004) noted that effective therapies are "patient-focused and include family members or significant others whenever possible." Promotion of treatment adherence was facilitated through a longitudinal interactional component between patients and care providers and frequently focused on issues of "appropriately taking medications to manage illness."

The effect of treatment for BD on other medical conditions

- The use of antipsychotic medications for bipolar disorder is associated with higher risk of weight gain, obesity and progression of diabetes. Other medication commonly used in BD may cause hypothyroidism, thyroid disease, polycystic ovarian syndrome, renal disease, and skin disorders. The adverse events and drug-drug interactions of the medications commonly used to treat BD (Lithium, first and second generation antipsychotics, and antidepressants for depressive episodes) are addressed in Module E.

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

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

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

EVIDENCE TABLE

	Evidence	Source	LE	QE	SR
1	Monitor and adjust treatment for mediation side effects.	APA, 2002	III	Poor	C
2	Psychoeducation to improve adherence.	Colom et al., 2000 Sajatovic et al., 2004 SR	I	Good	B
3	Assess for and address cognitive and functional barriers to compliance.	Martinez-Aran, 2004	I	Fair	C

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

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

BACKGROUND

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

ACTION STATEMENT

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

RECOMMENDATIONS

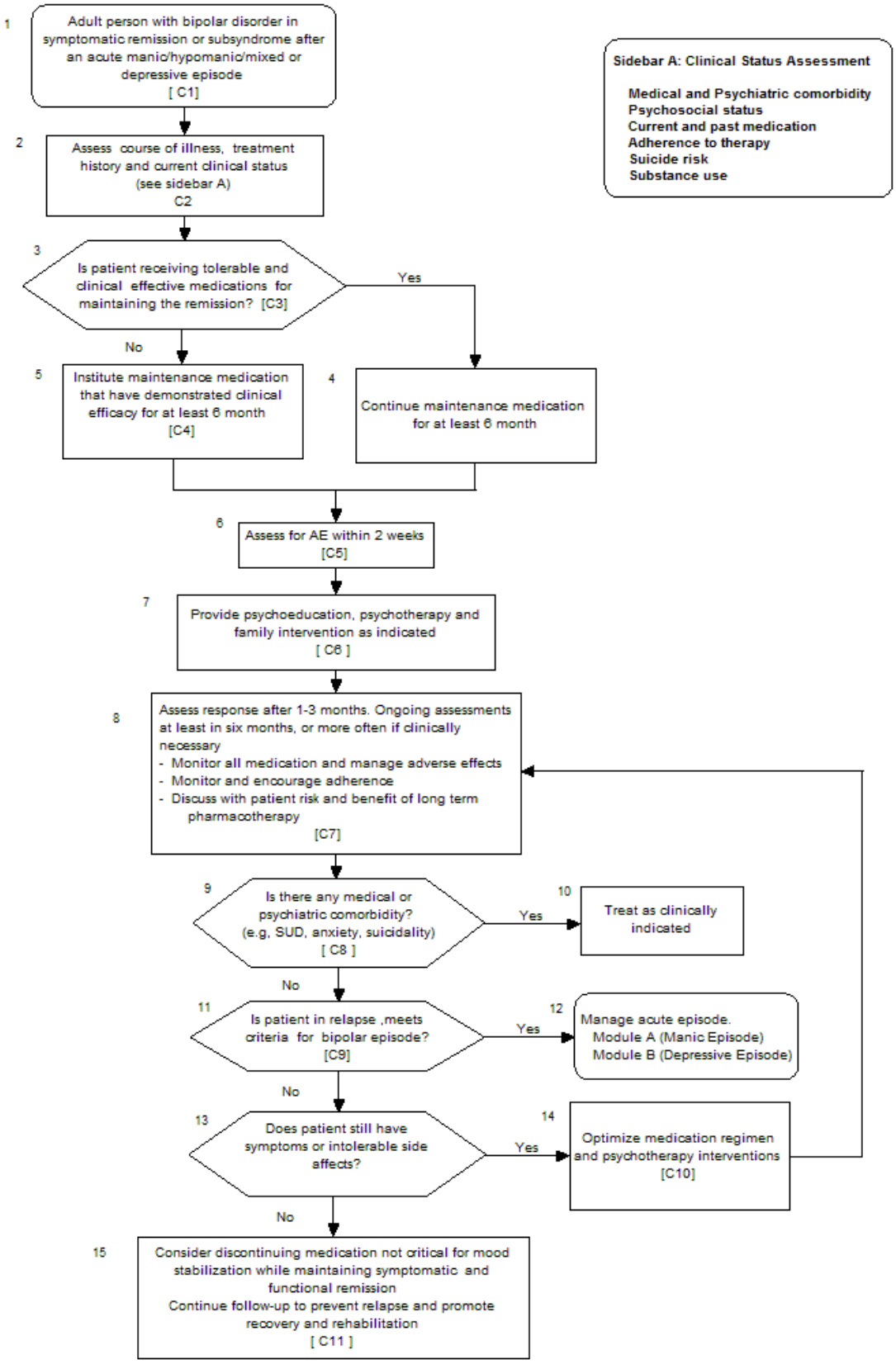
1. Electro-convulsive therapy (ECT) should be initiated in patients with severe or refractory bipolar depression who consent and have no absolute medical contraindications. [B]
2. The risk for mood destabilization or switching to mania should be evaluated and the patient should be monitored closely for emergent symptoms.

EVIDENCE STATEMENT

For discussion of the evidence see Module E: Interventions -ECT

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]

RATIONALE

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

EVIDENCE STATEMENTS

- The APA (2002) Guideline states that following remission of an acute episode, patients may remain at particularly high-risk of relapse for a period of up to 6 months; this phase of treatment, sometimes referred to as continuation treatment, is considered in this guideline to be part of the maintenance phase. Maintenance regimens of medication are recommended following a manic episode. Although few studies involving patients with bipolar II disorder have been conducted, consideration of maintenance treatment for this form of the illness is also strongly warranted
- According to Simon et al., (2005) “A systematic care program for bipolar disorder significantly reduces risk of mania over 12 months. Preliminary results suggest a growing effect on depression over time, but longer follow-up will be needed”.
- If a patient and/or physician elect to discontinue mood stabilizer medication, a very slow and gradual taper schedule should be used, since there is some data (Suppes et al., 1991; Faedda et al., 1993) stating that an episode of bipolar disorder may occur sooner, and there is an increase in suicide risk (Baldessarini et al., 1999), in patients who stop mood stabilizers abruptly.
- Suppes et al., (1991) compiled data from 124 patients with BD type I in 10 studies who were stable for an average of at least 30 months prior to lithium discontinuation. Fifty percent (50%) of persons relapsed within 5 months of discontinuation, and half of these relapsed within 6 weeks. Among those who relapsed, mania occurred more often than depression, and significantly earlier (2.7 versus 14

months). The time to relapse after discontinuation was shorter than the prior illness pattern would have predicted, suggesting that lithium discontinuation may have caused a physiological "stress" to otherwise stable persons. Suppes et al., (1993) reviewed another 15 studies of 632 persons with mood disorders and determined that relapse rates were almost threefold higher after lithium discontinuation (75 percent versus 27 percent).

- Faedda et al., (1993) compared rapid (< 2 weeks) versus slower (2 to 4 weeks) lithium discontinuation in a prospective naturalistic study of 64 bipolar type I or II persons stable for an average of 3.6 years. Rapid discontinuation resulted in more and earlier relapses.
- Bouman et al., (1986) found earlier and more frequent relapses in bipolar or schizoaffective persons after lithium was discontinued during lithium treatment. Mortality from suicide and from other medical causes (Muller-Oerlinghausen et al., 1992; Nilsson, 1995) appeared to be higher as well.
- Also, up to 20 percent of persons for whom lithium is discontinued respond less well to lithium if it is later reinstituted (Maj et al., 1995). Although there are no data regarding other mood stabilizers, similar concerns apply, and similar procedures should be followed.

EVIDENCE TABLE

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

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

C-2. Assess Course of Illness, Treatment History, and Current Clinical Status

BACKGROUND

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

Table C - 1 Clinical Status Assessment

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

RECOMMENDATIONS

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

DISCUSSION

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

- Bipolar disorder with a co-occurring substance use disorder (SUD) is a very common presentation. Substance abuse may precipitate mood episodes or be used by patients to ameliorate the symptoms of such episodes. Co-occurring substance use is typically associated with fewer and slower remissions, greater rates of suicide and suicide attempts, and poorer outcomes. Co-occurring SUD should be managed according to the VA/DoD Guideline for Substance Use Disorder.
- Suicide completion rates in patients with bipolar I disorder may be as high as 10 – 20%; thus, a careful assessment of the patient's risk for suicide is critical.
- The adverse effects of medication, the availability of medications, family and community support and the patient's ambivalence about medications all can affect their adherence to the medication regimen and can affect rates of relapse.

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

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

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

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

BACKGROUND

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

ACTION STATEMENT

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

RECOMMENDATIONS

1. Consider using the agent(s) that have been effective in the recent acute phase or in past mood episodes. (See Table C-2) [I]
2. Consider reducing to a single medication (monotherapy) that has been shown to be most effective in delaying/preventing relapse while minimizing the potential risks by monitoring the patient closely. [I]
3. Consider the pharmacokinetics, adverse effects, and drug-drug interactions when selecting the specific agent(s). [I]
4. Lithium [A] or olanzapine [B] should be considered as first-line maintenance treatment for adults with BD to delay/prevent the recurrence of mania.
5. Risperidone long-acting IM injection should be considered for patient with frequently relapses. [B]
6. Aripiprazole [B] may be considered as a second line treatment to prevent or delay the recurrence of mania.

7. Lithium, or lamotrigine, should be considered as a first-line treatment to prevent or delay the recurrence of bipolar depression. [B]
8. Olanzapine may be considered as a second line treatment to prevent /delay bipolar depressive episodes. [C]
9. Quetiapine augmentation of valproate or lithium should be considered a first-line maintenance treatment for adults with BP to maintain remission and prevent new episodes of all types.[B]
10. Adding Olanzapine to lithium or valproate may be used in maintenance treatment to delay or prevent symptomatic relapse. [C]
11. In patients with a history of severe or recent mania, lamotrigine should be used in combination with lithium, olanzapine, or aripiprazole. [I]
12. Valproate and carbamazepine may also be considered as alternatives for maintenance medication. [C]
13. There is insufficient evidence to recommend for or against other antipsychotic or anti-epileptic agents in the maintenance treatment of Bipolar Disorder.

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

Likely to be Beneficial [SR]	Trade off between Benefit and Harm [SR]	Unknown	Unlikely to Be Beneficial or May be Harmful
Monotherapy: - Lithium [B*/A**] - Lamotrigine [B*/C**] - Olanzapine [C*/B**] *Combination*: - 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 injetion for patient with frequent recurrences			

SR = Strength of Recommendation (See Appendix A)

EVIDENCE STATEMENTS

- There is good evidence to demonstrate that specific medication treatments delay/prevent the time to relapse in bipolar disorder. Therefore, long term maintenance medication is generally recommended. The choice of medication depends on the balance between effectiveness of the medication in maintaining euthymia and the tolerability of adverse effects (possible harm). It is general clinic practice to continue the medication that led to remission. In patients who are not currently on medications or who are not tolerating their current medications, providers should consider those medications which have the strongest evidence as a Maintenance Treatment.
- Data suggests that some medications are more effective in preventing the depressed phase while others are more effective in preventing the manic phase. The choice of a maintenance treatment needs to consider the individual's course of illness. As an example, if the individual has had a greater number of manic episodes, it may be logical to use agents that have been shown to be better in preventing

manic episodes (e.g. lithium, valproate, an antipsychotic). Clearly, both phases should be prevented, and all patients with recurrent bipolar disorder should be receiving prophylaxis medication therapy.

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

For a discussion of the supporting evidence used in grading the recommendation see **Module E Pharmacotherapy Interventions**

C-5. Assess for Adverse Events within 2 Weeks

BACKGROUND

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

ACTION STATEMENT

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

RECOMMENDATIONS

1. Using a standardized clinical tool in addition to a clinical interview, assess for response to treatment, adherence to treatment and adverse effects of treatment after initiating or changing treatment.
2. Identified side effects should be managed to minimize or alleviate if possible.

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]

EVIDENCE STATEMENTS

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

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

BACKGROUND

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

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

Other strategies include:

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

ACTION STATEMENTS

Patients' adherence to treatment should be assessed. Barriers to adherence should be addressed.

RECOMMENDATIONS

1. Patients whose BD is in remission should be followed by a scheduled visit to the clinic every 1 to 3 months with a thorough assessment of current and recent symptoms. [I]
2. All patients on medication should be monitored for potential adverse effects. [B] (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] (See **Table E** - 5 Recommended Pharmacotherapy Monitoring)
4. 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)

5. Adherence to medication therapy should be routinely evaluated at each visit. Reasons for noncompliance should be explored with the patient. [A]
6. Assess any changes in patient's family and community support (e.g., housing, care givers, employment, income, social networks). [C]

EVIDENCE STATEMENTS

- Treatment nonadherence is very common in bipolar disorder (Colom et al., 2000) and can be associated with rehospitalization and suicide. Treatment non-adherence secondary to disability and poor insight is a common problem during maintenance treatment. With nonadherence rates cited as 18 – 53% (Goodwin & Jamison, 2007) and 30% (Sajatovic et al., 2004), some of the factors influencing treatment adherence include illness denial, psychosis, feeling depressed, side effects, and comorbid disorders, (Jamison et al., 1979; Sajatovic et al., 2004). Minimizing medication side effects seems especially important in assuring medication adherence.
- One consequence of non-compliance is that rapid discontinuation of lithium leads to a high rate of relapse, greater than the 'natural' pattern; 50% of patients relapse within 5 months (mostly with mania) (Suppes et al., 1991).
- "Medication side effects, costs, and other demands of long-term treatment…need to be discussed realistically with the patient and family members. Many side effects can be corrected with careful attention to dosing, scheduling, and preparation" (APA Guidelines, 2002).
- "Patients with this disorder are frequently ambivalent about treatment. This ambivalence often takes the form of noncompliance with medication and other treatments, which is a major cause of relapse" (APA Guidelines, 2002).
- "Patients with bipolar disorder benefit from education and feedback regarding their illness, prognosis, and treatment. Frequently, their ability to understand and retain this information will vary over time. Patients will also vary in their ability to accept and adapt to the idea that they have an illness that requires long-term treatment. Education should therefore be an ongoing process in which the psychiatrist gradually but persistently introduces facts about the illness" (APA Guidelines, 2002).
- A systematic review by Sajetovic et al. (2004) noted that effective therapies are "patient-focused and include family members or significant others whenever possible." Promotion of treatment adherence was facilitated through a longitudinal interactional component between patients and care providers and frequently focused on issues of "appropriately taking medications to manage illness."

EVIDENCE TABLE

	Evidence	**Source**	**LE**	**QE**	**SR**
1	Monitor and adjust treatment for mediation of side effects.	APA Guidelines, 2002	III	Poor	I
2	Psychoeducation to improve adherence.	Colom et al., 2000 Sajatovic et al., 2004 SR	I	Good	B
3	Assess for and address cognitive and functional barriers to compliance.	Martinez-Aran, 2004	II	Poor	C
4	Assess for and address psychosocial barriers to compliance.	APA Guidelines, 2002	II	Poor	C

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

C-8. Is there any Medical or Psychiatric Comorbidity

BACKGROUND

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

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

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

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

ACTION STATEMENT

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

RECOMMENDATIONS

1. 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.

RATIONALE

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

DISCUSSION

Epidemiology of Medical Comorbidity and Bipolar Disorder

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

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

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

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

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

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

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

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

The effect of treatment for BD on other medical conditions

The use of antipsychotic medications for bipolar disorder is associated with higher risk of weight gain, obesity and progression of diabetes. Other medication commonly used in BD may cause hypothyroidism, thyroid disease, polycystic ovarian syndrome, renal disease, and skin disorders. The adverse events and drug-drug interactions of the medications commonly used to treat BD (Lithium, first and second generation antipsychotics, and antidepressants for depressive episodes) are addressed in Module E.

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

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

Co-occurring general medical conditions may also contribute to greater bipolar illness severity and reduced recovery, impaired quality of life and increased/premature mortality (Carney & Jones 2006; McIntyre et al. 2007). Chronic medical disorders are associated with a more severe course of BD, increased burden of

disease and psychosocial stressors (employment adjustment, disability reimbursement, and increased frequent utilization of health services). Comorbid medical disorders in bipolar disorder are associated with several indices of harmful dysfunction, decrements in functional outcomes, and increased utilization of medical services. (McIntyre et al. 2006)

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

Psychiatric comorbidity

- Medical conditions can lead to mood change episodes or can exacerbate the course of bipolar illness and complicate recovery.
- Patients with bipolar disorder are at greater risk for comorbid anxiety disorders, especially panic disorder and obsessive-compulsive disorder. Comorbid anxiety disorders may lead to longer recovery times from mood episodes.
- Co-occurring alcohol abuse or dependence is found in 46% of patients with a bipolar disorder. The prevalence of drug abuse or dependence is 41% in the bipolar population.
- The course of bipolar illness for comorbid personality disorders is frequently worse with lower recovery rates, greater impairment, and a higher risk for relapse.
- Patients with bipolar disorder are at high-risk for suicide. The completed suicide rate in bipolar I disorder is estimated to be 10-20%.
- There is insufficient evidence to indicate whether patients with a co-occurring SUD should be managed differently than other patients with BD. There is also insufficient evidence to indicate the order of treating BD and co-occurring SUD (Vornik 2006). Generally, practitioners treat the mood instability and address any immediate needs or detoxification for a given patient. Once stabilized, the substance abuse or dependence takes on a more primary focus of the treatment plan.

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

BACKGROUND

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

ACTION STATEMENT

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

RECOMMENDATIONS

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

See Module B – For management of Bipolar Acute Depressive Episode.

C-10. Optimize Medication Regimen and Psychotherapy Interventions

BACKGROUND

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

RECOMMENDATIONS

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

C-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.

PSYCHOEDUCATION

BACKGROUND

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

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

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

RECOMMENDATIONS

1. Patient should receive psychoeducation that emphasizes: [B]
    a The importance of active involvement in their treatment
    b The nature and course of their bipolar illness
    c The potential benefit and adverse effects of treatment options
    d The recognition of early signs of relapse
    e Behavioral interventions that can lessen the likelihood of relapse including careful attention to sleep regulation and avoidance of substance misuse.
2. With the patient's permission, family members or significant other should be involved in the psychoeducation process. [C]
3. A structured group format in providing psychoeducation and care management for patients with clinically significant mood symptoms should be considered. [A]

RATIONALE

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

EVIDENCE STATEMENTS

Johnson et al., (1997) found that negative life events were associated with slow recovery from bipolar depressive episodes. However, life events that were positive and involved goal attainment (e.g., getting promoted) were associated with an increase in manic symptoms (Johnson et al., 2000). A retrospective study found that bipolar patients often experienced events that disrupted their sleep/wake rhythms in the months preceding manic onset, although not prior to depressive onset (Malkoff, et al., 2000; Malkoff et al., 1998). These studies underlined the role of stress in mediating the relations between biological vulnerability and relapse, and paved the way for studies of psychosocial treatment as adjunctive to medication.

These interventions have many commonalities, as discussed by Scott and Gutierrez, (2004); they all include psychoeducation about BD, encouragement of medication adherence, recurrence prevention strategies, mood monitoring, and illness management skills.

- Patients with bipolar disorder benefit from education and feedback regarding their illness, prognosis, and treatment. Patients may experience considerable difficulty performing at the level for which their education has prepared them. Patients will also vary in their ability to accept and adapt to the idea that they have an illness that requires long-term treatment (APA, 2002). Education should therefore be an ongoing process and the goals of education need to be sustained and incremental. (APA, 2002).
- A systematic review by Sajetovic et al., (2004) noted that effective therapies are "patient-focused and include family members or significant others whenever possible." Promotion of treatment adherence was facilitated through a longitudinal interactional component between patients and care providers and frequently focused on issues of "appropriately taking medications to manage illness."
- Colom, et al., (2003) found that patients in a 21 week structured psychoeducation group had longer intervals prior to recurrences (relapse prevention) than patients in an unstructured support group. Colom, et al., (2005) found that during the Colom et al., (2003) 2-year study, relapses occurred earlier and more often among patients in the unstructured group (92%) than in the structured group (67%). Patients in the structured group had higher and more stable lithium concentration as well. However, the structured group had a higher drop-out rate (27%) than the unstructured groups (12%).

EVIDENCE TABLE

	Evidence	Source	LE	QE	SR
1	Psychoeducation to improve adherence.	Colom et al., 2000 Sajatovic et al., 2004 SR	I	Good	B
2	Assess for and address cognitive and functional barriers to compliance.	Martinez-Aran, 2004	I	Fair	C
3	Structured psychoeducation approach leads to longer intervals prior to recurrences	Colom et al., 2003 Colom et al., 2005	I	Fair	B
4	Structured group psychoeducation with systematic chronic care/disease models (CCM) leads to fewer weeks of mood episodes and fewer manic episodes	Bauer et al., 2006 a,b Simon et al., 2005 Simon et al., 2006	I	Good	A

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

PSYCHOTHERAPY STRATEGIES

COGNITIVE BEHAVIORAL (CBT)

BACKGROUND

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

RECOMMENDATIONS

1. Cognitive Behavioral Treatment (CBT) may be considered as an adjunct to pharmacotherapy for patients with BD who have achieved remission from an acute manic episode and who have had fewer than 12 previous BD acute episodes [A]
2. Implementation of CBT should include components of:
    a. Education regarding symptoms, course and treatment of BD,
    b. Scheduling of pleasurable events to alleviate inactivity,
    c. Teaching the skill of cognitive re-structuring,
    d. Learning to identify maladaptive thoughts and challenge them on logical grounds,
    e. Learning to replace maladaptive thoughts with balanced or adaptive thinking,
    f. Problem solving, and
    g. Learning to detect the earliest signs of recurrence and implement early intervention plans.
3. In considering patients for CBT it is recommended that careful screening for hypomanic episodes be conducted (dynamism, persuasiveness, productiveness) as there is some evidence to support that CBT is less effective with these patients.
4. CBT can be considered as an approach to reduce and prevent depressive symptoms in BD rather than manic symptoms as it has been found to be most effective in depression. [B]

RATIONALE

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

EVIDENCE STATEMENTS

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

CBT was evaluated in a five-site U.K. multicenter “effectiveness” trial for 253 bipolar patients treated at community mental health centers (Scott et al., 2006). Like the study by Lam et al., (2003), this study compared CBT (22 sessions) and medications with usual care and medications, but unlike the prior study,

patients could enter in any clinical state (recovered, subsyndromal, or syndromal). There were no differential effects of CBT and pharmacotherapy on time to recurrence over an 18-month follow-up. Patients with fewer than 12 prior illness episodes had fewer recurrences in CBT than in treatment-as-usual, but patients with 12 or more episodes had fewer recurrences in treatment-as-usual than CBT. Possibly, CBT is most appropriate for patients in the early stages of their disorder or those who are less recurrent.

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

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

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

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

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

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

EVIDENCE TABLE

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

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

INTERPERSONAL AND SOCIAL RHYTHM THERAPY (IPSRT)

BACKGROUND

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

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

RECOMMENDATIONS

1. Interpersonal and Social Rhythm Therapy (IPSRT) may be considered for patients with BD who have achieved remission from an acute manic episode and are maintained on prophylactic medication. [B]
2. Interpersonal and Social Rhythm Therapy (IPSRT) should contain the following components:
    a. Patients should complete the Social Rhythm Metric questionnaire which is a self-report instrument for tracking and quantifying daily and nightly routines, along with ratings of mood
    b. Providers need to assist patients in keeping regular routines (e.g., bed times, wake times, exercise) and minimizing the impact of events that could disrupt their moods and daily/nightly stability
    c. Providers need to maintain an interpersonal focus that concerns the resolution of the patient's current problems (e.g., how to communicate better with one's spouse) and developing strategies for preventing the same problems from recurring in the future.

RATONALE

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

EVIDENCE STATEMENTS

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

Frank and colleagues, (2005) also found that IPSRT was less effective among patients with medical co-morbidities.

Weismann et al., (2000) discusses the interpersonal psychotherapy of depression.

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

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

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

EVIDENCE TABLE

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

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

FAMILY THERAPY

BACKGROUND

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

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

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

RECOMMENDATION

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

RATIONALE

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

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

EVIDENCE STATEMENS

Fitzgerald, (1972) discussed family therapy as a way of augmenting response to lithium

Davenport et al., (1977) described the benefits of a psychoanalytic couples' group.

Clarkin et al., (1990) in a study conducted in the late 1980s; demonstrated the utility of psychoeducation for couples and families coping with bipolar disorder, either done on an inpatient or outpatient basis

Van Gent & Zwart (1991) in a study conducted in the late 1980s, demonstrated the utility of psychoeducation for couples and families coping with bipolar disorder, conducted on either an inpatient or outpatient basis

Miklowitz and Goldstein, (1990) developed a manual based family-focused treatment (FFT).

Simoneau et al., (1999) studied 101 patients who were randomly assigned to FFT and pharmacotherapy or an active crisis management comparison treatment consisting of two sessions of family education, crisis intervention sessions as needed, and pharmacotherapy. Patients in FFT were more likely to survive the two-year follow-up without recurrence (52%) than patients in active case management (17%). Patients in FFT also had less severe depressive and manic symptoms over the two year study.

Miklowitz et al., (2003) conducted post-hoc analyses of the Simoneau et al., (1999) study and uncovered two mediators of the effects: greater consistency of medication adherence and improvements in the emotional tone of patient/relative verbal interactions.

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

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

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

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

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

EVIDENCE TABLE

	Evidence	Source	LE	QE	SR

1	Development of manual-based, 21 session family focused treatment (FFT) model	Miklowitz & Goldstein, 1990	II-3	Fair	C
2	FFT adjunct to maintenance pharmacotherapy is effective	Simoneau et al., 1999 Miklowitz et al., 2003 Rea et al., 2003	II	Good	C
3	Family intervention does not improve recovery compared to pharmacotherapy alone.	Miller et al., 2004 & 2008	I	Fair	B
4	Positive effect among those from high impairment families	Miller et al., 2008	I	Fair	C
5	Intensive psychosocial treatment, as an adjunct to pharmacotherapy improved remission from BD depression	Miklowitz et al., 2007	I	Good	A

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

CHRONIC CARE MODELS INTERVENTIONS

BACKGROUND

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

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

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

RECOMMENDATIONS

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

DISCUSSION

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

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

Bauer et al., (2006a, b) randomized 330 patients from 11 VA sites around the U.S. to group-based psychoeducation combined with systematic chronic care management (CCM) or usual care. Group-based psychoeducation consisted of 5 weekly sessions based on the Life Goals program (Bauer and McBride, 1996) led by a nurse, who also followed up with patients via twice-monthly contacts and continuity procedures based on the chronic care model

(CCM). The patient sample included older individuals who had been recently hospitalized and had co-occurring substance use and medical disorders. The CCM combined patient structured group psychoeducation (Life Goals) with ongoing care management that provided access and continuity of care support along with guideline dissemination and outcomes monitoring. Compared to usual VA care, PE+CCM led to 6.2 fewer weeks of mood episodes (p=0.041), and 4.5 fewer weeks of manic episodes, improved overall function (+30%; p=0.003), improved mental health-related quality of life (37.6 vs. 34.1; p=0.01), as well as treatment satisfaction. There were no effects on depressive symptoms over time. Fidelity to PE-SSM exceeded 80% in the study sample.

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

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

EVIDENCE TABLE

	Evidence	Source	LE	QE	SR
1	CCMs reduce manic symptoms and improve overall quality of life	Lam et al., 2003, 2005 Bauer et al., 2006b Simon et al., 2006 Kilbourne 2008	I	Good	A
2	CCMs should be offered in addition to stand-alone psychotherapies in the management of patients with bipolar disorder	Scott et al., 2006 Sajatovic et al., 2009	I	Fair	B

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

POTENTIAL BENEFIT OF LITHIUM

USE IN ACUTE MANIA

In a review of placebo controlled trials lithium was shown to be significantly more effective than placebo in the treatment of acute mania (Licht et al., 2006). In recent trials, lithium has been frequently used as an active comparator and "gold" standard to assess newer compounds. These studies have tended to show that lithium was more effective than placebo and was as effective as the newer agents.

Niufan et al., (2008) in a double blind RCT, compared lithium (N=69) and olanzapine (N=71) and found both medications had equivalent remission rates, although in this 4-week study olanzapine was significantly better in decreasing the score on the mania scale. Adverse effects were, however, less frequent in the lithium treated population. Olanzapine was more frequently associated with increases in weight and body mass index.

Bowden et al., (2008) in an open randomized 12 week study evaluated lithium (N=149) and valproate (N=149). There were no significant differences in the remission rate at 3 months. Median blood concentrations at the end of the study were 57.9 mcg/mL for valproate and 0.68 mEq/L for lithium. In this study both responder and remission rates were unusually high. Tremor was more common in patients on lithium while fatigue was more common in the valproate group.

Keck et al., (2009) carried out a double-blind, placebo-controlled study comparing aripiprazole (N=155) and lithium (N=165) to placebo (N=160). This 3 week study showed that both aripiprazole and lithium significantly improved clinical symptoms on the YMRS compared to placebo. The study did not show a statistically significant difference between lithium and aripiprazole.

Hirschfeld et al., (2003) looked at numerous treatment regimens for acute mania including lithium up to 300 mg three times per day (N=54), valproate with a rapid loading dose up to 1000 mg per day (N=80), valproate at a standard titration (N=87), olanzapine up to 20 mg per day (N=55) , and placebo (N=72). At these low doses the rapid loading dose of valproate was more effective than the lithium on the Behavior and Ideation Scale.

Bowden et al., (2005) compared quetiapine up to 800 mg per day (N=107) with lithium with a targeted blood concentration between 0.7 -1.4 mEq/L (N=98), and placebo (N=97). The lithium arm of this trial showed significant improvements on a number of scales including the YMRS, PANSS, MADRS, GAS, and the CGI-BP compared to placebo. It also demonstrated a greater remission rate than placebo.

USE IN ACUTE DEPRESSION

Lithium based on clinical experience is a first line for treating depression.

Zornberg & Pope, (1993) reviewed the clinical literature on the acute treatment of the depressed phase of bipolar disorder. Eight of nine controlled comparisons found lithium superior to placebo in depressed bipolar patients. Three controlled comparisons of lithium to tricyclic antidepressants suggest that lithium is equivalent to tricyclic drugs in such patients.

Suppes et al., (2008) studied bipolar II acute depression response in a single-blind, open, and randomized comparison of lithium versus lamotrigine. Both medications were effective in this moderate size (n=98) single blind open trial.

USE IN MAINTENANCE (PROPHYLAXIS)

Systematic reviews

Baker, (1994) conducted a systematic review which included meta-analysis on 19 studies (n=546) reported that lithium is an effective prophylactic treatment for patients with affective disorders. However, as with many drugs that operate to prevent rather than to cure, one must be careful about the consequences of discontinuing a treatment which is effectively keeping an illness at bay. Patients discontinuing lithium do appear to be more likely to relapse than those who continue to take the drug. While statistically significant, this difference is not as great as has been reported in other reviews, although it still clearly indicates that lithium use can be efficacious in suspending symptoms of manic-depressive illnesses.

Burgess et al. (2001) Cochrane Systematic Review concluded that "This systematic review of nine randomized controlled trials comparing lithium with placebo in the maintenance treatment of mood disorder shows that for mixed diagnoses of mood disorder and in bipolar disorder, lithium is more efficacious than placebo in preventing relapse over periods of up to four years." There remains uncertainty over the value of lithium maintenance treatment in unipolar disorder. The number of participants in the studies is small (835 participants) and the included studies have various methodological shortcomings. The results should be interpreted in light of this. The modest number of participants has also meant that sub-groups analyses (e.g., analyzing efficacy in participants with longer or shorter histories of mood disorder) have not been possible.

Geddes et al. (2004) conducted a meta-analysis of placebo-controlled randomized maintenance studies with lithium. Their analysis combined 5 trials with 770 participants. Lithium was protective against manic recurrences (random effects risk ratio = 0.65, 95% confidence limits 0.5 – 0.84) and for all recurrences (risk ratio 0.62, confidence limits 0.4 – 0.95). Its effects against depressive episodes were not quite statistically significant (risk ratio 0.72, confidence limits 0.49 – 1.07).

Cipriani et al., (2005) conducted a systematic review and meta-analysis of randomized trials to investigate the effect of lithium, compared to placebo and other active treatments, on the risk of suicide, deliberate self-harm and all-cause mortality in patients with mood disorder. In 32 trials, 1,389 patients were randomly assigned to receive lithium and 2,069 to receive other compounds. Patients who received lithium were less likely to die by suicide (data from seven trials; two versus 11 suicides; odds ratio=0.26; 95% confidence interval [CI] =0.09-0.77). The composite measure of suicide plus deliberate self-harm was also lower in patients who received lithium (odds ratio=0.21; 95% CI=0.08-0.50). There were fewer deaths overall in patients who received lithium (data from 11 trials; nine versus 22 deaths; odds ratio=0.42, 95% CI=0.21-0.87).

RCTs

Bowden et al (2003) randomized 175 stabilized adult patients with Bipolar Disorder Type I to lamotrigine, lithium (0.8-1.1 mEq/L) or placebo for up to 18 months. All patients were required to enter manic, then stabilized and to remain stable on lamotrigine alone before randomization. Therefore, the sample was enriched for response to and toleration of lamotrigine, but not lithium. Both lamotrigine and lithium were superior to placebo at prolonging the time to intervention for any mood episode (lamotrigine vs. placebo, P =.02; lithium vs. placebo, P =.006). Lamotrigine was superior to placebo at prolonging the time to a

depressive episode (P =.02). Lithium was superior to placebo at prolonging the time to a manic, hypomanic, or mixed episode (P =.006). Lithium was superior to placebo in prolonging time to intervention (p=.003)

Calabrese et al., (2003) reported on data from patients stabilized on open-label treatment of lamotrigine (N = 463) who were randomly assigned to lamotrigine, lithium (0.8-1.1 mEq/L; N = 121), or placebo (N = 121) monotherapy for up to 18 months. As in the study by Bowden et al (2003), the sample was enriched for stabilization on lamotrigine. The primary outcome measure was time from randomization to intervention (addition of pharmacotherapy) for any mood episode (depressive, manic, hypomanic, or mixed). Time to intervention for any mood episode was statistically superior (p = .029) for both lamotrigine and lithium compared with placebo-median survival times were 200, 170, and 93 days, respectively. The proportions of patients who were intervention-free for depression at 1 year were lamotrigine 57%, lithium 46%, and placebo 45%. Lithium was statistically superior to placebo at prolonging the time to intervention for a manic or hypomanic episode (p = .026). The proportions of patients who were intervention-free for mania at 1 year were lamotrigine 77%, lithium 86%, and placebo 72%. Headache was the most frequent adverse event for all 3 treatment groups.

Goodwin, Bowden, Calabrese et al., (2004) provided pooled analysis of the above 2 placebo controlled 18-month trials of maintenance therapy with lamotrigine and lithium in bipolar I patients. Both lamotrigine and lithium were more effective than placebo in delaying the time to treatment for a mood episode. Lamotrigine was effective in delaying both depression and mania, with more robust efficacy in prevention of depression. Lithium was more effective in delaying manic episodes than both placebo and lamotrigine. This finding is particularly notable because the design was enriched for lamotrigine response and not for lithium response.

Tohen and colleagues, (2005) reported a randomized controlled trial for the prevention of mood episode relapse/recurrence in adults with BD-I. Subjects were randomized to 52 weeks of double-blind monotherapy with olanzapine, 5-20 mg/day (N=217), or lithium (target blood concentration: 0.6-1.2 mEq/liter) (N=214). The noninferiority of olanzapine relative to lithium (primary objective) in preventing relapse/recurrence was met. Depression relapse/recurrence occurred in 15.7% of olanzapine-treated and 10.7% of lithium-treated patients. Mania relapse/recurrence occurred in 13.8 of olanzapine-treated and 23.4% of lithium-treated patients.

Sajatovic et al., (2005) showed, in a secondary analysis, that lamotrigine and lithium may be effective and well-tolerated maintenance therapies in delaying the onset of mood symptoms in age 55 and older adults.

Bowden et al., (2000) in a one year study with 187 patients compared valproate, lithium, and placebo. Neither lithium nor valproate was significantly better than placebo in preventing mood episodes. The lack of significant differences in response may have been attributable to the low severity of illness in the treatment groups. However, it must also be kept in mind that subjects in this study were randomized to lithium, valproate, or placebo regardless of their initial treatment, and there has never been a positive maintenance study with this design.

ADVERSE EVENTS

Table E - 1 Adverse Events – Lithium

Many of lithium's adverse effects are dose or serum concentration related.

- 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 $\leq$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.

EVIDENCE TABLE

	Evidence	Source	LE	QE	NE	SR
1	**Acute: Mania:** Lithium is effective as a monotherapy for the acute mania	Licht et al., 2006 Keck et al., 2009 Niufan et al., 2008 Bowden et al., 2008 Bowden et al., 2005 Suppes et al., 2008 Hirschfeld et al., 2003	I	Good	Subst.	A
2	**Acute: Depression**- Lithium is effective as a monotherapy for the acute bipolar depression	Suppes et al., 2008 Zornberg & Pope, 1993	I-II	Fair	Mod	B
3	**Maintenance: Anti-Mania** Lithium is more effective in delaying manic episodes than both placebo and lamotrigine and is superior to placebo in prolonging time to intervention	Bowden et al., 2003 Bowden et al., 2000 Calabrese et al., 2003 Geddes, 2004 Goodwin, Bowden, Calabrese et al., 2004 Tohen et al., 2005 Sajatovic et al., 2005	I	Good	Subst.	A
4	**Maintenance: Anti-Depressive**	Bowden et al., 2003 Calabrese et al., 2003 Geddes, 2004 Goodwin et al., 2004	I	Fair	Mod	B
5	Lithium has additional benefit in preventing suicide	Cipriani, 2005	I	Fair	Mod	B

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

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.

The studies that have been included in the review of the evidence for the antiepliptic drugs are presented in the following sections.

ANTIEPILEPTIC/ VALPROATE

BACKGROUND

Although valproate (valproate) was developed as a medication for seizures it has a long history of being used for the treatment of mania. Studies of valproate treatment for mania go back as far as the mid 1960's. In the 1990's a number of American studies were published and valproate received an FDA approval for the treatment of acute mania of bipolar disorder. Valproate can be used in a number of various formulations including sodium valproate, valproate semi-sodium, and valproate. These various forms are assumed to be equally effective, but this has not been rigorously studied. We will generally refer to all of the various formulations as valproate or valproate in this document.

USE IN ACUTE MANIA/HYPOMANIA EPISODE

Systematic Reviews

Emilien et al., (1996) evaluated 7 double blinded, randomized controlled studies which looked at the effectiveness of carbamazepine or valproate in the treatment of mania. Four of the studies included valproate. The patient population varied by study and included both DSM-III and DSM-III-R diagnoses of bipolar disorder with or without coexisting symptoms of depression. The outcome measures (Good/Poor) are ratings of global evaluation as indicated by the assessment measures (e.g., use of rating scales and behavioral observations). Although it was unclear what the basis was for determination of results as "improved" or "not improved", the summary of this meta-analysis was that valproate and carbamazepine are as effective as lithium in the acute pharmacological management of manic-depressive illness.

Macritchie et al., (2003) in a Cochrane Review, reported on 10 randomized controlled trials of valproate or related compounds in the treatment of mania or mixed episode. Eight of the studies involved mania and two involved mixed episode. The trials included comparisons of valproate with placebo, lithium, olanzapine, haloperidol, and/or carbamazepine. Four of the trials included gradual increasing doses while six involved oral loading dose.

The meta-analysis found that:

1. In alleviating symptoms of mania:
    a. Valproate vs. placebo: Three trials (N=316) found that valproate was more efficacious than placebo.
    b. Valproate vs. lithium: Three trials (N=158) found that there was no significant difference between lithium and valproate.
    c. Valproic Acid vs. carbamazepine: Two trials (N=59) found that there was no significant difference in the numbers who failed to respond clinically by the end of the study.

d. Valproate vs. olanzapine: One study (N=251) found that valproate was slightly less effective than olanzapine in leading to remission. Two studies (N=363) looked at reduction of symptoms on valproate and olanzapine. There was a marginally significant difference between valproate and olanzapine in favor of olanzapine

2. When looking at overall global functioning using the Clinical Global Impression scale, the studies found that:

   a. Valproate vs. placebo: One trial (n=133) found that the improvement on valproate was statistically significant. Two trials provided sufficient information on the Global Assessment Score for analysis. There was a significant difference between valproate and placebo. Two trials looked at Global Assessment Scale changes and found that there was a significant difference in favor of valproate

   b. Valproate vs. lithium: One trial (n=28) looked at the difference between valproate and lithium. There was no significant difference.

   c. Valproate vs. carbamazepine: 2 trials (n=59) found no significant difference.

   d. Valproate vs. haloperidol: 1 study found no significant difference.

3. When looking at tolerability:

   a. Valproate vs. placebo: 3 trials found no significant difference between the numbers of patients dropping out of treatment in the valproate group compared to the placebo group. Two trials looked at the number of patients withdrawing from the study because they were released from the hospital. There was no significant difference between valproate and placebo.

   b. Valproate vs. lithium. There was no significant difference between the two interventions in the number of patients dropping out of the study. One trial looked at patients withdrawing from the study because they were released from the hospital on these two medications and found no significant difference.

   c. Valproate vs. carbamazepine: There were two trials that found no significant difference between the two interventions in the number of patients dropping out of the study.

4. Looking at patients withdrawing from studies because of side effects found that:

   a. Valproate vs. Placebo: 3 studies found no significant difference.

   b. Valproate vs. Lithium: 1 study found no significant difference.

   c. Valproate v. carbamazepine: One study looking at this comparison found that there were no study withdrawals.

   d. Valproate v. antipsychotics: One study (n=251) provided data on this outcome and found that there was no significant difference between the two interventions.

There were no reports of deaths of patients on valproate in any of the studies.

In conclusion this meta-analysis found that there is a consistent, though numerically limited, evidence from randomized trials that valproate is an efficacious treatment for acute mania. The relative efficacy of valproate compared to lithium and carbamazepine is unclear. Valproate may be less effective than olanzapine in reducing manic symptoms, but may cause less sedation and weight gain.

RCTs

Hirschfeld et al., (2003) reported on subjects pooled from three randomized, double-blind, parallel-group studies. Subjects were inpatients diagnosed with an acute manic episode associated with bipolar disorder. Patients were either treated with a loading dose strategy of valproate (N=80), standard titration of valproate (N=87), olanzapine (N=72), lithium (N=54), or placebo (N=72). Oral loading strategies of valproate demonstrated some superiority to standard titration strategies, lithium, and placebo on several measures over the first 10 days of the study. The effectiveness of oral loaded valproate and olanzapine did not differ

at any time point. The overall results of the study suggested that "oral loading of valproate leads to a more rapid antimanic effect when compared to standard titration of valproate, lithium, or placebo."

Revicki et al., (2003) led a multicenter study of hospitalized patients with mania. These patients were placed on either valproate sodium (N=63) or olanzapine (N=57). The maximum dose of valproate was 20 mg/kg/day plus 1,000 mg/day. There were no statistically significant differences between valproate and olanzapine treatment observed at baseline, 12 weeks, or at any interim time point using the Mania Rating Scale. There were no statistically significant differences in scores on the Hamilton Rating Scale for Depression after 3 weeks of treatment or at any follow-up time. There were no statistically significant differences over a 12-week follow-up on mean number of days of restricted activity or bed days or on the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).

Bowden, Swann, et al. (2006) compared valproate (N=192) to placebo (N=185) in acute mania. These patients were followed for 21 days. Valproate was initially dosed at 25 mg/kg/day and then titrated to serum concentrations of 85 to 125 mcg/mL. Treatment response was achieved in a significantly greater percentage of patients receiving valproate (48%) versus placebo (34%). Valproate was also significantly more likely to lead to improvement on five MRS subscales (less need for sleep, more energetic, increased activity, generalized motor hyperactivity, and racing thoughts). Significantly fewer people stopped their valproate for ineffectiveness.

Tohen et al. (2008b) conducted a three way, 12-week comparison of valproate (N=201), olanzapine (N=215), and placebo (N=105). The olanzapine was dosed from 5-20 mg per day while the valproate was 500 – 2500 mg per day. The original study found that valproate was not differentiated from placebo on the YMRS at 3 or 12 weeks. At 12 weeks the decrease in YMRS was significantly greater with olanzapine (-13.3) than with valproate or placebo (-10.7, -7.4). By the end of the study clinical response rates were greater in the active arms than with placebo. The number needed to treat to differentiate the active medications from placebo was 11 with olanzapine and 12 with valproate. A post-hoc analysis found that that a sizeable portion of patients on valproate were receiving inadequate doses of medication with 57% having plasma concentration below 50 mcg/mL at the end of the study. Valproate was associated with significant decreases in leukocytes and platelets vs. olanzapine, but had less weight gain than olanzapine.

USE IN ACUTE DEPRESSION

Two small placebo-controlled studies (Davis et al., 2005; Ghaemi et al., 2007) examined the responses of patients with bipolar disorder to valproate. Due to small sample size the data was not conclusive.

USE IN MAINTENANCE

There has been one large placebo-controlled study of valproate in maintenance in patients with BD I (Bowden et al., 2000). In this study lithium was used as an active control. In the primary outcome there were no differences between valproate nor lithium as compared to placebo. This suggests this is a "failed" study versus a definitive result regarding valproate's potential as a maintenance agent. Post-hoc studies have found various interesting findings from this trial, including that patients started openly on valproate and then randomized to valproate had fewer recurrences than those randomized to lithium or placebo (McElroy, Young et al. 2008). This supports other results in that, for all positive placebo-controlled maintenance studies in bipolar disorder, patients who did better were initially stabilized on the study drug.

Gyulai et al., (2003) in a secondary analysis of the above study, reported that valproate significantly reduced the rate of relapse to a depressive episode when compared to placebo. This finding held for all subjects, not just those initially stabilized with valproate.

Tohen et al., (2003b) reported on patients with mania or mixed episode who were placed on olanzapine (N=125) or valproate (N=126). Patients were randomly assigned to treatment with either olanzapine (5-20 mg/day) or valproate (500-2500 mg/day, recommended therapeutic serum concentration of 50-125 µg/ml). These patients were followed for 47 weeks. Patients on olanzapine had a statistically greater decrease in the Young Mania Rating Scale than did those on valproate. There were no statistically significant differences in relapse to depression or mania, the Hamilton Rating Scale for Depression, the Positive and Negative Syndrome Scale or the CGI severity of illness. Among patients treated with valproate, nausea,

nervousness, rectal disorder, and manic reaction were statistically more common. Valproate dosing did not use a loading strategy (as in Zajeka et al., 2002) which may account for the differences reported. Olanzapine was associated with significantly more somnolence, nausea, weight gain, and dry mouth.

Suppes et al., (2005) in a secondary post-hoc analysis, found that neither valproate nor olanzapine was beneficial over the long term in rapid cyclers.

EVIDENCE TABLE - VALPROATE

	Evidence	Source	LE	QE	NE	SR
1	**Acute-Mania:** -Valproate is effective as a monotherapy for the acute mania	Emilien et al., 1996 (SR) Macritchie et al., 2003(SR) Tohen et al., 2000a Tohen et al., 2008b Revicki et al., 2003 Bowden, et al., 2006 Kruger et al., 2008	I	Good	Subst	A
2	**Acute Depression**: Insufficient evidence to recommend for or against	Davis et al., 2005 Ghaemi et al.,2007	I	Poor	Mod	I
3	**Maintenance:** Valproate is somewhat effective as a maintenance treatment for Bipolar Disorder. Consider valproate as maintenance treatment in those patients whose acute episode responded to valproate.	Bowden et al., 2000 McElroy, Young et al., 2008 Gyulai et al., 2003 Tohen et al., 2003b Zajeka, 2002	I	Fair	Mod	C

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

ANTIEPILEPTIC/ CARBAMAZEPINE

BACKGROUND

In the late 1980's several investigators started looking at the anticonvulsant carbamazepine (CBZ) as a possible treatment for bipolar disorder. It was generally recognized that carbamazepine was an effective treatment for acute mania (Goodwin & Jamison, 1990; Janicak et al., 1993). Several studies have found that it is roughly equivalent in efficacy to lithium. However, acceptance of carbamazepine treatment was always hampered by its auto-induction of the Cytochrome P450 system which made drug monitoring more essential and drug-drug interactions more complicated. There was also the belief that its side effects were more troublesome than those of valproate. Recently however an extended release form of carbamazepine has been released and interest in it as a medication for bipolar disorder has been renewed.

USE IN ACUTE MANIA/HYPOMANIA EPISODE

Systematic Review/Meta analysis

Emilien et al., (1996) published a systematic review of seven double-blinded randomized trials comparing the efficacy of lithium to that of carbamazepine and valproate for mania. Their search criteria included studies looking at manic or mixed manic episodes. Although they did not clearly describe criteria for "improved" versus "not improved" they concluded that carbamazepine and valproate were as effective as lithium in the treatment of mania.

Davis et al., (1999) published a systematic review intended to determine by meta-analysis the efficacy of mood stabilizers in preventing recurrence of bipolar or unipolar mood disorders and to consider the

evidence for a lithium withdrawal-induced relapse syndrome. This paper reported on 31 studies of which 19 were blinded randomized controlled trials (n=865) and 15 were specifically studies of patients with bipolar disorder. In the studies of 572 patients which compared maintenance of remission on lithium versus carbamazepine, carbamazepine did slightly better than lithium with a 55% relapse rate on carbamazepine and a 60% relapse rate on lithium. This paper however had considerable heterogeneity in the results being reported. Since these studies ranged from reports published in 1967 through 1998, there were also likely variations in diagnostic criteria being used. For frequency of relapse, all follow-up times and dose levels were included. There was no placebo or other type of control considered for comparison in these studies and "frequency" did not appear to pertain to any specific time frame (hours, years).

Poolsup et al., (2000) conducted a systematic review of 5 trials (total of 397 patients) comparing the efficacy of carbamazepine and valproate to that of lithium for mania. In acute mania, both carbamazepine and valproate were not statistically different from lithium in terms of responder rate and improvement in symptoms.

Ceron-Litvoc et al., (2009) reviewed 15 randomized controlled trials involving carbamazepine in the treatment of all phases of bipolar disorder. Carbamazepine was compared to placebo, lithium, and valproate in patients in the manic phase. Carbamazepine was compared to placebo in the treatment of the depressive phase, and was compared to placebo in the maintenance phase. In acute mania, carbamazepine was as effective as lithium when comparing withdrawal due to adverse effects, number of patients with at least one adverse effect, and CGI. In the maintenance phase, carbamazepine was similar to lithium in relapses and hospitalizations.

RCTs

Weisler et al., (2004) studied patients on either extended–release carbamazepine (n=101) or placebo (n=103). Extended release carbamazepine (ERC-CBZ) was started at 200 mg twice per day and titrated by daily increments of 200 mg to final doses between 200 mg/day and 1600 mg/day. The patients on carbamazepine experienced greater decreases in the Young Mania Rating Scale at week 2 and week 3. They also had higher response rates at week 2 and week 3. Patients on carbamazepine also had greater improvements on Clinical Global Impression Improvement and Severity scores. Carbamazepine also had more patients with adverse events.

Weisler et al., (2005) reported on 239 patients on either extended-release carbamazepine (n=122) or placebo (n=117) in a multi-center trial. Extended-release carbamazepine (ERC-CBZ) was started at 200 mg twice daily, increasable by 200 mg/day up to 1600 mg/day. The patients on carbamazepine experienced greater decreases in Young Mania Rating Scales, greater response rates as measured by the YMRS, greater improvement in CGI Improvement and Severity scores and greater improvement on the Hamilton Rating Scale for Depression.

Both of the Weisler studies included patients with mixed episode as well as with mania.

EVIDENCE TABLE

	Evidence	Source	LE	QE	NE	SR
1	**Acute-Mania:** Carbamazepine ER is effective as monotherapy in the treatment of acute mania [A] and may be considered for patients with mixed episode [I]	Baethge et al., 2003 Goodwin & Jamison, 1990 Janicek et al., 1993 Emilien et al., 1996 Davis et al., 1999 Poolsup et al., 2000 Weisler et al., 2004 Weisler et al., 2005	I	Good	Subst	A
2	**Acute Depression**: There is insufficient evidence to recommend for or against the use of carbamazepine in bipolar depression					I
3	**Maintenance:** Carbamazepine is somewhat effective as a maintenance treatment for Bipolar Disorder.	Expert Opinion				C

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

ANTIEPILEPTIC/ LAMOTRIGINE

BACKGROUND

Lamotrigine is approved by the US Food and Drug Administration for the prevention of mania and depression in patients with bipolar disorder. Two separate randomized controlled trials demonstrated a greater time to intervention for any mood episode for both lamotrigine and lithium, when compared with placebo (Bowden et al., 2003; Calabrese et al., 2004). Of interest, in these trials lamotrigine was predominantly effective against the prevention of depression and lithium was predominantly effective against the prevention of mania.

USE IN ACUTE MANIA/HYPOMANIA EPISODE

Lamotrigine does not have evidence showing that it is an effective treatment for acute mania. Lamotrigine should not be used as monotherapy in the treatment of acute mania (Goldsmith et al., (2003); Bhagwagar & Goodwin, (2005)).

USE IN ACUTE DEPRESSION

Calabrese et al., (1999) randomized 195 outpatients with bipolar I depression to lamotrigine (50 or 200 mg/day) or placebo as monotherapy for 7 weeks. Lamotrigine 200 mg/day demonstrated significant antidepressant efficacy on the 17-item HAM-D and secondary outcome measures. Lamotrigine 50 mg/day demonstrated efficacy compared with placebo on several measures. The proportions of patients exhibiting a response on CGI-I were 51%, 41%, and 26% for lamotrigine 200 mg/day, lamotrigine 50 mg/day, and placebo groups, respectively.

Van de Loos et al., (2009) compared lamotrigine in combination with lithium to lithium plus placebo in the treatment of bipolar depression. The combination resulted in a significant change from baseline in the MADRS after 8-weeks compared to lithium + placebo, p=0.024. The combination also resulted in a significantly lower overall MADRS score, p=0.006. The reported response rate to the combination vs. lithium + placebo was 57% vs. 32%.

Brown et al., (2006) in a 7-week trial, found that the combination of olanzapine/fluoxetine (OLZ/FLX) to have a shorter time to response than lamotrigine, (17 vs. 23 days, p=0.01). Changes in mean behavioral

scale scores CGI-S, MADRS, YMRS were significantly greater for OLZ/FLX. Suicidal and self-injurious behavior was significantly lower with OLZ/FLX, while somnolence, sedation, increased appetite, weight gain, elevations in total cholesterol and triglycerides, dry mouth, and tremor were significantly more common with OLZ/FLX. The benefits to risk ratio modestly favors the combination (SR B).

Calabrese et al., (2008) and Geddes and Calabrese, (2009) pooled 5 RCTs comparing lamotrigine to placebo in acute depression. The overall pool effect was modest for lamotrigine and it did not demonstrate efficacy in 4 out of the 5 trials. Patients with more severe depression tended to manifest a greater response to lamotrigine than placebo. Lamotrigine was well tolerated.

USE IN MAINTENANCE

Lamotrigine is recommended for the prophylaxis of mood episodes in patients with bipolar disorder.

Calabrese et al., (2003) conducted a placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. Patients stabilized on open-label treatment (N = 463) were randomly assigned to lamotrigine (50, 200, or 400 mg/day; N = 221), lithium (0.8-1.1 mEq/L; N = 121), or placebo (N = 121) monotherapy for up to 18 months. The primary outcome measure was time from randomization to intervention (addition of pharmacotherapy) for any mood episode (depressive, manic, hypomanic, or mixed). Time to intervention for any mood episode was statistically superior (p = .029) for both lamotrigine and lithium compared with placebo-median survival times were 200, 170, and 93 days, respectively. Intervention for depression was more frequent than for mania by a factor of nearly 3:1. Lamotrigine was statistically superior to placebo at prolonging the time to intervention for a depressive episode (p = .047). The proportions of patients who were intervention-free for depression at 1 year were lamotrigine 57%, lithium 46%, and placebo 45%. Lithium was statistically superior to placebo at prolonging the time to intervention for a manic or hypomanic episode (p = .026). The proportions of patients who were intervention-free for mania at 1 year were lamotrigine 77%, lithium 86%, and placebo 72%.

Bowden et al., (2003) conducted a placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. After an 8- to 16-week open-label phase during which treatment with lamotrigine was initiated and other psychotropic drug regimens were discontinued, patients were randomized to lamotrigine (100-400 mg daily; N= 59), lithium (0.8-1.1 mEq/L; N = 46), or placebo (N= 70) as double-blind maintenance treatment for as long as 18 months. Both lamotrigine and lithium were superior to placebo at prolonging the time to intervention for any mood episode (lamotrigine vs. placebo, P =.02; lithium vs. placebo, P =.006). Lamotrigine was superior to placebo at prolonging the time to a depressive episode (P =.02). Lithium was superior to placebo at prolonging the time to a manic, hypomanic, or mixed episode (P =.006).

Goodwin et al., (2004) performed a pooled analysis of Calabrese et al., (2003) and Bowden et al., (2003) that supported the individual trial findings that lamotrigine was superior to placebo in maintenance for depression and the lithium was significantly superior to placebo in maintenance for mania. Tremor and diarrhea were significantly more common with lithium than lamotrigine, $p<0.05$.

Sajatovic et al., (2005) conducted a subanalysis of the two trials [Calabrese et al., (2003) and Bowden et al., (2003)] in subjects age 55 and older (LTG: 33, lithium: 34, placebo: 31) and reported comparable results. Mean modal total daily doses were lamotrigine 240 mg and lithium 750 mg.

Bowden, Calabrese et al., (2006) in a post hoc analysis stratified subjects into non-obese (BMI<30) or obese ($\geq$30) to determine if either group was more prone to weight gain after 52-weeks of treatment with Li or LTG. Patients taking LTG had significant decreases in their mean weight compared to those taking Li, $p<.05$. Li was associated with a significant weight gain vs. placebo. There was no difference in weight change between Li, LTG and placebo in non-obese subjects.

EVIDENCE TABLE - LAMOTRIGINE

	Evidence	Source	LE	QE	NE	SR
1	**Acute-Mania:** Lamotrigine is not effective as monotherapy for acute mania or mixed episode.	Bowden et al., 2003 Calabrese et al., 2004 Goldsmith et al., 2003 Bhagwager & Goodwin, 2005	I	Good	Zero	D
2	**Acute Depression**: Effective as a monotherapy for the acute bipolar depression	Bowden et al., 2003 Calabrese et al., 2008 Calabrese et al., 2004 Calabrese et al., 1999 Geddes et al., 2009 Van de Loos et al., 2009 Brown et al., 2006	I	Good	Mod	B
3	**Maintenance-**: Lamotrigine is effective in the maintenance phase of BD. It is more effective in preventing depressive relapse [B] than manic relapse [C]	Bowden et al., 2003 Goodwin et al., 2004 Calabrese et al., 2003 Sajatovic et al., 2005 Bowden Calabrese et al., 2006	I	Fair	Mod	B/C

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

ANTIEPILEPTIC/ OXCARBAZEPINE

BACKGROUND

Oxcarbazepine (Trileptal) is a keto derivative of carbamazepine that offers several advantages over carbamazepine. Oxcarbazepine does not require blood cell count, hepatic, or serum drug concentration monitoring. It causes less cytochrome P450 enzyme induction than carbamazepine (but may decrease effectiveness of oral contraceptives containing ethinyl estradiol and levonorgestrel). As opposed to carbamazepine, oxcarbazepine does not induce its own metabolism. These properties, combined with its similarity to carbamazepine have led many clinicians to use this medication for the treatment of bipolar disorder.

USE IN ACUTE MANIA/HYPOMANIA EPISODE

Suppes et al., (2007) compared oxcarbazepine (N=15) with valproate (N=15) in a randomized, single-blinded treatment trial of hypomania. These medications were used as either monotherapy or augmentation of the subject's current medication. The oxcarbazepine resulted in a 64% reduction in YMRS while valproate resulted in a 79% reduction in YMRS by week 8.

While there are older randomized controlled trials suggesting efficacy in the treatment of acute mania compared to lithium and haloperidol, these trials were insufficient evidence to make a recommendation either way. These early trials did not include a placebo control. In a recent monotherapy placebo-controlled study in children and adolescents oxcarbazepine was not found to be significantly better than placebo (Wagner et al., 2006). In a recent add-on of double-blind oxcarbazepine or carbamazepine to lithium for acute mania or hypomania in those patients not adequately responding to monotherapy lithium, oxcarbazepine was more effective over the 8 week trial ($p < .04$) (Juruena et al., 2009). In this add-on study, oxcarbazepine was better tolerated.

USE IN ACUTE DEPRESSION

There are no placebo-controlled studies of oxcarbazepine in acute bipolar depression.

USE IN MAINTENANCE

No specific placebo-controlled studies of oxcarbazepine in the maintenance phase of bipolar disorder

EVIDENCE TABLE - OXCARBAZEPINE

	Evidence	Source	LE	QE	NE	SR
1	**Acute-Mania:** Oxcarbazepine may be an effective treatment for mania	Suppes et al., 2007 Juruena et al., 2009	I	Fair	Small	C

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

ANTIEPILEPTIC/ TOPIRAMATE

USE IN ACUTE MANIA//HYPOMANIA EPISODE

Systematic Review

Vasudev et al., (2006) in a Cochrane Review found only one randomized control trial of topiramate in acute mania. In this trial topiramate was compared to bupropion SR. The authors of the study concluded that there was insufficient evidence to recommend for or against the use of topiramate as monotherapy or adjunct therapy in any phase of bipolar disorder.

Controlled Trials

Kushner et al., (2006) combined 4 placebo-controlled topiramate studies of patients with mania or mixed manic episodes. Doses of topiramate were 200 mg, 400 mg, or 600 mg per day compared to placebo. At 3 weeks there was no significant difference between patients on topiramate and placebo as measured by YMRS. Topiramate was not associated with mood destabilization or treatment-emergent depression.

USE IN DEPRESSION

Vasudev et al., (2006) identified one controlled trial meeting inclusion criteria that compared topiramate and bupropion SR as adjunctive treatment of bipolar depression. High dropout rates were noted in both groups. The authors concluded that there is insufficient (poor quality) evidence for the use of topiramate in any phase of bipolar illness, either as monotherapy or as an adjunctive treatment.

USE MAINTENANCE

No randomized or placebo-controlled studies were located.

EVIDENCE TABLE/ TOPIRAMATE

	Evidence	Source	LE	QE	NE	SR
1	**Acute-Mania**: Topiramate is ineffective in the treatment of acute mania	Vasudev et al., 2006 Kushner et al., 2006	I	Fair	Zero	D
2	**Acute Depression**: Insufficient evidence to recommend for or against use in any phase of BD either as monotherapy or adjunctive treatment	Vasudev et al., 2006	I	Poor	Zero	I
3	**Maintenance:** There is insufficient evidence to recommend for or against the use of topiramate in the maintenance phase of BD.	No randomized or placebo-controlled studies were located				

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

ANTIEPILEPTIC/ GABAPENTIN

USE IN ACUTE MANIA//HYPOMANIA EPISODE

One placebo-controlled study in acute mania, hypomania or mood destabilization found no differences between gabapentin and placebo (Pande et al. 2000).

Pande et al., (2000) looked at the use of gabapentin as an adjunctive medication. The trial was double blinded and placebo controlled and included bipolar type I patients who were already on lithium and/or valproate for a mania, hypomania, or mixed manic state. Patients who were given adjunctive placebo did significantly better than did those receiving gabapentin.

USE IN ACUTE DEPRESSION

Frye et al., (2000) used a randomized, double blinded crossover trial comparing lamotrigine and gabapentin, and placebo as monotherapies in 31 patients with refractory unipolar and bipolar mood disorders. Using a CGI-Bipolar Disorder assessment of "much" or "very much" improved found that lamotrigine was significantly better than placebo (52% vs. 23% respectively). There were no significant differences in efficacy between gabapentin compared to placebo.

EVIDENCE TABLE/ GABAPENTIN

	Evidence	Source	LE	QE	NE	SR
1	**Acute-Mania:** No difference shown between gabapentin and placebo	Pande et al., 2000	I	Fair	Zero	D
2	**Acute Depression:** No difference shown between gabapentin and placebo.	Frye et al., 2000	I	Fair	Zero	D
3	**Maintenance:** insufficient evidence for or against the use of gabapentin in the maintenance phase of BD					I

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

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	Hepatoxicity 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/hypnatremia Stephens-Johnson syndrome Thrombocytopenia
Carbamazepine	Ataxia Drug interactions Rash	Agranulocytosis Aplastic anemia AV block/bradycardia Pregnancy Category D SIADH/hypnatremia Stephens-Johnson syndrome Thrombocytopenia

Table E - 5 Recommended Pharmacotherapy Monitoring:Lithium, Antiepileptics

	Starting Therapy		Follow-up during Ongoing Therapy (Stable Outpatient)
Medication	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
Carbam-azepine 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, LFTSs= 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.

Systematic Reviews/Meta analyses of Antipsychotics

Jeste and Dolder, (2004) conducted a review of the literature on the use of atypical antipsychotics to treat a variety of psychiatric illnesses, including bipolar disorder. When evaluating treatments for bipolar disorder, the authors considered only adults and compared the efficacy of clozapine, risperidone, olanzapine, quetiapine, and ziprasidone to conventional medication. They located 24 studies of patients with bipolar disorder that considered a variety of changes in psychiatric symptoms measured using the BPRS, YMRS, and CGI. Based on their review, Jeste and Dolder concluded that second generation

antipsychotics represent a promising treatment modality when considering the improved side effect profile of these agents compared to conventional agents.

Gao and Calabrese (2005) **c**onducted a systematic review assessment of first and second generation antipsychotics in bipolar depression. Twenty-one randomized trials and 13 nonrandomized prospective trials were reviewed. The data suggest that second generation antipsychotic (SGA) drugs (quetiapine and olanzapine in the only RCTs) have a role in acute and long-term treatment of depression. No evidence was found to support the idea that the first generation antipsychotics (FGAs worsen bipolar depression (Calabrese et al., 2005).

Seemuller et al., (2005) focuses mainly on the safety and tolerability of SGAs in patients with bipolar disorder. The authors of this study reviewed double-blind randomized controlled trials with SGAs in both mono-and combination treatment of acute mania, bipolar depression, and maintenance therapy. They identified 21 studies with a total of 6,177 subjects. Sixteen of the 21 studies were placebo-controlled. The primary outcomes considered include dropout rates due to side effects, central nervous system related side effects, weight gain, and metabolic and hormonal issues. The authors specifically considered olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole. They concluded that since little is known about the long-term efficacy and safety of this class of medication, information should continue to be gathered.

Tohen et al., (2001) examined the usage of FGAs in bipolar disorder. The authors identified 16 studies with a total of 1753 patients. Through meta-analysis, the authors estimated that 85% of bipolar patients were receiving typical antipsychotic agents. Approximately 47% of patients were using the typical antipsychotic agents with a mood stabilizer. The authors concluded that FGAs are commonly used in the treatment of bipolar disorder.

ANTYPSYCHOTIC/ OLANZAPINE

BACKGROUND

Olanzapine is a second generation antipsychotic (SGA) that has demonstrated efficacy as monotherapy and as an adjunct in combination with other mood stabilizers in the treatment of acute mania. It has also proved to be effective for the treatment of bipolar depression when combined with fluoxetine and with a significant though smaller effect size as a monotherapy in acute depression. Olanzapine also has established efficacy as a maintenance treatment to reduce or delay manic episodes. Common adverse effects of olanzapine include weight gain, diabetes mellitus, sedation, and anticholinergic effects.

USE IN ACUTE MANIA/HYPOMANIA EPISODE

OLANZAPINE MONOTHERAPY

Systematic Review

Two systematic reviews were identified that included studies related to olanzapine's efficacy and safety, either as monotherapy or in combination, for the treatment of acute mania.

Jeste & Dolder, (2004) evaluated 24 studies which looked at the use of antipsychotic medications in the treatment of a variety of psychiatric illnesses. They concluded that there was "strong support" for olanzapine in the treatment of acute mania.

Seemuller et al., (2005) looked at the safety and tolerability of antipsychotics used in the treatment of bipolar disorder. They reported that olanzapine showed a favorable efficacy profile, particularly in acute illness, and noted that dropout rates due to adverse events were no different from placebo, valproate, and haloperidol. Somnolence and weight gain, however, were more common with olanzapine than placebo.

RCTs

Hirschfeld et al., (2003) looked at numerous treatment regimens for acute mania including lithium up to 300 mg three times daily (N=54), valproate with a rapid loading dose up to 1000 mg per day (N=80), valproate at a standard titration (N=87), olanzapine up to 20 mg per day (N=55) , and placebo (N=72). At these doses the rapid loading dose of valproate was more effective than the lithium on the Behavior and Ideation Scale. There was no significant difference between the loading dose strategy of valproate and olanzapine.

Pooled, Post Hoc Analyses

Data from Tohen et al., (1999) & Tohen et al., (2000) were used in several post hoc analyses. The data from these two RCTs were previously included in the above systematic reviews which compared olanzapine and placebo in acute mania. Shi et al., (2004) reported that olanzapine reduced PANSS-cognitive scores and Hamilton Depression scores, as well as YMRS, in acute manic. Baker et al., (2004) examined response characteristics in patients with dysphoric or nondysphoric mood. The analysis suggested that olanzapine is effective for treating coexisting mania and depressive symptoms, particularly when depressive symptoms are moderate to severe. Baldessarini et al., (2003) used the pooled data to test for differences in the treatment response in subgroups. Patients were more responsive to olanzapine if they were younger at illness onset, lacked prior treatment with an antipsychotic, or did not have a history of substance abuse. Chengappa et al., (2003) reanalyzed the data using stringent criteria for remission (YMRS $\leq$7 and endpoint, HAM-D-21 $\leq$7 and CGI BP overall total severity score $\leq$2). Overall, the remission rate was greater with olanzapine (18%) compared to placebo (7%), p=0.015, as well as in pure mania, mania with psychotic features, and non-rapid cycling. Remission rates did not differ from placebo in patients with mixed episode, mania without psychotic features or with rapid cycling.

Head to Head Trials

OLANZAPINE VS. VALPROATE

Tohen et al., (2002a) compared olanzapine 5-20 mg/d (n=125) to valproate (500-2500 mg/d) (n=123) in a 3-week study. The initial dose of olanzapine was 15 mg/d, while valproate was 750 mg three times daily. Antimanic response to olanzapine was significantly greater than that for valproate. Interestingly, response to the two drugs was identical in the subset of patients with psychotic mania. Weight gain was 2.5 kg with olanzapine and 0.9 kg with valproate.

Tohen, Vieta et al., (2008) compared olanzapine 5-20 mg/d (n=215), valproate 500-2500 mg/d (n=201), and placebo (n=105) in a 3-week randomized study followed by a 9 week extension in responders. Subjects had "mild to moderate" mania. Responses in both olanzapine and valproate groups differed significantly from placebo but response in the two groups did not differ. Subjects randomized to olanzapine had higher weight gain, cholesterol, and triglycerides than those receiving valproate.

Zajecka et al., (2002) compared valproate (initial dose 20 mg/kg/d, n=63) to olanzapine (initial dose 10 mg/d, n = 57) in a 3 week inpatient study with 9 week outpatient double-blind follow-up. Doses could be adjusted for tolerability or effectiveness. There were no significant differences between the drugs in antimanic responses (SADS Mania Rating Scale decrease of 14.8 with valproate vs. 17.2 for olanzapine. Responses in psychotic manic subjects were identical. Subjects randomized to olanzapine reported greater weight gain and more somnolence than those with valproate.

These studies suggest that olanzapine and valproate have generally comparable efficacy as monotherapies, particularly if valproate dose is loaded. The lower incidence of metabolic side effects favors valproate.

OLANZAPINE VS HALOPERIDOL

Tohen et al., (2003a) compared olanzapine 5-20 mg per day (n=234) to haloperidol 3-15 mg per day (n=219) in a 12-week study of patients with acute mania. By week 12 the average dose of medication was 11.4 mg per day for olanzapine and 5.2 mg per day for haloperidol. By the end of the study the groups did not differ in proportion of subjects entering remission, time to remission, rate of remission, proportion who relapsed, or time to relapse. Subjects randomized to olanzapine were less likely to develop depressive symptoms. Nonpsychotic subjects with olanzapine had more improvement in YMRS scores than

corresponding subjects with haloperidol. Subjects with olanzapine had higher weight gain and somnolence, while those with haloperidol had more drug-related movement disorder symptoms.

OLANZAPINE VS. RISPERIDONE

Perlis et al., (2006) compared olanzapine (N=165) at a dose of 5-20 mg per day with risperidone (N=164) at a dose of 1-6 mg per day, in the treatment of acute manic and mixed episodes. Olanzapine and risperidone were associated with similar improvement of acute manic symptoms after 3 weeks, as measured by the YMRS, as well as similar response and remission rates. Significantly more patients on olanzapine completed the study. More patients on olanzapine experienced dry mouth and weight gain while more patients on risperidone experienced a worsening of sexual function.

REDUCE AGITATION

Meehan et al., (2001) was a randomized, placebo-controlled trial of 201 patients, which evaluated the efficacy and safety of various interventions to reduce agitation in patients with acute mania. The patients received intramuscular olanzapine 10-25 mg, compared to intramuscular placebo, or intramuscular lorazepam 2-5 mg. Patients who were still agitated after two doses of placebo were given olanzapine 10 mg IM. Agitation was measured using the PANSS-Excited Component and two additional agitation scales. Agitation was measured at baseline, every 30 minutes for two hours and then at 24 hours. Olanzapine was significantly better than placebo or lorazepam at 2 hours and better than placebo at 24 hours. There were no differences in measures such as treatment-emergent extrapyramidal symptoms, acute dystonia, or changes in the QTc interval.

RAPID CYCLING

Olanzapine's efficacy in rapid cycling compared to non-rapid cycling has been the focus of two post hoc analyses.

Vieta et al., (2004) using the same two studies, Tohen et al., (1999) & Tohen et al., (2000), determined that rapid cycling BD-I patients treated with olanzapine had initial differences and a more rapid initial clinical change as measured by the YMRS and HAM-D, especially towards depression, with less favorable long-term outcomes than non-rapid cyclers.

Suppes et al., (2005) pooled data from two RCTs comparing olanzapine to valproate in the treatment of bipolar mania and maintenance of remission (out to 47 weeks). Rapid cyclers did not differ in their response between treatment groups. Non-rapid cyclers treated with olanzapine were found to have a significantly greater improvement compared to those treated with valproate ($p<.001$). No other differences between the treatments by cycling status were found on the CG-Mania Severity, CGI-Bipolar Severity or HAM-D scales.

OLANZEPINE COMBINATION THERAPY

OLANZAPINE AND LITHIUM OR VALPROATE

Tohen et al., (2002b) compared the addition of olanzapine or placebo in 344 patients with bipolar mania who had been "partially nonresponsive" to lithium or valproate which they had been given for at least two weeks. Improvement in mania scores was significantly higher with the addition of olanzapine (-13.11) than with the addition of placebo (-9.1). While mania scores improved substantially more in subjects given olanzapine plus lithium or valproate than in those given placebo plus lithium or valproate, the concentrations of lithium (about 0.75 mEq/L) or valproate (68 mcg/ml) may not have been adequate for treating acute mania, and the physicians were not allowed to adjust lithium or valproate doses upward for efficacy. Therefore, this study does not really address the question of whether addition of olanzapine would increase response to optimized lithium or valproate doses in severe mania, but does show that in subjects not responding to modest doses of lithium or valproate, addition of a modest dose of olanzapine can be effective. Subjects given olanzapine had more weight gain than those randomized to placebo.

Namjoshi et al., (2004) looked at olanzapine plus valproate or lithium vs. placebo plus valproate or lithium. There were significantly greater improvements from baseline on both the Y-MRS and HAM-D ($p<0.01$) in patients on olanzapine augmentation. Patients receiving olanzapine also experienced significantly greater improvements from baseline on the Lehman's brief Quality of Life (QLI)

OLANZAPINE AND CARBAMAZEPINE

Tohen, Bowden et al., (2008) randomized 119 bipolar manic subjects treated with carbamazepine (400-1200 mg/day) to receive olanzapine (10-30 mg/day) or placebo. There were no significant differences between the groups using the primary measurement (YMRS) or in any other outcome measures. Subjects randomized to olanzapine had higher triglyceride concentrations and weight gain (24.6% vs. 3.4% of subjects gaining >7% of baseline body weight, $p = 0.002$) at the end of six weeks treatment.

DYSPHORIC MANIA

Baker et al., (2004) studied the efficacy of olanzapine in combination with valproate or lithium in the treatment of dysphoric mania. Patients with therapeutic concentrations of lithium or valproate were randomized to placebo or olanzapine (flexible daily dosing from 5 mg to 20 mg) for this 6 week trial. In both dysphoric and non-dysphoric patients, improvement in HRSD total score and the YMRS total score were significantly greater for those receiving a combination compared to monotherapy. Suicidality rating (from the HRSD) showed significant improvement in dysphoric patients receiving combination therapy compared to those receiving monotherapy. There was no improvement or differences between treatment groups in the non-dysphoric patients.

USE IN ACUTE DEPRESSION

Systematic Review/Meta analysis

Only one systematic review included a focus on olanzapine's role in the treatment of bipolar depression**.** Gao and Calabrese (2005) concluded that olanzapine was better than placebo in the treatment of acute bipolar depression and in preventing depressive relapses.

MAINTENANCE

OLANZAPINE VS PLACEBO

Tohen et al., (2006) compared olanzapine (5-20 mg/d, n=225) to placebo (n=136) in a one year study of patients with bipolar I disorder who had responded acutely to olanzapine. A greater percentage of patients receiving olanzapine completed the study (21.3% vs. 6.6% $p<0.001$). Subjects receiving olanzapine had longer times to discontinuation (83d vs. 26 d), longer time to relapse to any mood episode (174 d vs. 22 d) and higher probability of remaining free of mania for at least one year (83%, $p < 0.001$). Subjects on placebo were less likely to discontinue for an adverse event (0% vs. 7.6%, $p < 0.001$). Significant weight gain (greater than 7%) was more common in patients receiving olanzapine than placebo (17.7% vs. 2.2%).

OLANZAPINE VS VALPROATE

Tohen, Ketter et al., (2003b) followed the subjects described in the acute valproate-olanzapine comparison (Tohen et al 2002) for an additional 47 weeks. Recurrence rates to depression and mania were the same for the two groups, though in general symptom levels were slightly lower in subjects on olanzapine (for YMRS, $p = 0.03$). Weight gain was greater in subjects on olanzapine (listed as adverse event in 24.8% vs. 11.9%).

OLANZAPINE VS LITHIUM

Tohen et al., (2005) compared 12 month maintenance responses in 431 subjects, initially treated with lithium plus olanzapine for acute mania, and randomized to continue with olanzapine (15 mg/day, n=217) or lithium (concentration 0.6-1.2, n = 214). Subjects given olanzapine had a lower rate of relapses to mania (13.8% vs. 23.4%, $p = 0.03$). 10.7% of subjects given lithium compared to 15.7% on olanzapine

experienced depressive episodes. Subjects randomized to lithium had slight weight loss (probably because of initial co treatment with lithium); weight gain was higher with olanzapine than with lithium.

EVIDENCE TABLE - OLANZAPINE

	Evidence	Source	LE	QE	NE	SR
1	Acute Mania: Olanzapine as effective as a monotherapy for the acute mania	Jeste & Dolder, 2004 (SR) Seemuller et al., 2005 (SR) Tohen et al., 1999 Tohen et al., 2000 - Shi et al., 2004§ - Baldessarini et al., 2003§ - Chengappa et al., 2003§ - Baker et al., 2004§ Tohen & Baker et al., 2002 Tohen et al., 2003a Tohen & Vieta et al., 2008 Zajecka et al., 2002 Perlis et al., 2006 Meehan et al., 2001	I	Good	Subst	B
2	Effective as an adjunct medication with other mood stabilizers for the treatment of acute mania or mixed episode	Tohen & Chengappa et al., 2002 Hirschfeld et al., 2003 Tohen & Bowden et al., 2008 Baker et al., 2004	I	Good	Subst	A
3	**Acute: Depression**: Olanzapine may be considered as monotherapy for the treatment for bipolar depression	Gao & Calabrese 2005 (SR)	I	Good	Mod	C
4	Maintenance: Effective as monotherapy for the maintenance phase of BD. It seems to be more effective in preventing manic and hypomanic episodes [B] than in preventing depressive episodes [C]	Cipriani et al., 2009 [SR] Tohen et al., 2004 Tohen et al., 2003b Tohen et al., 2006 Tohen et al., 2005 Namjoshi et al., 2004	I	Fair	Mod Subst Modest Subst	B/C

LE = Level of Evidence; QE = Quality of Evidence; NE- Net Benefit; SR = Strength of Recommendation (See Appendix A)
§ - Secondary analyses of previous RCTs

ANTIPSYCHOTIC: OLANZEPINE/ FLUOXETINE COMBINATION

BACKGROUND

The olanzapine-fluoxetine combination (OFC) is approved by the FDA specifically for the treatment of depression in patients with bipolar I disorder. This indication was based on data from a double-blind randomized study in which the combination was superior to both olanzapine monotherapy and placebo. Treatment-emergent mania or hypomania did not occur more frequently in the OFC group than the placebo group during the acute trial.

USE IN ACUTE MANIA/HYPOMANIA EPISODE

No controlled studies of OFC in the treatment of acute mania have been identified. Based on the availability of medications that do not contain antidepressants, OFC should not be used to treat acute mania.

USE IN ACUTE DEPRESSION

Tohen et al., (2003c) (benefit modest though significant for olanzapine and significant for olanzapine-fluoxetine combination) compared olanzapine 5-20 mg/d plus fluoxetine, up to 50 mg/d (n=86), olanzapine alone, 5-20 mg/day (n=370) and placebo (n=377) in an 8-week study of bipolar I depressed subjects. Olanzapine alone was modestly but significantly better than placebo for overall MADRS scores, though improvements were generally in non-depression items such as agitation, insomnia, and loss of appetite. The combination of olanzapine and fluoxetine was significantly better than placebo in all depression measures. Weight gain was substantially higher than placebo in both groups receiving olanzapine.

Brown et al., (2006) evaluated olanzapine-fluoxetine combination versus lamotrigine for acute bipolar depression in an 8 week double-blind study. The OFC was found significantly better in this short term trial in terms of acute depression symptoms, but lamotrigine was better in terms of side effect profile including weight gain and related factors.

EVIDENCE TABLE

	Evidence	Source	LE	QE	NE	SR
1	**Acute: Depression**: Olanzapine in combination with fluoxetine is an effective treatment for bipolar depression	Tohen et al., 2003c Brown et al., 2006	I	Good	Subst	C/B
2	There is insufficient evidence to recommend for or against the combination of olanzapine and fluoxetine in the maintenance phase of BD	No controlled studies of OFC for maintenance				I

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

ANTIPSYCHOTIC/QUETIAPINE

BACKGROUND

Quetiapine is a second generation antipsychotic which has been shown to be an effective drug for the treatment of acute manic and depressive episodes and for the prevention of new episodes of mania (hypomania) or depression. For mania, quetiapine may be used as monotherapy or as an adjunct to lithium or valproate. For depression, quetiapine has demonstrated efficacy as a monotherapeutic agent for both bipolar I and bipolar II depression. There are also two studies looking at the use of quetiapine in combination with either lithium or valproate in maintenance therapy. The studies show that when quetiapine was added to sub optimal doses of lithium or valproate it was well tolerated and led to significant improvement in mania score, although the patients in these studies were not necessarily patients who had severe symptoms or patients who had not responded to single treatment.

USE IN ACUTE MANIA/HYPOMANIA EPISODE

McIntyre et al., (2005) conducted a 12-week, double blind randomized trial comparing quetiapine up to 800 mg per day (N=102), haloperidol up to 8 mg per day (N=99), and placebo (N=101) in the treatment of mania. Subjects were required to have a minimum score of 20 on the Young Mania Rating Scale (YMRS), plus a score of least 4 on two of the YMRS core items of Irritability, Speech, Content, and Disruptive/Aggressive Behavior at screening and at randomization. Patients who met the DSM-IV-TR criteria for mixed episodes and rapid cycling were excluded. Quetiapine was increased to 400 mg/day on Day 4, but could be adjusted up to 800 mg/day (Days 6 to 84). Haloperidol was initiated at the target dose of 2 mg/day on Days 1 and 2, with stepwise increase to 4 mg/day Day 4. The dose could be adjusted to between 2 and 8 mg/day on Days 6 to 84. Quetiapine and haloperidol were both superior to placebo in response rates and YMRS change (quetiapine = -17.5, haloperidol = -18.9, placebo = -9.5) as well as in CGI-BP, total PANSS, and GAS. There was no significant difference between quetiapine and haloperidol in any measurement of efficacy. Subjects given haloperidol were substantially more likely to experience extrapyramidal syndromes (33.3% vs. 5.9% for quetiapine or placebo, $p < 0.001$).

Bowden et al., (2005) was an international, multicenter trial looking at monotherapy using quetiapine, lithium, or placebo for the treatment of mania. The 107 patients on quetiapine were increased to a dose of 800 mg per day while the 98 on lithium were maintained between 0.6-1.4 mEq/L (placebo- N= 97). Both active arms showed a significant decrease in YMRS (quetiapine/lithium/placebo = -20.3/-20.76/-9.0). Both had a significantly greater response rate than placebo (quetiapine/lithium/placebo = 72.0%/72.4%/41.1%). The active arms also had significant decreases in PANSS, MADRS, and GAS.

Combination Treatment

Sachs et al., (2004) reported on a 3-week study looking at patients who were on either valproate acid or lithium and then were randomized to receive either placebo or quetiapine. These patients had Bipolar I disorder and had most recently experienced a manic episode. Subjects were required to have a minimum score of 20 on the Young Mania Rating Scale (YMRS), plus a score of least 4 on two of the YMRS items of Irritability, Speech, Content, and Disruptive/Aggressive Behavior. Patients with rapid cycling and mixed episodes were excluded. Initial target doses of quetiapine were 100 mg/day at Day1, 200 mg/day at Day 2, 300 mg/day at Day 3, and 400 mg/day at Day 4. The dose was adjusted between 200 and 600 mg at Day 5, and 200 and 800 mg/day at Day 6 to 21. Lithium was dosed to 0.7-1.0 mEq/L and valproate to 50-100µg/ml. Patients were randomly assigned to quetiapine plus Lithium/valproate (N=91) or placebo (PBO) plus lithium/valproate (N=100) for 21 days.

The group receiving quetiapine augmentation experienced a significantly greater mean reduction in the total YMRS score. YMRS response rate was significantly higher in the quetiapine group as was the proportion of patients achieving clinical remission. At day 21, the quetiapine augmentation group also had a greater improvement in PANSS Supplement Aggression Risk scores. There was no statistically significant difference between groups in the rate of emergent depression.

Yatham et al., (2004) This 3 week study looked at the addition of quetiapine or placebo to patients already on lithium or valproate. These patients' most recent episode was manic and they had at least one manic or

mixed episode in the previous 5 years. Patients had to have a YMRS score of at least 20, including a score of at least 4 on two of the core YMRS items of irritability, speech, content, and disruptive/aggressive behavior, and a CGI-BP severity of illness score of at least 4. Quetiapine (QTP) (initial dose 100 mg/day at day 1, 200 mg/day at day 2, 300 mg/day at day 3, and 400 mg/day at day 4, up to 600 mg/day at day 5, and up to 800 mg/day at day 6 until the end of treatment) with lithium or valproate (n=197). There were 205 patients in the group who received placebo in addition to lithium or valproate. The group receiving quetiapine augmentation experienced a significant improvement in YMRS and CGI-BP severity scores. The quetiapine group also had a greater rate of response (≥50% reduction in YMRS) and remission (Score ≤12 on YMRS).

USE IN ACUTE DEPRESSION

Calabrese et al., (2005) Conducted a double-blind placebo-controlled trial in which 360 patients with bipolar I and 182 patients with bipolar II, in a major depressive episode, were randomized to quetiapine or placebo. To be entered into the study patients were required to have a Hamilton Depression Rating Scale (HDRS) 17-item score ≥20, a HDRS item 1 score ≥2, and a YMRS score ≤12 at both screening and randomization visits. Patients were randomly assigned to 8 weeks of quetiapine (600 mg or 300mg day). Quetiapine was initiated at 50 mg /day and administered to achieve a target dose of 300 mg/day by day 4 or 600 mg day by week 1.

Quetiapine at either dose demonstrated statistically significant improvement in MADRS total scores compared to placebo from week 1 onward for patients with bipolar I or II ($p<0.001$).The proportion of patients meeting response criteria (≥50% MADRS score improvement) at the final assessment in the group taking 600 and 300 mg/day of quetiapine were 58.2% and 57.6%, respectively, versus 36.1% for placebo ($p<0.001$). The proportion of patients meeting remission criteria (MADRS score ≤12) was 52.0% in the group taking 600mg and 300mg /day of quetiapine vs. 28.4% for placebo ($p<0.001$).

Quetiapine-treated patients experienced a statistically significant improvement ($p<0.001$) on the Clinical Global Impression (CGI) severity scale, the Hamilton Anxiety Scale total scores, the Pittsburg Sleep Quality scores and the Quality of Life Enjoyment and Satisfaction Questionnaire total scores at the end of the study for both quetiapine doses versus placebo. Both doses of quetiapine were effective in patients with a recent history of rapid cycling.

Thase et al., (2006) published a double blind, placebo-controlled study of acute depression in patients with bipolar I or II looking at two dosages of quetiapine, 300 mg and 600 mg per day. The Intent-to-Treat populations for this study were: quetiapine 600 mg per day (n=151), quetiapine 300 mg per day (n=155), and placebo (n=161). The study was designed to look at quetiapine's effect on bipolar I and bipolar II depression. Both dosages (600 mg/300mg/placebo) resulted in a significant decrease in MADRS (-16.0/-16.9/-11.9) and HAM-D (-13.0/-13.8/-9.9). Both dosages had significantly greater rates of response at week 8. Completion of the study was more common in placebo (65.5%) than 300 mg (58.7%), or 600 mg dose (53.3%).

Suppes, Hirschfeld et al., (2008) conducted a secondary analysis of two previously published studies which looked specifically at Bipolar II depression. It demonstrated that MADRS scores were significantly decreased in patients taking quetiapine at 300 mg and 600 mg per day in patients with bipolar II depression for 8 weeks. The overall efficacy and effect size were larger for patients with bipolar I than bipolar II.

Weisler et al., (2008) reported on a secondary analysis of two previously published studies looking at depression in Bipolar I Disorder. It demonstrated that quetiapine at 500-600 mg per day and at 200-300 mg per day led to significant decreases in MADRS scores and led to a greater rate of remission and responders than did placebo.

McElroy, Bowden et al., (2008) in an 8-week study of two doses of quetiapine monotherapy (300 and 600 mg/day) were compared to placebo and paroxetine monotherapy (at 20 mg/day) in patients with bipolar I and bipolar II depression. Quetiapine was significantly better than placebo in improving depressive symptoms. Paroxetine was not statistically significantly superior to placebo. There was significant improvement in most depressive rating scale items.

In both studies discussed below, there was an open phase with combination treatment, followed by a double blind randomized placebo phase.

Suppes et al., (2009) reported on a 104-week study looking at the effect of augmenting lithium or valproate with either quetiapine or placebo. Three hundred ten patients were started on quetiapine while 313 were given placebo. The patients' dose of lithium or valproate was not altered once the study began. Average lithium concentrations were 0.71 mEq/L for those on placebo and 0.74 mEq/L for those on quetiapine. Average valproate concentrations were 71.4 mcg/ml for those on placebo, and 68.9 mcg/ml for those on quetiapine. The median dose of quetiapine was 519 mg per day. Patients on valproate augmentation had an increased time to recurrence of any mood event and fewer patients with a mood event. They also had a significantly lower level of mania and depression symptoms during the remission.

Vieta et al., (2008c) investigated quetiapine as an adjunctive treatment to lithium or valproate in prevention of recurrent episodes in patients with bipolar I disorder. Before randomization, patients received open-label quetiapine (400-800 mg/day; flexible, divided doses) with lithium or valproate (target serum concentrations 0.5-1.2 mEq/L and 50-125 microg/mL, respectively) for up to 36 weeks. Those achieving at least 12 weeks of clinical stability were then randomized to double-blind treatment with quetiapine (400-800 mg/day), or placebo, added to ongoing open-label lithium or valproate for up to 104 weeks. Quetiapine augmentation significantly increased the time to recurrence of any mood event compared with placebo plus lithium/valproate. The proportion of patients having a mood episode was lower for quetiapine than placebo (18.5% versus 49.0%). The hazard ratio for time to any recurrence for quetiapine vs. placebo augmentation of lithium/valproate was 0.28 ($P<0.001$), for mania 0.30 ($P<0.001$), and for depression 0.26 ($P<0.001$).

Metabolic effects: During randomization, there was an increase in weight of 0.5 kg in the quetiapine group and a reduction of 1.9 kg in the placebo group. These figures are distorted, however, by the fact that all subjects received open-label quetiapine for up to 36 weeks before randomization, so the weight loss in the placebo group probably represents loss of weight that had been gained during open-label quetiapine. The incidence of a single emergent fasting blood glucose value $\geq$ 126 mg/dL was higher with quetiapine than with placebo (9.3% versus 4.1%; 17.6 versus 9.5 patients per 100 patient-years). Study strengths: Size of sample; randomized trial; inclusion of recently manic, depressed, or mixed subjects; 2 year duration. Study limitations: An enriched sample of patients with bipolar I disorder who had responded to, and tolerated, initial treatment with quetiapine plus lithium/valproate.

EVIDENCE TABLE - QUETIAPINE

	Evidence	Source	LE	QE	NE	SR
1	**Acute mania**: Effective as a monotherapy for the acute mania	Jeste and Dolder, 2004 (SR) Bowden et al., 2005 McIntyre et al., 2005 - Vieta, Mullen et al., 2005 § - Sajatovic, Calabrese et al., 2008 §§	I	Good	Subst	A
	Combination: Effective as an adjunct to lithium or valproate for the treatment of acute mania	Sachs et al., 2004 Yatham et al., 2004 - Ketter et al., 2007	I	Fair	Subst	A
2	**Acute depression**: Quetiapine is effective as monotherapy for the treatment of depression in both bipolar I and bipolar II depression	Calabrese, 2005 Thase et al., 2006 - Suppes, Hirschfeld et al., 2008 ** - Weisler et al.,2008 *** - Vieta et al., 2007 § - Cookson et al., 2007 §	I	Good	Subst	A
3	**Maintenance**: Quetiapine is effective as an adjunct to lithium or valproate in the maintenance phase of BD	Suppes et al., 2009 Vieta, Suppes et al., 2008		Good	Subst	B

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

§ - Secondary analyses of previous RCTs
§§ subgroup – elderly
** sub group analyses for BDII
*** sub group analyses for BDI

ANTIPSYCHOTIC/ RISPERIDONE

BACKGROUND

Risperidone is a second generation antipsychotic (SGA) which has demonstrated efficacy as monotherapy and combination therapy in the treatment of acute mania.

USE IN ACUTE MANIA/HYPOMANIA EPISODE

MONOTHERAPY

Risperidone was superior to placebo (Hirschfeld et al., 2004; Khanna et al., 2005) and comparable to olanzapine (Perlis et al., 2006) and haloperidol (Smulevich et al., 2005) in reduction of manic and mixed symptoms as monotherapy in 3 week trials

Khanna et al., (2005) evaluated the safety and efficacy of risperidone monotherapy for acute mania in a randomized, double blind study with inpatients with a YMRS score exceeding 19. Flexible doses (1-6 mg/day) of risperidone (n=146) were compared to placebo (n=144). Significantly greater improvement in YMRS was seen in the risperidone group as early as week one. By the end of the study the patients in the risperidone group experienced significantly greater improvement in YMRS, CGI, GAS, PNSS, and MADRS scores.

Hirschfeld et al., (2004) demonstrated the efficacy and safety of risperidone monotherapy in the treatment of acute bipolar mania. Patients diagnosed with acute manic episode were randomly assigned to 21 days of treatment with flexible dose (1-6 mg/day, mean dose 4.1 mg/day) risperidone (n=134) or placebo (n=125). The risperidone treatment group experienced a significantly greater reduction in YMRS. The benefit began to emerge within 3 days. The risperidone group also experienced significant improvements in CGI, MADRS, PANSS, and GAS. The most common adverse effect of risperidone was somnolence. EPS was seen more frequently in the risperidone group but mean scores were relatively low.

Smulevich et al., (2005) examined risperidone monotherapy in patients with acute mania. They treated patients with either risperidone up to 6 mg per day (n=154), haloperidol 2-12 mg per day (n=144), or placebo (n=140) for 21 days, followed by risperidone or haloperidol for 9 weeks. At 21 days, the patients receiving risperidone and haloperidol demonstrated significant improvement in YMRS scores compared to placebo. Both risperidone and haloperidol showed significant improvements in CGI, MADRS, BPRS and GAS scores at 3 weeks. Further reductions in YMRS scores were seen in patients taking both risperidone and haloperidol during the following 9 weeks. Extrapyramidal disorder was more likely in haloperidol (40%) than with risperidone (17%) or placebo (9%).

Gopal et al., (2005) performed **a** double blind, placebo-controlled trial of risperidone monotherapy for bipolar mania, in India. Adult patients (n=291) meeting DSM-IV-TR criteria for bipolar mania or mixed episode were given flexible doses of risperidone (n=146) or placebo (n=145) for up to 21 days. Remission was achieved by 42% of patients in the risperidone group and 13% of the patients in the placebo group. After adjusting for the presence of psychosis, baseline YMRS, gender, and number of mood cycles in the previous year, odds of remission for patients receiving risperidone was 5.6 and hazard of remission was calculated at 4.

COMBINATION THERAPY

Risperidone was superior to placebo as adjunctive therapy with lithium or valproate in one placebo-controlled trial (Sachs et al., 2002), but not in a second placebo-controlled trial in combination with lithium, valproate, or carbamazepine (Yatham et al., 2003).

Yatham et al., (2003) examined patients with acute mania who were on lithium, valproate, or carbamazepine. They were stratified according to prescribed mood stabilizer. They were randomized in a double blind fashion to receive either risperidone (N=75) or placebo (N=76) as an adjunct. Those on risperidone were started on 2 mg per day. The dose range was 1-6 mg per day with a mean modal dose of 3.7 mg per day. They were continued on their previous mood stabilizer and kept in therapeutic ranges of 0.6 mEq/L to 1.4 mEq/L for lithium, 50 mcg/mL to 125 mcg/mL for valproate, or 4-12 mcg/mL for carbamazepine. Although there was no statistically significant difference between risperidone and placebo in the decrease of YMRS scores, there was a statistically significant increase in response rates in the group treated with risperidone (59% vs. 41%). Improvements in CGI and BPRS were also more marked in the risperidone group. Patients who were on carbamazepine and received risperidone had dose-normalized plasma concentrations which were 40% lower than those on other mood stabilizers. A post-hoc analysis, which excluded patients on carbamazepine, found that risperidal led to a significantly greater decrease in YMRS scores. The overall rate of adverse events was equal in both groups, but a significantly higher percentage of patients in the risperidone group reported EPS.

Sachs et al., (2002) was a randomized 3-week trial of 156 patients with a manic or mixed manic episode who were started on either lithium or valproate and then randomized to receive either risperidone (N=52), haloperidol (N=53), or placebo (N=51) as an adjunct. The target therapeutic range for lithium was 0.6-1, 4 mEq/l and for valproate it was 50-120 mcg/ml. The patients on risperidone started at 2 mg per day and could be adjusted to 1-4 mg per day (mean modal dose was 3.8 mg per day). Patients on haloperidol were started on 4 mg per day and that could be adjusted to 2-8 mg per day (mean modal dose of 6.2 mg per day).

By the endpoint of the study both risperidone and haloperidol showed statistically greater decreases in YMRS than did placebo (-14.3, -13.4, and -8.2 respectively). Patients on haloperidol experienced a significantly greater increase in their Extrapyramidal Symptoms Rating Scale.

USE IN ACUTE DEPRESSION

No large RCTs have been published. Small studies and case reports cannot provide sufficient evidence on the efficacy of risperidone for acute depression episode.

MAINTENANCE

The effectiveness of risperidone for long-term use and/or maintenance use has not been established through controlled clinical trials.

A randomized double-blind, placebo-controlled study published in late 2009, demonstrated that adjunctive risperidone long-acting IM injection significantly delayed time to relapse in patients with bipolar I disorder and a history of frequent relapses compared to adjunctive placebo over 52-weeks.

> Macfadden W, Alphs L, Haskins JT, Turner N, Turkoz I, Bossie C, Kujawa M, Mahmoud R. A randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive risperidone long-acting therapy in patients with bipolar I disorder who replase frequently. Bipolar Disorders 2009;11:827-839.

EVIDENCE TABLE - RISPERIDONE (RIS)

	Evidence	Source	LE	QE	NE	SR
1	**Acute-Mania**: Effective as a monotherapy for the acute mania	Gopal et al., 2005 Hirschfeld et al., 2004 Jeste and Dolder, 2004 (SR) Khanna et al., 2005 Smulevich et al., 2005	I	Good	Subst.	A
2	**Combination**: effective as adjunct to lithium or valproate in the treatment of acute mania	Bahk et al., 2005 Sachs et al., 2002 Yatham et al., 2003	I			A
	Depression: Insufficient evidence to recommend for or against the use of risperidone in acute bipolar depression	No large RCTs have been published				I
	Maintenance: Risperidone long-acting IM injection significantly delayed time to relapse	Macfadden 2009	I	Good	Subst	B

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

ANTIPSYCHOTIC/ ARIPIPRAZOLE

BACKGROUND

Aripiprazole is a second-generation antipsychotic (SGA) that has been shown to be an effective drug for the treatment of manic episodes. Aripiprazole may be used as monotherapy or as an adjunct to lithium or depakote in the treatment of acute mania. There is also evidence that aripiprazole prevents relapse into mania.

USE IN ACUTE MANIA/HYPOMANIA EPISODE

RCTs

Keck, Marcus et al., (2003) was a 3 week double blind, placebo-controlled study with 262 inpatients who met DSM IV criteria for bipolar I, acute mania. They were randomized to receive either aripiprazole at 30 mg/day (N=130) or placebo (N=132). Exclusion criteria included cognitive disorders or substance abuse disorders. Primary outcomes measures in this study were the Young Mania Rating Scale (YMRS), Clinical Global Impressions – Bipolar Version (CGI-BP). Aripiprazole demonstrated a significant reduction in YMRS scores (p=0.002), as well as greater improvements in CGI-BP scores for mania (p=0.001), for depression (p=0.03) and overall score (0.001).

Vieta, Bourin et al., (2005) conducted a 12-week, double blind comparative trial of 347 patients with an acute manic or mixed manic episode. They were randomized to receive aripiprazole 15 mg per day (N=175) or haloperidol 10 mg per day (N=172). At the end of week 1 or 2, patients showing a poor response to treatment as defined by a Clinical Global Impression-Bipolar Scale score of 3 or above, could have their daily dose increased to aripiprazole 30 mg or haloperidol 15 mg. By the end of the study, the average dose of aripiprazole was 21.6 mg per day and was 11.1 mg per day for haloperidol. The continuation rate for patients on aripiprazole was 50.9% at week 12 while it was only 29.1% for haloperidol. The aripiprazole group had a response rate of 49.7% of patients while the response rate in the haloperidol arm was 28.4% (p<0.001). Among patients remaining in therapy, aripiprazole produced a significantly greater mean reduction in YMRS total score at week 12 than haloperidol (-29.0 v -27.4, p=0.044). The proportion of patients in remission (YMRS score <12) at week 12 was significantly higher in the aripiprazole group than in the haloperidol group (50% vs. 27%, p<0.001). No significant group differences were observed in mean scores on the CGI-BP severity scale at any time point. Extrapyramidal adverse events were more frequent in the haloperidol group than the aripiprazole group (62.7% vs. 24.0%).

Sachs et al., (2006) described a 3 week placebo-controlled trial of patients with an acute manic or mixed manic episode who received either aripiprazole 30 mg per day (N=137) or placebo (N=135). The dose of aripiprazole could be decreased to 15 mg per day if patients had difficulty tolerating it. By the end of the study the median dose of aripiprazole was 27.7 mg per day. Of the 272 starting the study, only 145 completed it. The completion rate for those on placebo was 52% and was 55% on aripiprazole. Individuals on aripiprazole had a greater response rate on days 7 (39% vs. 27%) and 21 (53% vs. 32%) and a greater decrease in YMRS scores (-12.5 vs. -7.2). There was also significantly greater improvement in CGI and PANSS scores in the aripiprazole group.

Keck et al., (2009) conducted a 12 week, placebo-controlled trial looking at patients with acute mania who were receiving either aripiprazole 15-30 mg per day (N=155), lithium at a blood concentration of 0.6-1.2 mEq/L (N=165), or placebo (N=160). Both lithium and aripiprazole were associated with significant greater reductions in YMRS compared to placebo (lithium = –12 aripiprazole = -12.6; placebo = -9). The study was insufficiently powered to detect any significant difference between the lithium and aripiprazole groups.

Young et al., (2009) conducted a 12 week haloperidol and placebo-controlled study which looked at patients with acute mania who were on aripiprazole 15-30 mg per day (N=167), haloperidol 5-15 mg per day (N=165), or placebo (N=153). Placebo was studied for only 3 weeks. After three weeks the placebo group was switched to aripiprazole in a masked fashion. The average dose of aripiprazole at 3 weeks was 23.6 mg per day and was 22.0 mg per day at week 12. The average dose of haloperidol was 8.5 mg per day at week 3 and 7.4 mg per day at week 12. The 3 week completion rate was 75% for aripiprazole, 63% for

haloperidol, and 71% for placebo. At week 3, both aripiprazole and haloperidol had greater improvement in YMRS (starting at day 2) and greater improvements in PANSS, MADRS and CGI-Bipolar Mania scores compared to placebo. Total adverse events associated with extrapyramidal symptoms were more frequent in the haloperidol group (53.3%) than in the aripiprazole group (23.5%). Serious adverse events were more likely with aripiprazole (11%) than haloperidol (3%).

COMBINATION

Vieta, et al., (2008) was a multicenter randomized trials, which looked at patients with manic or mixed manic episodes who had partial nonresponse to either lithium or valproate monotherapy. They were then randomized to receive either aripiprazole (N=253) or placebo (N=131). The target dose of lithium was 0.6-1.0 mmol/liter and for divaplroic acid was 50-125 mcg/ml. After being weaned off of other psychotropic medications, the patients received open label lithium or valproate. After confirming nonresponse they were started on placebo or aripiprazole at 15 mg per day. The dose of aripiprazole could then be increased to 30 mg per day. At the end of week six the blood concentration of lithium was 0.72 mmol/liter in the placebo group and 0.76 mmol/liter in the aripiprazole group. The blood concentration of valproate at week 6 was 68.4 mcg/ml in the placebo group, and 68.2 mcg/ml in the aripiprazole group. At week 6 the aripiprazole group had a significantly greater decrease in YMRS (-13.3 vs. -10.7). Adjunctive aripiprazole was also associated with significant improvement as measured by the CGI-BP and PANSS. Discontinuation rates because of adverse effects were higher in the aripiprazole group. Akathisia was statistically more likely in the aripiprazole group as well.

USE IN ACUTE DEPRESSION

Thase, Jonas et al., (2008) analyzed results of two placebo-controlled trials in patients with bipolar I disorder who were acutely depressed but had no psychotic features, and found no significant difference at endpoint of 8 weeks in either of the well-powered studies. The first study included 164 subjects on aripiprazole at 10 mg per day compared to 177 subjects on placebo. The second study had 176 subjects on aripiprazole 5-30 mg per day (based on efficacy and tolerability) compared to 178 on placebo. In neither study was aripiprazole significantly better than placebo.

USE IN MAINTENANCE

Keck et al., (2006) in a 26 week double blind placebo-controlled trial randomized 161 subjects with recent mania or mixed episode to aripiprazole (15 or 30 mg per day) or placebo. To be eligible, subjects must have had a Young Mania rating scale score of $\leq$ 10 and a Montgomery-Asberg Depression rating score of $\leq$13. Primary endpoint was the time to relapse for manic, mixed or depressive episode. Results showed that aripiprazole is superior to placebo in delaying time to manic recurrence (p=.020). There was no significant differences in time to depressive relapse (p=-.68).

Keck et al., (2007)– This is a continuation of Keck 2006. There were 39 subjects on aripiprazole at a mean dose of 23.8 mg per day and 27 subjects on placebo. They were followed for an additional 74 weeks. Patients on aripiprazole had lower rates and longer time to a recurrence of mania. They also had a significantly lower overall rate of relapse to any mood episode (12% on aripiprazole and 28% on placebo).

EVIDENCE TABLE – ARIPIPRAZOLE

	Evidence	Source	LE	QE	NE	SR
1	**Acute-Mania**: Effective as a monotherapy for the acute mania	Keck, Marcus et al., 2003 Vieta, Bourin et al., 2005 Sachs et al., 2006 Keck et al., 2009 Young et al., 2009	I	Good	Subst	A
2	**Combination**: Aripiprazole is an effective adjunct in the treatment of acute manic or mixed manic episodes	Vieta, T'Joen et al., 2008	I	Good	Subst	A
	Depression: Not effective in the treatment of acute bipolar depression	Thase, Jonas et al., 2008	I	Good	None	D
	Maintenance: Somewhat effective in the maintenance phase of bipolar disorder. More effective at preventing mania and hypomania than depressive episodes.	Keck et al., 2006 Keck et al., 2007	I	Fair	Subst	B

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

ANTYPSYCHOTIC/ZIPRASIDONE

BACKGROUND

Ziprasidone is a second generation antipsychotic which has been shown to be an effective drug for the treatment of manic episodes. Ziprasidone may be used as monotherapy or as an adjunct to lithium or valproate in the treatment of acute mania (including mixed episode). As of yet, there is no data concerning the efficacy of ziprasidone for bipolar depression or for maintenance treatment in bipolar disorder.

USE IN ACUTE MANIA/HYPOMANIA EPISODE

Keck et al., (2003) performed a randomized three week, placebo-controlled trial of ziprasidone. Patients were at least 18 years of age and met DSM-IV criteria for Bipolar I disorder currently experiencing a manic or mixed episode. Subjects also had a Mania Rating Scale (MRS) score of at least 14. Patients received either ziprasidone starting at 80-160 mg per day in divided doses (N=140) or placebo (N= 70). With the ziprasidone group there were significant improvements in the total YMRS as well as the YMRS manic subscale, and the behavior and ideation subscale, compared to placebo. There was also significant improvement on the CGI and the PANSS. The ziprasidone group reported significantly more somnolence, extrapyramidal symptoms, and dizziness. There was one suicide in the ziprasidone group. In general, ziprasidone was well tolerated and was superior to placebo in improving symptoms of mania, with changes occurring as early as day 2 of treatment.

Potkin et al., (2005) conducted a three-week, placebo-controlled trial of ziprasidone. Patients with acute mania were randomized to receive either ziprasidone 80-160 mg per day in divided doses (N=85) or placebo (N=36). The enrollment criteria were the same as in Keck et al., 2003. The ziprasidone group demonstrated significantly greater improvement than the placebo group as measured by the YMRS as well

as the YMRS manic subscale, and the behavior and ideation subscale. The PANSS total and PANSS positive subscale scores were significantly improved in the ziprasidone group. Improvement in the GAF was twice as great in the ziprasidone group. There were no differences between groups on the depressions scales: HAMD and MADRS. The significant side effects were as noted in the first study

Vieta, Ramey et al.,(2008) found that ziprasidone was inferior to haloperidol (but superior to placebo) in a 12-week trial. Changes from baseline Mania Rating Scale (MRS) scores for ziprasidone and haloperidol were superior to placebo from day 2 ($P = 0.001$) to week 3 ($P < 0.001$) while change from baseline at week 3 was greater for haloperidol than ziprasidone ($P \leq 0.001$). At week 3, the response rate (>/=50% decrease from baseline MRS score) was 36.9, 54.7 and 20.5% for ziprasidone, haloperidol and placebo, respectively ($P \leq 0.05$, active treatments versus placebo and ziprasidone versus haloperidol). Responses were maintained through the twelve week visit for 88.1% receiving ziprasidone and 96.3% receiving haloperidol. Ziprasidone was shown to be effective monotherapy for acute treatment of bipolar mania. Although haloperidol showed greater efficacy, ziprasidone showed a superior tolerability profile.

USE IN ACUTE DEPRESSION

No published controlled studies of ziprasidone in acute bipolar depression.

USE IN MAINTENANCE

No specific controlled study of ziprasidone in maintenance treatment in bipolar disorder.

EVIDENCE TABLE - ZIPRASIDONE

	Evidence	Source	LE	QE	NE	SR
1	**Acute-Mania:** effective drug for the treatment of manic episodes.	Jeste and Dolder, (2004) (SR) Keck et al, 2003 (RCT) Potkin et al, 2005 (RCT) Vieta, Ramey et al., 2008	I	Good	SIG	A
	Acute – Combination: Ziprasidone may be an effective adjunct to lithium and valproate for the treatment of acute manic or mixed manic episodes	Group consensus	III	Poor		I
	Depression: There is insufficient evidence to recommend for or against the use of ziprasidone in the treatment of bipolar depression	No specific controlled study available				I
	Maintenance: There is insufficient evidence to recommend for or against the use of ziprasidone during the maintenance phase of bipolar disorder	No specific controlled study available				I

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

ANTYPSYCHOTIC/HALOPERIDOL

BACKGROUND

Haloperidol is a first generation antipsychotic agent. This class of agents has been considered to be effective for the treatment of acute manic episodes. Compared to the second generation antipsychotics, haloperidol may be similar in antimanic effectiveness. Haloperidol likely has less prominent metabolic effects, but is more likely to be associated with drug-induced movement disorders, including acute parkinsonian syndromes, akathisia, and tardive dyskinesia. Because of its status as a standard treatment predating current agents, there is growing experience in controlled trials where haloperidol is a comparison drug for newer agents.

USE IN ACUTE MANIA/HYPOMANIA EPISODE

MONOTHERAPY

McIntyre et al., (2005) was a 12-week, double-blind randomized trial compared quetiapine up to 800 mg per day (N=102), haloperidol up to 8 mg per day (N=99), and placebo (N=101) in the treatment of mania. Subjects were required to have a minimum score of 20 on the Young Mania Rating Scale (YMRS), plus a score of least 4 on two of the core of the YMRS items of Irritability, Speech, Content, and Disruptive/Aggressive Behavior at screening and at randomization. Patients who met the DSM-IV criteria for mixed episodes and rapid cycling were excluded. Quetiapine was increased to 400 mg/day on Day 4, but could be adjusted up to 800 mg/day (Days 6 to 84).Haloperidol was initiated at the target dose of 2 mg/day on Days 1 and 2, with stepwise increase to 4 mg/day Day 4. The dose could be adjusted to between 2 and 8 mg/day on Days 6 to 84. Quetiapine and haloperidol were both superior to placebo in response rates and YMRS change (quetiapine = -17.5, haloperidol = -18.9, placebo = -9.5) as well as in CGI-BP, total PANSS, and GAS. There was no significant difference between quetiapine and haloperidol in any measurement of efficacy. Subjects given haloperidol were substantially more likely to experience extrapyramidal syndromes (33.3% vs. 5.9% for quetiapine or placebo, $p < 0.001$).

HALOPERIDOL VS ARIPIPRAZOLE

Vieta, Bourin et al., (2005) conducted a 12 week, double-blind comparative trial of 347 patients with an acute manic or mixed episode. They were randomized to receive aripiprazole 15 mg per day (N=175) or haloperidol 10 mg per day (N=172). At the end of week 1 or 2, patients showing a poor response to therapy as defined by a Clinical Global Impression-Bipolar Scale score of 3 or above, could have their daily dose increased to aripiprazole 30 mg or haloperidol 15 mg. By the end of the study the average dose of aripiprazole was 21.6 mg per day and was 11.1 mg per day for haloperidol. The continuation rate for patients on aripiprazole was 50.9% at week 12 while it was only 29.1% for haloperidol. The aripiprazole group had a response rate of 49.7% of patients while the response rate in the haloperidol arm was 28.4% ($p<0.001$). Among patients remaining in therapy, aripiprazole produced a significantly greater mean reduction in YMRS total score at week 12 than haloperidol (-29.0 v -27.4, $p=0.044$). The proportion of patients in remission (YMRS score <12) at week 12 was significantly higher in the aripiprazole group than in the haloperidol group (50% vs. 27%, $p<0.001$). No significant group differences were observed in mean scores on the CGI-BP severity scale at any time point. Extrapyramidal adverse events were more frequent in the haloperidol group than the aripiprazole group (62.7% vs. 24.0%).

Young et al., (2009) conducted a 12 week study looking at aripirazole (N=167), haloperidol (N=165) and placebo (N=153) in patients with acute mania. The patients on aripiprazole took 15-30 mg per day while those on, haloperidol took 5-15 mg per day. Placebo was only studied for 3 weeks. After three weeks the placebo group was switched to aripiprazole in a masked fashion. The average dose of aripiprazole at 3 weeks was 23.6 mg per day and was 22.0 mg per day at week 12. The average dose of haloperidol was 8.5 mg per day at week 3 and 7.4 mg per day at week 12. The 3 week completion rate was 75% for aripiprazole, 63% for haloperidol, and 71% for placebo. At week 3, both aripiprazole and haloperidol had greater improvement in YMRS (starting at day 2) and greater improvements in PANSS, MADRS and CGI-

Bipolar Mania scores compared to placebo. Total adverse events associated with extrapyramidal symptoms were more frequent in the haloperidol group (53.3%) than in the aripiprazole group (23.5%). Serious adverse events were more likely with aripiprazole (11%) than haloperidol (3%).

OLANZAPINE VS HALOPERIDOL

Tohen et al., (2003a) compared olanzapine 5-20 mg per day (n=234) to haloperidol 3-15 mg per day (n=219) in a 12-week study of patients with acute mania. By week 12 the average dose of medication was 11.4 mg per day for olanzapine and 5.2 mg per day for haloperidol. By the end of the study the groups did not differ in proportion of subjects entering remission, time to remission, rate of remission, proportion who relapsed, or time to relapse. Subjects randomized to olanzapine were less likely to develop depressive symptoms. Nonpsychotic subjects with olanzapine had more improvement in YMRS scores than corresponding subjects with haloperidol. Subjects with olanzapine had higher weight gain and somnolence, while those with haloperidol had more drug-related movement disorder symptoms.

RISPERIDONE VS HALOPERIDOL

Smulevich et al., (2005) examined risperidone monotherapy in patients with acute mania. They treated patients with either risperidone up to 6 mg per day (n=154), haloperidol 2-12 mg per day (n=144), or placebo (n=140) for 21 days, followed by risperidone or haloperidol for 9 weeks. At 21 days, the patients receiving risperidone and haloperidol demonstrated significant improvement in YMRS scores compared to placebo. Both risperidone and haloperidol showed significant improvements in CGI, MADRS, BPRS and GAS scores at 3 weeks. Further reductions in YMRS scores were seen in patients taking both risperidone and haloperidol during the following 9 weeks. Extrapyramidal disorder was more likely in haloperidol (40%) than with risperidone (17%) or placebo (9%).

ARIPIRAZOLE VS HALOPERIDOL

Vieta, Bourin et al., (2005) conducted a 12-week, double blind comparative trial of 347 patients with an acute manic or mixed manic episode. They were randomized to receive aripiprazole 15 mg per day (N=175) or haloperidol 10 mg per day (N=172). At the end of week 1 or 2, patients showing a poor response to treatment as defined by a CGI-Bipolar Scale score of 3 or above, could have their daily dose increased to aripiprazole 30 mg or haloperidol 15 mg. By the end of the study, the average dose of aripiprazole was 21.6 mg per day and was 11.1 mg per day for haloperidol. The continuation rate for patients on aripiprazole was 50.9% at week 12 while it was only 29.1% for haloperidol. The aripiprazole group had a response rate of 49.7% of patients while the response rate in the haloperidol arm was 28.4% ($p<0.001$). Among patients remaining in therapy, aripiprazole produced a significantly greater mean reduction in YMRS total score at week 12 than haloperidol (-29.0 v -27.4, $p=0.044$). The proportion of patients in remission (YMRS score <12) at week 12 was significantly higher in the aripiprazole group than in the haloperidol group (50% vs. 27%, $p<0.001$). No significant group differences were observed in mean scores on the CGI-BP severity scale at any time point. Extrapyramidal adverse events were more frequent in the haloperidol group than the aripiprazole group (62.7% vs. 24.0%).

COMBINATION THERAPY

Sachs et al., (2002) was a randomized 3-week trial of 156 patients with a manic or mixed manic episode who were started on either lithium or valproate and then randomized to receive risperidone (N=52), haloperidol (N=53), or placebo (N=51) as an adjunct. The target therapeutic range for lithium was 0.6-1, 4 mEq/l and for valproate it was 50-120 mcg/ml. The patients on risperidone started at 2 mg per day and could be adjusted to 1-4 mg per day (mean modal dose was 3.8 mg per day). Patients on haloperidol were started on 4 mg per day and that could be adjusted to 2-8 mg per day (mean modal dose of 6.2 mg per day). By the endpoint of the study both risperidone and haloperidol showed statistically greater decreases in YMRS than did placebo (-14.3, -13.4, and -8.2 respectively). Patients on haloperidol experienced a significantly greater increase in their Extrapyramidal Symptoms Rating Scale.

USE IN ACUTE DEPRESSION

There are no published controlled studies of haloperidol in bipolar depressive episodes.

MAINTENANCE

There are no published controlled studies of haloperidol in bipolar depressive episodes.

EVIDENCE TABLE

	Evidence	Source	LE	QE	NE	SR
1	**Acute-Mania (monotherapy):** has been considered to be effective for the treatment of acute manic episodes but with increased risk of side effects compared to second generation antipsychotics	McIntyre et al., 2005 (RCT) Smulevich et al., 2005 (RCT) Tohen et al., 2003a (RCT) Vieta, Bourin et al., 2005 (RCT) Young et al., 2009	I	Good	Mod	B
	Acute Mania (combination) – Haloperidol may be an effective adjunct when combined with lithium or valproate in the treatment of an acute manic or mixed manic episode	Sachs et al., 2002	I	Good	Mod	B
	Maintenance: There is insufficient evidence to recommend for against the use of haloperidol in the maintenance phase of bipolar disorder	There are no published controlled studies				

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

ANTYPSYCHOTIC/CLOZAPINE

BACKGROUND

Clozapine was the first second-generation antipsychotic (SGA) and has apparent efficacy in improving symptoms in treatment-resistant bipolar disorder. Although research examining clozapine's role in the treatment of bipolar disorders is limited, several retrospective reviews and prospective, open-label studies indicate that clozapine has pronounced antimanic and mood-stabilizing effects for episodes of dysphoric or psychotic mania. Clozapine is also an important clinical option for treatment-refractory patients who have failed trials of lithium or valproate. Clozapine has been associated with agranulocytosis in 1-2% of patients in addition to increased risk of seizure, myocarditis, and metabolic syndrome.

Systematic Review

Surprisingly few reviews have specifically addressed effectiveness of clozapine in bipolar disorders. Only two reviews have focused on clozapine in severe affective disorders. Five years after clozapine's FDA approval, Zarate and colleagues, (1995) comprehensively reviewed the literature examining clozapine in severe mood disorders. They concluded that clozapine was effective and well tolerated in short-term and maintenance treatment in psychotic and major affective syndromes in serious mental illnesses (i.e., schizophrenia, schizoaffective disorder, major depression, and bipolar disorder), noting substantial methodological flaws in many of the studies they reviewed.

Frye et al., (1998) concentrated on clozapine as the prototypical SGA in the treatment of bipolar disorders but also reviewed effectiveness of risperidone, olanzapine, sertindole, and trimipramine. The authors noted clozapine's effectiveness in treatment-resistant schizophrenia, hypothesizing that SGA work in bipolar disorder because of similarities between negative symptoms and depression and positive symptoms and mania.

USE IN ACUTE MANIA

Barbini and colleagues, (1997) prospectively compared randomized adjunctive chlorpromazine treatment to adjunctive clozapine treatment in an open study of thirty acutely manic bipolar patients. Study physicians were aware of patient treatment assignment. Patients were randomly assigned to a chlorpromazine (n=15) or clozapine (n=15) group. While the study was only 3 weeks in duration, significant decreases in YMRS scores were observed in both conditions with clozapine patients exhibiting symptom reduction more rapidly than the chlorpromazine group. Adjunctive clozapine appears to be as effective as and quicker than an adjunctive typical antipsychotic in the treatment of acute mania.

Calabrese and colleagues, (1996) recruited twenty-five patients with treatment-refractory bipolar disorder or schizoaffective disorder with at least one episode of mania during the past two years for an open-label trial of clozapine monotherapy. Treatment with clozapine was preceded by a 7-day washout period from any concomitant medications. Of the twenty-five patients, 88% (22) completed a 13-week clozapine trial and 72% (18) manifested significant improvement (> 50% decrease in score) on the YMRS. Additionally, patients with bipolar disorder improved more on the BPRS than did schizoaffective patients. The authors cautioned that bipolar patients seemed to respond negatively to rapid titration of clozapine.

An open-label, prospective trial (Green, et al., 2000**)** (Design – Fair; Benefit - Moderate) recruited 22 inpatients diagnosed with treatment-refractory bipolar disorder to receive a 12-week trial with clozapine monotherapy. Included patients had experienced at least three episodes of mania in the past 2 years or recent mania with psychotic symptoms lasting at least 6 months. Outcome measures BPRS, YMRS, and CGI saw reductions of 56.7%, 56.6%, and 39.1%, respectively, for the entire group of twenty-two patients. Most of this clinical improvement was observed in the first eight weeks of clozapine treatment. A significant consideration when interpreting results from this study was its high dropout rate. Eight of 22 subjects (36.4%) dropped out before week ten in the study. The authors suggested that the observed dropouts may have resulted from a rigid study design. Nonetheless, they conclude that clozapine is effective for treatment-refractory psychotic mania.

USE IN ACUTE DEPRESSION

No published controlled studies of clozapine in acute depression

USE IN MAINTENANCE

Suppes et al., (1999) compared adjunctive clozapine with treatment as usual (i.e., no additional clozapine) in a sample of patients diagnosed with treatment-resistant bipolar I disorder (n=26) or treatment-resistant schizoaffective disorder, bipolar type (n=12) with a history of mania in a prospective, naturalistic, randomized, 1-year study. Clinical response was defined as 30% reduction in 18-item BPRS scores. After 3 months, 65% of clozapine-treated subjects had responded compared with 48% of treatment-as-usual subjects. By 6 months, those numbers increased to 82% and 57%, respectively. The authors suggest that the substantially greater reduction in BPRS scores in the clozapine-treated group versus the treatment-as-usual group demonstrates mood-stabilizing in addition to anti-manic properties for clozapine. Furthermore, when response to clozapine was subsequently analyzed in psychotic vs. non-psychotic bipolar patients, similar reductions in BPRS scores were observed. This study suggested that clozapine may be an effective treatment in nonpsychotic affective disorders.

Three published reports detail results from a 48-month, prospective, open, naturalistic trial with clozapine in 101 treatment-refractory patients diagnosed with schizophrenia (N=34), schizoaffective disorder (N=30); or bipolar disorder with psychotic features (N=37).

Ciapparelli et al., (2000, 2003, 2004) enrolled subjects were required to be depot neuroleptic-free for at least 8 weeks before beginning adjunctive treatment or monotherapy with clozapine. Patients with bipolar disorder demonstrated the most accelerated improvement in both BPRS and GAF scores. More than 50% of bipolar patients responded to clozapine (> 50% reduction in BPRS) within 6 months of treatment inception. By 48 months, 83.6% of patients with bipolar disorder had responded to clozapine. While female gender, university education, and early age at onset were related to psychosocial functioning (GAF scores) at 48 months, only a diagnosis of bipolar disorder was significantly predicted clinical response (Ciapparelli et al., 2004). The authors contend that clozapine is a useful treatment for treatment-refractory bipolar disorder in addition to schizophrenia and schizoaffective disorder however they caution that theirs is only preliminary evidence since adequate parallel control groups were not available for analyses.

EVIDENCE TABLE

	Evidence	Source	LE	QE	NE	SR
1	**Acute mania (Monotherapy:** Clozapine may be effective as monotherapy in the treatment of mania and mixed episode.	Calabrese et al., 1996	II	Fair	Mod-Subst	B
2	**Acute Mania: (Adjunct);** Clozapine appears to be somewhat effective in the treatment of acute manic or mixed manic episodes when used as an adjunct	Barbini et al., 1997 Green et al., 2000	II	Fair	Mod	C
3	**Maintenance:** There is evidence that clozapine is somewhat effective in the treatment of the maintenance phase of bipolar disorder	Ciapparelli et al., 2000, 2003, 2004 Suppes et al., 1999	II I	Fair	Mod-Subst	B

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

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

Extrapyramidole 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 NCPE and USPSTF guidelines.
Pregnancy test *For women of childbearing potential*	Baseline	

BMI – Body Mass Index (kg/m^2); LDL – Low Density Lipoprotein
NCPE – National Cholesterol Education Program (http://www.nhlbi.nih.gov/about/ncep/)
USPSTF – U.S. Preventative Services Task Force (http://www.ahcpr.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.

USE IN ACUTE DEPRESSION

Risk for Switching

There is considerable controversy regarding the rate of response to antidepressants and the risk of a switch in mood polarity into hypomania or mania when these agents are used as adjunctive treatment to mood stabilizers in bipolar illness. Studies show that a substantial minority of patients with bipolar disorder who respond to antidepressant therapy will develop treatment-emergent affective switches. For example, in a follow-up of the study of Post et al., (2006), 46 out of 176 patients had treatment emergent mania or hypomania during acute or continuation pharmacotherapy. The meta-analysis of Gijsman et al., (2004) and the reports of Vieta et al. (2002) and Post et al., (2006) suggest that the risk of switching is greater with tricyclic antidepressants and venlafaxine than with other antidepressants, despite concurrent therapy with mood stabilizers. However, the findings of the study of Amsterdam et al., (2009), which focused on bipolar II patients who were not taking mood stabilizers, did not document an increased risk of treatment-emergent affective switches, which suggests that at least a subgroup of bipolar II patients may obtain benefit from antidepressants without undue risk of mood destabilization.

Goldberg, (2000) reported that patients undergoing antidepressant induced affective switch had undergone more antidepressant trials per year than those who did not, and were more likely to have a co-morbid substance use disorder (OR=6.99 P<0.007).

Therefore, patients with an unstable course of illness, comorbid substance use disorders, or subtle subsyndromal manic symptoms appear to be at greater risk for antidepressant induced switch.

Systematic Reviews

Gijsman et al., (2004) performed a systematic review and meta-analysis of RCTs using antidepressant medication for bipolar depression. Twelve randomized controlled trials with a total of 1,088 randomly assigned patients were included. Five trials compared one or more antidepressants with placebos (with 75% on concurrent mood stabilizer or second generation antipsychotics). Antidepressants were significantly more effective than placebo. In the 5 placebo-controlled trials, antidepressants did not induce more switching to mania (event rate for antidepressant was 3.8%, as compared to 4.7% in the placebo group). In six trials comparing between two antidepressants, the rate of switching for tricyclic antidepressants was 10%, and for all other antidepressants combined it was only 3.2%.

There has been debate as to whether in some of the studies reviewed patients were counted as improved that actually were patients developing manic symptoms. As well this review included and counted studies with patients having a range of diagnoses, considering their response to antidepressant treatment as though they had bipolar disorder versus anergic depression occurring during unipolar illness. These limitations of the conclusions of this systematic review must be taken into consideration in the context of other RCTs reported.

RCTs

Post et al., (2006) looked at the use of blinded adjunctive bupropion (N= 51), sertraline (N= 58), and venlafaxine (N=65) for bipolar depression. The patients in this study had either Type I or II Bipolar Disorder, and were on conventional mood stabilizers. Across 10 weeks of double blind adjunctive therapy, the three antidepressants were comparably effective in terms of response and remission rates. The

risk of treatment-emergent affective switches into hypomania or mania was significantly greater for the patients treated with venlafaxine as compared with those who received adjunctive therapy with bupropion or sertraline.

Sachs et al., (2007) was a double blinded controlled study of antidepressants vs. placebo in patients who were taking an antimanic medication (i.e., a conventional mood stabilizer or atypical antipsychotic). The patients all had bipolar depression (Type I or Type II) and the primary outcome was the percentage of patients with a durable recovery as defined by 8 consecutive weeks of euthymia. The antidepressants studied were bupropion and paroxetine. Overall, there was no evidence of efficacy for antidepressants versus placebo. For example, 42 of 179 patients (23.5%) randomly assigned to adjunctive therapy with one of the active antidepressants achieved durable recovery as compared to 51 of 187 patients (27.3%) who received an adjunctive placebo. Rates of treatment-emergent switch to mania or hypomania early in the course of treatment were similar in the two groups. In interpreting the data from this study one must keep in mind that the antidepressants studied had been in wide use for more than a decade when the study started and, as such, it is unlikely that patients who had experienced robust responses to these medications in the past would have been likely to enroll in this placebo-controlled trial. Likewise, patients known to have experienced multiple affective switches on antidepressants would be unlikely to enroll. Consistent with these points, the investigators evaluated 2689 patients with a major depressive episode in order to enroll 366 into the randomized trial.

Vieta et al., (2002) randomized 60 patients with bipolar depressive episodes treated with mood stabilizers to 6 weeks of single blind treatment with either paroxetine (N=30) or venlafaxine (N=30) for 6 weeks in a single-blind manner. Treatment with both drugs resulted in significant reductions in depressive symptoms, intent-to-treat response rates of 43% and 48% for the groups treated with paroxetine and venlafaxine, respectively. There were no statistically significant differences in either efficacy or safety measures between the 2 drugs, although only 3% (n=1) of paroxetine patients switched to hypomania or mania as compared to 13% (N = 4) in the group treated with venlafaxine.

Goldberg et al., (2007) conducted a naturalistic study that looked at the utility of adjunctive antidepressant therapy in 335 participants from the STEP-BD study. Patients who received adjunctive antidepressants had significantly higher mania symptom severity at 3 months. By contrast, those taking adjunctive antidepressant were no more likely to recover than those who were not prescribed antidepressants.

Amsterdam et al., (2009) conducted a 12 week randomized, but open-label study comparing lithium (300 to 2100 mg/day) and the antidepressant venlafaxine (37.5-375mg/day) in 86 bipolar II patients treated for major depressive episodes. Contrary to the findings of Vieta et al. (2002) and Post et al. (2006), venlafaxine therapy was no more likely to be associated with affective switches than lithium therapy; this was true even among the subset of patients with a past history of rapid cycling. Venlafaxine therapy also resulted in significantly greater reductions in HAM-D scores and higher response and remission rates than lithium therapy.

USE IN MAINTENANCE

Ghaemi et al., (2008) (Systematic Review) summarized randomized controlled trials for bipolar depression involving $\geq$ 6 months of treatment with antidepressants (AD) +/- mood stabilizers vs. placebo +/- mood stabilzers. This meta-analysis examined 7 trials, totaling 350 patients, which included 12 contrasts. Overall, he found that long-term treatment with various ADs yielded 27% lower risk of new depression vs. mood stabilizer-only or no treatment [pooled relative risk, RR = 0.73; 95% CI 0.55-0.97; number-needed-to-treat (NNT) = 11]. This modest benefit was largely offset by a 72% greater risk for new mania or hypomania [RR = 1.72; 95% CI 1.23-2.41; number-needed-to-harm (NNH) = 7]. When the contrast was limited to the studies that compared adjunctive antidepressant therapy versus a mood stabilizer alone, the level of prophylaxis conveyed against depressive relapse was neither statistically nor clinically significant (RR = 0.84; 95% CI 0.56-1.27; NNT = 16), although the risk of mania/hypomania also was not greatly elevated in this subset of studies (RR = 1.37; 95% CI 0.81-2.33; NNH = 16). The authors concluded that the efficacy of preventive therapy was not established in patients with bipolar depression.

Altshuler et al., (2003) examined the effect of antidepressant discontinuation or continuation on depressive relapse risk among 86 bipolar subjects who were followed for one year after successfully treated for an acute depressive episode. The 43 subjects who stopped antidepressant treatment within 6 months after remission experienced significantly shorter period of euthymia before depressive relapse. Seventy percent of these subjects experienced a depressive relapse compared with 36% of among the 41 subjects who continue taking antidepressant. By the 1-year follow-up evaluation, 15 (18%) of the 84 subjects had experienced a manic relapse; only six of these subjects were taking an antidepressant at the time of manic relapse. The author concluded that the risk of depressive relapse in patients with bipolar illness was significantly associated with discontinuing antidepressants soon after remission. The risk of manic relapse was not significantly associated with continuing use of antidepressant medication and, overall, was substantially less than the risk of depressive relapse.

EVIDENCE TABLE- ANTIDEPRESSANTS

	Evidence	Source	LE	QE	NE	SR
1	**Acute mania:** Antidepressants are ineffective in the treatment of acute mania and may cause significant adverse effects	Amsterdam et al., 1998 Bottlender et al., 2001 Gijsman et al., 2004 Nemeroff et al., 2001 Altshuler et al., 1995 Bauer et al., 1994 Wehr & Goodwin, 1987	I	Good	Small	D
2	**Bipolar Depression (Monotherapy);** Antidepressant monotherapy is ineffective in the treatment of bipolar depression and may cause significant adverse effects	Gjisman et al., 2004 Vieta et al., 2002 Goldberg et al., 2007 Sachs et al., 2007	I	Good	Small	D
3	**Bipolar Depression (Adjunct):** Adjunctive use of antidepressants in bipolar depression does not convey significant additional benefit and is associated with worsened adverse effects	Gijsman et al., 2004 Post et al., 2006	I	Fair	Small	D
4	**Maintenance:** Use of antidepressants during the maintenance phase of bipolar disorder is not associated with significant benefit and is associated with increased risk of adverse events	Ghaemi et al., 2008 Altshuler et al., 2003	I	Good	Small	D

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

ADVERSE EVENTS OF ANTIDEPRESSANTS

Table E - 9 Adverse Events – Antidepressants

	Adverse Events	
Drug Class	**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.

ACUTE TREATMENT OF MANIC OR MIXED EPISODES

Few studies assessed clinical outcomes of treatment of acute mania with ECT:

- Small et al., (1988), in a RCT (n=44) compared treatment with ECT with lithium for 8 weeks followed by lithium maintenance. Greater improvement was found in the ECT group.
- Sikdar et al., (1994) randomly assigned 32 manic patients to receive six ECT sessions compared to sham ECT sessions. Both groups received Chlorpromazine (600mg/d). ECT was found to be significantly better than those treated with sham ECT.
- Hiremani et al., (2008), in a study of 36 patients, found that mania patients treated with bifrontal ECT responded faster than those treated with bitemporal ECT, with comparable cognitive adverse effects. The author conclusion suggests that since ECT is usually prescribed for rapid

control of symptoms, bifrontal ECT may be preferred over bitemporal ECT in the treatment of acute mania.

- Barekatain et al. (2008) randomly assigned 28 patients with severe mania to moderate dose bifrontal ECT or low dose bitemporal ECT. All patients received at least 6 sessions of ECT. There was a significant difference between the MMSE scores of the bifrontal compared with the bitemporal group after both the sixth ECT and final ECT treatments. Young Mania Rating Scale scores did not differ between the 2 groups after either the sixth or the last ECT sessions.

Although all of these studies had small study group sizes, the results were consistent with other earlier retrospective comparisons of ECT treatment outcome in mania.

ACUTE TREATMENT OF DEPRESSIVE EPISODES

ECT is recommended for patients with severe depression. (VA/DoD guideline for MDD, 2008). Several studies have evaluated ECT outcomes in bipolar depressive episodes as compared to unipolar major depressive episodes.

- Zornberg and Pope reviewed the clinical literature on acute somatic treatment of acute bipolar depression. Five of seven studies comparing ECT with antidepressant agents find ECT more effective (Zornberg & Pope, 1993).
- Although patients with bipolar depressive episodes required fewer treatments, both groups of patients showed comparable responses to ECT (Daly et al., 2001; Grunhaus et al., 2002), regardless of electrode placement.
- Adverse cognitive effects were detected 6 months following the acute treatment course of ECT in a large community sample in which about 15% of patients had a bipolar depressive episode (Sackeim et al., 2007). Cognitive outcomes varied across treatment facilities and differences in ECT technique largely accounted for these differences. Treatment resulted in pronounced slowing of reaction time, both immediately and 6 months following ECT. Bilateral ECT resulted in more severe and persisting retrograde amnesia than right unilateral ECT. Advancing age, lower premorbid intellectual function, and female gender were associated with greater cognitive deficits.

MAINTENANCE TREATMENT

No randomized trials were found for evaluating efficacy of maintenance ECT for patients with bipolar disorder.

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.

ACTION STATEMENT

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

RECOMMENDATIONS

1. The likelihood of possible benefits with all medications used to treat BD in older adults needs to be balanced against potential risks.
2. Polypharmacy in older adults should be avoided.
3. Lithium can be used in older adults to treat acute mania, as maintenance, and also to treat bipolar depression.
4. Overall, valproate appears to be better tolerated than lithium in older adult patients with BD.
5. Carbamazepine is an alternative treatment to lithium for older patients with severe cardiovascular or renal disease.
6. Generally, benzodiazepines should be used with caution. However, they may be needed to treat extreme agitation. Care should be taken in the presence of comorbid medical conditions or possible drug-drug interactions. Older adults may be more sensitive than younger adults to central effects of benzodiazepines leading to ataxia, confusion, disinhibition, and delirium. If needed, a shorter-acting benzodiazepine which is metabolized by conjugation could be used, e.g., lorazepam.
7. The role of antidepressants in the management of BD is complex and sometimes controversial. Older adults are more likely than younger adults to develop initial manic episodes during antidepressant therapy. The provider should use tricyclics with caution in the older populations as these have been shown to cause an increased risk of treatment-emergent affective switches in this age group. It has been reported that the first line treatments for bipolar depression are mood stabilizers, and that adjunctive antidepressants should be used with caution. However, older adults with BD treated with a mood stabilizer and an antidepressant may be less likely to attempt suicide.
8. The treatment of secondary mania in older adults is relatively similar to the treatment of primary mania and typically does not usually require prophylaxis unlike primary mania. However, there may be increased sensitivity to side effects of medications, so dosages should be modified. Mania associated with structural central nervous system disease may respond better to carbamazepine or valproate. Newer anticonvulsant agents, such as topiramate and lamotrigine, have not been specifically studied yet in this patient population. Secondary
9. The preferred treatment for older adults with acute mania is an atypical antipsychotic (e.g. risperidone, quetiapine, olanzapine, and aripiprazole) combined with a mood stabilizer. Comorbid medical conditions such as diabetes, constipation, hypotension, weight may influence medication choice.
10. The provider needs to consider that mood stabilizers may impact cognitive functioning in older adults. Adverse effects were reported to be least likely in those taking lamotrigine or oxcarbazepine, intermediate with lithium, and greatest with valproate, carbamazepine, and topiramate. In a study of older adults with BD, lithium was no more likely to impair cognition than other therapies, but this study was limited by low statistical power.
11. There is growing concern regarding metabolic issues related to second-generation antipsychotics. The risk is greatest with clozapine and olanzapine, followed by quetiapine and risperidone, and then followed by aripiprazole and ziprasidone. If an older individual is to be maintained on a second-generation antipsychotic, baseline measures of weight, waist circumference, fasting blood glucose, and HbA1c should be obtained. Weight or waist

circumference can be monitored every two months and fasting blood glucose checked every six months or sooner if there is significant weight gain.

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

RATIONALE

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

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

EVIDENCE STATEMENTS

LITHIUM

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

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

VALPROATE

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

There are limited case reports and case series data that suggest that valproate is safe and effective in the treatment of mania in older adults (Chen et al., 1999; Goldberg, Sacks, & Kocsis, 2000; Kando, Tohen, Castillo, & Zarate, 1996; McFarland, Miller, & Straumfjord, 1990; Mordecai, Sheikh, & Glick, 1999; Niedermier & Nasrallah, 1998; Noaghiul, Narayan, & Nelson, 1998; Norton and Quarles, 2000; Puryear, Kunik, & Workman, 1995; Risinger, Risby, & Risch, 1994;

Sanderson, 1998; Schneider and Wilcox, 1998; Sharma, Persad, Mazmanian, & Karunaratne, 1993). In these reports, mean valproate doses were approximately 750 to 1500 mg/day, with mean valproate serum concentrations of 50 to 75 mg/mL.

CARBAMAZEPINE

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

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

LAMOTRIGINE

The FDA, for maintenance treatment in adults with BD, approved Lamotrigine in 2003. Its tolerability, efficacy for the depressive symptoms, and relatively limited drug interactions make it particularly useful in older adults.

No systematic studies in older adults with BD have been conducted. Limited case report data in older adults suggests that lamotrigine may help delay relapse or recurrence of bipolar depression (Robillard & Conn, 2002).

In a post-hoc analysis, controlled data suggested lamotrigine maintenance delayed overall and depressive episodes and was well tolerated in older adults with Bipolar I Disorder (Sajatovic et al., 2005). See section above on lithium for further details. Both treatments were generally well tolerated, with the most common adverse events with lamotrigine being back pain and headache. No serious rash was reported.

The possible benefits of lamotrigine need to be weighed against potential risks in older adults. Prescribing information includes a boxed warning regarding the risk of serious rashes, including Stevens-Johnson syndrome. The risk of rash may be higher when given in combination with valproate, or if the recommended initial dose or dose escalation of lamotrigine are exceeded. However, lamotrigine is generally very well tolerated in older adults (Bowden et al., 2004; Brodie et al., 1999).

ANTIPSYCHOTICS

Previously, first-generation antipsychotics were often prescribed for psychotic symptoms associated with depression or mania, but adverse events such as emotional blunting, and neurological side effects have limited their use.

The use of second-generation antipsychotics in the acute treatment and maintenance of adults with BD has expanded. As a class, the second-generation antipsychotic medications are associated with increased risk of stroke and death in those with dementia. There is currently no data to suggest that this is also the case for older adults with BD (Brooks et al., 2009).

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

FIRST-GENERATION ANTIPSYCHOTICS

The FDA approved chlorpromazine in 1973, for use in acute mania.

There are limited data case reports on the use of first-generation antipsychotics in older adults with BD (Chen et al., 1999; Stone, 1989).

The incidence of TD is higher in older adults (26%, 52%, and 60%, after 1, 2, and 3 years, respectively (Jeste et al., 1995) than in younger adults (5% per year) (Kane, Woerner, & Lieberman, 1988). Higher potency antipsychotics (e.g., haloperidol, fluphenazine) have a higher incidence of extrapyramidal symptoms, which may increase agitation. Older patients experience extrapyramidal symptoms more often than younger patients (Lanctot et al., 1998). First-generation antipsychotics (particularly higher potency agents) may also exacerbate the depressive component of BD (Ahlfors et al., 1981; Sachs & Thase, 2000).

The lower potency first-generation antipsychotics chlorpromazine and thioridazine have greater anticholinergic effects. In older adults, these side effects are associated with confusion, cognitive impairment and even delirium. Sedation and orthostatic hypotension are also more common among low-potency compared to high-potency first-generation antipsychotics

Cardiac arrhythmias may also occur: Thioridazine has been associated with abnormal QT intervals and ventricular arrhythmias (Timell, 2000). Haloperidol has been associated with torsade de pointes and increased risk of sudden death, but the greatest risk may be with thioridazine (Glassman & Bigger, 2001). Therefore, baseline EKG's are needed and histories reviewed for any syncopal episodes.

SECOND-GENERATION ANTIPSYCHOTICS

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

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

A vital safety concern with second-generation antipsychotics in older adults is the increase in mortality with these agents observed in older adults with dementia. In 2005, the FDA noted that in 17 controlled trials including 5,106 older adult demented patients with behavioral disorders; olanzapine, risperidone, quetiapine, and aripiprazole yielded an approximately 1.7 fold (typically increased from 2.6% to 4.5% with 10 weeks exposure) increase in mortality, primarily due to cardiovascular related events (e.g., heart failure, sudden death) or infections (mostly pneumonia) (Brooks et al., 2009)

The FDA has also mandated prescribing information warnings of the increased risk of developing hyperglycemia and diabetes mellitus from all second-generation antipsychotics. The greatest risk appears to be with clozapine and olanzapine, followed by risperidone, quetiapine, ziprasidone and aripiprazole in that order.

OLANZAPINE

Olanzapine is approved as monotherapy for the treatment of acute mania/mixed episode in Bipolar I disorder. Combination treatment with lithium or valproate as well as maintenance treatment in bipolar disorder is also approved. The olanzapine/fluoxetine combination has been approved for bipolar depression. A rapid-acting intramuscular formulation of olanzapine has been approved for the treatment of agitation associated with bipolar I mania in adults. However, olanzapine's use has

been limited by safety and tolerability concerns including sedation, weight gain, metabolic problems, and risks of increased mortality and cerebrovascular accidents in dementia patients.

There are very limited data regarding the use of olanzapine in older adults with BD (Nicolato, Romano-Silva, et al., 2006; Samuels & Fang, 2004),

RISPERIDONE

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

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

QUETIAPINE

Quetiapine is approved for the treatment of acute mania in bipolar I disorder as monotherapy or in combination with either lithium or valproate.

Quetiapine's use has been limited by safety and tolerability concerns including sedation, weight gain, metabolic problems, and postural hypotension. As a second-generation antipsychotic, it also poses an increased risk of mortality in dementia patients.

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

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

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

ARIPIPRAZOLE

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

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

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

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

EVIDENCE TABLE

	Evidence	Source	LE	QE	SR
1	**Acute: Mania**				
	Aripiprazole adjunctive	Sajatovic et al., 2008			
	Lithium	Retrospective: Chen et al., 1999, Sanderson, 1998	II	Fair	C
	Quetiapine	Sajatovic et al., 2005	I	Fair	B
	Valproate	Mordecai et al., 1999 Risinger et al., 1994			
2	**Acute: Depression**				
	Lamotrigine added to lithium or valproate	Robillard et al., 2002	I	Fair	C
	Lamotrigine	Rhodes, 2000			
	Lithium	Lepkifker, 2007			
3	**Maintenance**:		I	Fair	B
	Aripiprazole	Open label add-on: Sajatovic et al., 2008			
4	Rapid Cycling Valproate	Retrospective: Schneider and Wilcox, 1998	II	Fair	C

PSYCHOSOCIAL INTERVENTIONS IN OLDER ADULTS

There is an increasing body of evidence supporting the use of psychosocial interventions for individuals with BD. However, to date there remains limited data regarding the efficacy of such interventions in older adults with BD. Thus, clinicians are left to extrapolate from studies of younger adults with BD or older adults with depressive disorders.

Psychotherapeutic interventions are useful in older adults with depression, particularly cognitive behavioral therapy (CBT). A recent meta-analysis reviewed five randomized controlled trials (153 participants) that suggested CBT was more effective than a waiting list control condition. (Wilson, Mottram & Vassilas, 2008)

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

Integrated psychosocial interventions may also benefit older patients with BD, however currently the data remains limited. In one report of 441 mixed-age (mean age 44.2 years) BD patients, a systematic care management plan (structured group psychoeducation; monthly telephone monitoring; and feedback to, and coordination with, a mental health treatment team) was provided by nurse care managers and yielded lower mean mania ratings over 24 months (Simon, Ludman, Bauer, Unützer & Operskalski, 2006). In another randomized controlled trial of 306 mixed-age

(mean age 46.6 years) veterans with BD, a collaborative model for chronic care (group psychoeducation; nurse care coordinators to improve information flow, access to care, and continuity of care; and clinician decision support with simplified practice guidelines) reduced weeks in (primarily manic) mood episodes, and improved social role function, mental quality of life, and treatment satisfaction over 36 months (Bauer et al., 2006a).

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

APPENDICES

APPENDIX A: GUIDELINE DEVELOPMENT PROCESS

The development of the 2009 update of the VA/DoD Clinical Practice Guideline for Bipolar Disorder (BD) followed the steps described in "Guideline for Guidelines", an internal working document of the VA/DoD Evidence Based Practice Working Group that requires an ongoing review of guideline works in progress.

The Offices of Quality and Performance and Patient Care Services of the VA, and the US Army Medical Command, in coordination with the Air Force and Navy members of the Evidence-Based Workgroup, identified clinical leaders to champion the guideline development process. During a preplanning conference call, the clinical leaders defined the scope of the guideline and identified a group of clinical experts from the VA and DoD to form the Management of BD Working Group (WG). Working Group participants were drawn from the fields of Psychiatry, Family Practice, Internal Medicine, Psychology, Social work, Pharmacology and Nursing, from a wide variety of specialty and primary care settings, diverse geographic regions, and both VA and DoD health care systems. This Working Group of the VA/DoD was charged to update the algorithms and recommendations of the original clinical practice guideline published in 2002.

The WG defined a set of clinical questions within the focus area of the guideline. This ensured that the guideline development work outside the meeting focused on issues that practitioners considered important and produced criteria for the search and a protocol for systematic review of the literature.

The Working Group participated in an initial face-to-face meeting and two subsequent meetings to reach consensus about the guideline algorithms and recommendations and to prepare a draft update document. The draft continued to be revised by the WG through numerous conference calls and individual contributions to the document. Following the initial effort, an editorial panel of the WG convened to further edit the draft document. Recommendations for the performance or inclusion of specific treatment interventions or services were derived through a rigorous methodological approach that included the following:

- Determining appropriate criteria, such as effectiveness, efficacy, population benefit, or patient satisfaction
- Reviewing literature to determine the strength of the evidence in relation to these criteria
- Formulating the recommendations and grading the level of evidence supporting the recommendation

Experts from the VA and DoD reviewed the final draft and their feedback was integrated into the document.

This update of the BD Guideline is the product of many months of diligent effort and consensus building among knowledgeable individuals from the VA, DoD, and academia, as well as guideline facilitators from the private sector. An experienced moderator facilitated the multidisciplinary Working Group. The list of participants is included in Appendix E.

Formulation of Questions

The Working Group developed researchable questions (see Appendix C) and associated key terms to facilitate text-based searches of the literature. Following the template suggested by the Evidence-Based Medicine toolbox, Center for Evidence-Based Medicine, [http://www.cebm.net], the questions specified:

- **P**opulation – Characteristics of the target patient population
- **I**ntervention – Exposure, diagnostic, or prognosis
- **C**omparison – Intervention, exposure, or control used for comparison
- **O**utcome – Outcomes of interest.

These specifications served as the preliminary criteria for selecting studies. Literature searches were conducted on all topics identified in the algorithm or recommendations of the original guidelines.

Selection of Evidence

The evidence selection was designed to identify the best available evidence to address each key question and ensure maximum coverage of studies at the top of the hierarchy of study types. Published, peer-reviewed Randomized Trials (RCTs), as well as meta-analyses and systematic reviews that included randomized controlled studies, were considered to constitute the strongest level of evidence in support of guideline recommendations. This decision was based on the judgment that RCTs provide the clearest, most scientifically sound basis for judging comparative efficacy. The WG made this decision while recognizing the limitations of RCTs, particularly considerations of generalizability with respect to patient selection and treatment quality. When available, the search sought out critical appraisals already performed by others that described explicit criteria for deciding what evidence was selected and how it was determined to be valid. The sources that have already undergone rigorous critical appraisal include Cochrane Reviews, Best Evidence, Technology Assessment, and AHRQ systematic evidence reports.

In addition to Medline/PubMed, the following databases were searched: Database of Abstracts of Reviews of Effectiveness (DARE) and Cochrane Central Register of Controlled Trials and PsychINFO. For Medline/PubMed searches, limits were set for language (English), and type of research (RCT, systematic reviews and meta-analysis).

As a result of the literature reviews, articles were identified for possible inclusion. The following inclusion criteria were used for selection of studies:

- English language only of studies performed in United States, United Kingdom, Europe, Australia, Japan, New Zealand
- Full published articles only
- Study populations age limited to adults 18 years of age or older; all races, ethnicities, cultural groups
- Key outcomes cited
- Published from 2002- 2009.

Admissible evidence (study design and other criteria):

- Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of the data and results
- Randomized controlled trials (RCTs), systematic reviews (including EPC and HTA reviews), and meta-analyses
- Includes relevant outcomes that can be abstracted from data presented in the articles.
- Appropriate sample sizes for the study question addressed in the paper. RCTs will be included only if they are initiated with 10 or more subjects.

Preparation of Evidence Tables (Reports) and Evidence Rating

The results of the searches were organized and data was abstracted from the studies into evidence reports. The reports, as well as copies of the original studies, were provided to the WG for further analysis. Each reference was appraised for scientific merit, clinical relevance, and applicability to the populations served by the Federal healthcare system. A group of research analysts read and coded each article that met inclusion criteria.

Recommendations and Overall Quality Ratings

Evidence-based practice involves integrating clinical expertise with the best available clinical evidence derived from systematic research. A group of research analysts read and coded each article that met inclusion criteria. The articles were assessed for methodological rigor and clinical importance. Clinical experts from the VA and DoD WG reviewed the results and evaluated the strength of the evidence, considering quality of the body of evidence (made up of the individual studies) and the significance of the net benefit (potential benefit minus possible harm) for each intervention.

The overall strength of each body of evidence that addresses a particular Key Question was assessed using methods adapted from the U.S. Preventive Services Task Force (USPSTF) (Harris 2001). The number, quality, and size of the studies, as well as the consistency of results between studies and the directness of the evidence were considered in assigning an overall quality[QE] of the evidence (i.e., good, fair, or poor) (see Table A-2). Consistent results from a number of higher-level studies [LE] (see Table A-1) that were conducted across a broad range of populations support a high degree of certainty that the results of the studies are true. In such case the entire body of evidence would be considered ‘‘good” quality. The quality of the body of evidence was considered ‘fair” when the results could be due to true effects or to biases present across some or all of the studies. For a ‘‘poor” quality body of evidence, any conclusion is uncertain due to serious methodological shortcomings, sparse data, or inconsistent results.

For interventions that were supported by studies of ‘Fair’ or “Good” quality, the clinical experts evaluated the benefits and the potential harms as demonstrated by the results of the studies. In the final step, the Strength of Recommendation [SR] was determined based on the Quality of the Evidence [QE], and the clinical significance of the Net Benefit [NE] (see Table A-3) for each intervention. Thus, the grade (i.e., A, B, C, D or I) assigned to guideline recommendations reflects both, the Quality of the evidence and the potential clinical benefit that the intervention may provide to patients (see Table A4).

Table A-1: Level of Evidence (LE)	
I	At least one properly done RCT
II-1	Well-designed controlled trial without randomization
II-2	Well-designed cohort or case-control analytic study, preferably from more than one source
II-3	Multiple time series evidence with/without intervention, dramatic results of uncontrolled experiment
III	Opinion of respected authorities, descriptive studies, case reports, and expert committees

Table A-2: Overall Quality [QE]	
Good	High grade evidence (I or II-1) directly linked to health outcome
Fair	High grade evidence (I or II-1) linked to intermediate outcome; *or* Moderate grade evidence (II-2 or II-3) directly linked to health outcome
Poor	Level III evidence or no linkage of evidence to health outcome

Table A-3: Net Effect of the Intervention [NE]	
Substantial	More than a small relative impact on a frequent condition with a substantial burden of suffering; *Or* A large impact on an infrequent condition with a significant impact on the individual patient level.
Moderate	A small relative impact on a frequent condition with a substantial burden of suffering; or A moderate impact on an infrequent condition with a significant impact on the individual patient level.
Small	A negligible relative impact on a frequent condition with a substantial burden of suffering; *Or* A small impact on an infrequent condition with a significant impact on the individual patient level.
Zero or Negative	Negative impact on patients; *or* No relative impact on either a frequent condition with a substantial burden of suffering, or an infrequent condition with a significant impact on the individual patient level.

Table A-4: Final Grade of Strength of Recommendation [SR]				
	The net benefit of the intervention			
Quality of Evidence	**Substantial**	**Moderate**	**Small**	**Zero or Negative**
Good	A	B	C	D
Fair	B	B	C	D
Poor	I	I	I	I

Strength of Recommendation [SR]

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

Lack of Evidence – Consensus of Experts

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 Working Group.

Algorithm Format

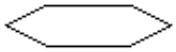
The clinical algorithm incorporates the information presented in the guideline in a format which maximally facilitates clinical decision-making. The use of the algorithmic format was chosen because of evidence showing that such a format improves data collection, diagnostic and therapeutic decision-making, and changes patterns of resource use.

The algorithmic format allows the provider to follow a linear approach to critical information needed at the major decision points in the clinical process and includes:

- An ordered sequence of steps of care
- Recommended observations
- Decisions to be considered
- Actions to be taken

A clinical algorithm diagrams a guideline into a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm (Society for Medical Decision-Making Committee, 1992). Arrows connect the numbered boxes indicating the order in which the steps should be followed.

Symbols used in the Clinical Algorithm

	Rounded rectangles represent a clinical state or condition.
	Hexagons represent a decision point in the guideline, formulated as a question that can be answered Yes or No. A horizontal arrow points to the next step if the answer is YES. A vertical arrow continues to the next step for a negative answer.
	Rectangles represent an action in the process of care.
	Ovals represent a link to another section within the guideline.

A letter within a box of an algorithm refers the reader to a corresponding annotation. The annotations elaborate on the recommendations and statements that are found within each box of the algorithm. Included in the annotations are brief discussions that provide the underlying rationale and specific evidence tables. Annotations indicate whether each recommendation is based on scientific data or expert opinion. A complete bibliography is included in the guideline.

REFERENCES

Agency for Health Care Policy and Research (AHCPR). Manual for conducting systematic review. Draft. August 1996. Prepared by Steven H. Woolf.

Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Atkins D; Methods Work Group, Third US Preventive Services Task Force, Current methods of the U.S. Preventive Services Task Force: a review of the process. Am J Prev Med 2001 Apr;20(3 Suppl):21-35. Available at; http://www.ahrq.gov/clinic/ajpmsuppl/harris1.htm

Society for Medical Decision-Making Committee (SMDMC). Proposal for clinical algorithm standards, SMDMC on Standardization of Clinical Algorithms. Med Decis Making 1992 Apr-Jun;12(2):149-54.

United States Preventive Service Task Force (USPSTF). Guide to clinical preventive services. 2nd edition. Washington, DC: US Department of Health and Human Services, Office of Disease Prevention and Health Promotion, 1996.

Woolf SH. Practice guidelines, a new reality in medicine II. Methods of developing guidelines. Arch Intern Med 1992 May;152(5):946-52.

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

EVIDENCE STATEMENTS

Screening:

- While it is important to inquire about suicidal tendencies and to account for risk factors, research has shown that attempts to predict suicidal behavior may be unreliable. Nonetheless, the clinician should routinely address concerns about suicide and document this assessment. The presence of one or more of the factors cited does not, in and of itself, justify hospitalization or emergency treatment. Clinical judgment as to the likelihood of imminent harm to the patient or others is the most important consideration.
- Hawton, et al, 2005, in a systematic review of 55 cohort, case control and cross sectional studies, found the strongest risk factors for completed suicide in bipolar patients to be male gender, a history of prior suicide attempts and expressed hopelessness. However, few of these articles addressed most of the general risk factors listed above. From the same review, the following risk factors were identified for attempted suicide in bipolar disorder: single marital status, family history of suicide, history of early physical or sexual abuse, early onset of bipolar disorder, history of attempted suicide, severity of the depressive or manic symptoms, rapid cycling, comorbid anxiety disorder, alcohol and drug abuse and comorbid eating disorder.
- Several cohort studies have found the highest risk for suicidal behavior in bipolar disorder to be in the depressive phase of the disorder, followed by the mixed state (Isometsa, et al, 1994; APA Guidelines, 2002; Baldessarini et al, 1999).
- Several systematic reviews have estimated the lifetime risk for suicide in bipolar disorder to range from 10-20% (Harris, Barraclough, 1997;Hawton et al, 2005; Baldessarini et al, 2003). Although one report recalculated these rates and estimated a somewhat lower lifetime rate of 6-8% (Inskip, Harris and Barraclough, 1998), the risk for suicide is still 10-20 times that of the general population.
- Mann et al, 2005, in a systematic review, found that in the recognition of depression and suicidal risk factors and of restricting access to lethal means for suicide was associated with a reduction in suicide rates.
- Tsai (2002) found an increased risk of suicide to be associated with mood incongruent psychotic features, a family history of suicide and a history of suicide attempts.

Acute treatment

- Tondo et al (2003) in a review, articulated the clinical axiom that systematic consideration of risk and protective factors enhances the assessment of suicidal patients while short term interventions

employed empirically to manage acute suicidality should include close clinical supervision, rapid hospitalization and use of ECT when indicated.

- Sharma (2003) reported a beneficial effect of ECT for acute treatment of suicidality in bipolar disorder.

Lithium maintenance:

- Baldessarini et al (2003) in a pooled review of 34 studies of patients with affective disorders (16,201 patients, 64,233 person years) found risks for all suicidal behaviors to be reduced by 93% with lithium treatment compared with no lithium (3.10/100 person years without lithium vs. 0.21/100 person years with lithium vs. 0.315/100 person years for the general population). The bipolar patients in the sample had a reduction in suicidal acts of 95%. For suicide attempts, the reduction was 93% while for completed suicides, the reduction was 82%.
- Cipriani et al (2005) in a systematic review of randomized controlled trials of the use of lithium in bipolar, schizoaffective depressive, dysthymic and rapid cycling disorders, covering 32 trials, in a post hoc analysis of data from effectiveness trials found patients on lithium less likely to die by suicide (OR=0.26, 95% CI 0.09-0.77).
- Muller-Oerlinghausen et al (2003, 2005) found patients on lithium to have 8 times lower suicide risk than those off lithium.
- Goodwin et al (2003) in a review of prescription use found, after adjustment for several variables, that bipolar patients on lithium had significantly fewer suicide attempts, attempts leading to hospitalization and completed suicides than patients on valproate and also had fewer attempts than those on carbamazepine.
- Several other cohort studies and systematic reviews have shown lithium maintenance to be associated with lower suicidal acts and deaths (Nilsson, 1999; Schou, 1998; Muller-Oerlinghausen et al 2003; Ernst and Goldberg 2004; Oqendo et al 2005)
- Several reviews (in addition to Goodwin et al 2003) have found no beneficial effect of the use of other maintenance medications in reduction of suicidal risk in bipolar disorder, including carbamazepine and valproate (Ernst and Goldberg, 2004) and antidepressants (Ernst and Goldberg, 2004) but the data overall are insufficient to draw a firm conclusion for these agents.

Psychotherapeutic/educational interventions:

- Gray and Otto (2001) in a review of 17 RCTs, found 3 strategies effective in reducing psychosocial risk factors for suicide in bipolar disorder:

    - Educating patients to elicit emergency care at times of distress.
    - Training in problem solving strategies.
    - Comprehensive interventions that include problem solving with intensive rehearsal of cognitive, social, emotional-labeling and distress tolerance skills.

- Rucci et al (2002) , in a randomized control trial of two types of intensive therapy, found in a two year follow up that in comparison to the preintervention period there was a threefold reduction in suicide attempts during the maintenance period.

EVIDENCE TABLE:

	Evidence	Source	LE	QE	SR
1	Screening for potential suicide	APA Guidelines, 2002 Hawton, et al, 2005 Isometsa et al, 1994 Baldassarini et al, 1999 Harris and Barraclough, 1997 Baldessarini et al, 2003 Mann et al, 2005 Tsai, 2002	III	Fair	I
2	Acute treatment	Tondo et al, 2003 Sharma, 2003	III	Fair	I
	Lithium Maintenance	Baldessarini et al,2003 Cipriani et al, 2005 Muller-Oerlinghausen et al, 2005 Goodwin et al, 2003 Nilsson et al, 1999 Muller-Oerlinghausen et al, 2003, 2005 Schou, 1998 Ernst and Goldberg, 2004 Oqendo, 2005	II	Moderate	B
3	Psychotherapeutic/ Educational Interventions	Gray and Otto, 2001 Rucci et al, 2002	I	Good	A

REFERENCES

American Psychiatric Association Guidelines: Major Depressive Disorder, 2002.

Baldessarini RJ, Tondo L, Hennen J: Effects of lithium treatment and its discontinuation on suicidal behavior in bipolar manic-depressive disorders. J Clin Psychiatry. 1999;60 (Suppl 2):77-84.

Baldessarini RJ, Tondo L, Hennen J: Lithium treatment and suicide risk in major affective disorders: update and new findings. J Clin Psychiatry. 2003;64 Suppl5:44-52.

Cipriani A, Pretty H, Hawton K, Geddes JR: Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials., Am J Psychiatry.2005;162:1805-19.

Ernst CL, Goldberg JF: Antisuicide properties of psychotropic drugs: a critical review. Harv Rev Psychiatry. 2004;12:14-41.

Goodwin FK, Fireman B, Simon GE, Hunkeler EM, Lee J, Revicki D: Suicide risk in bipolar disorder during treatment with lithium and divalproex. JAMA 2003;290:1467-73.

Gray SM, Otto MW: Psychosocial approaches to suicide prevention: applications to patients with bipolar disorder.J. Clin Psychiatry. 2001;62 Suppl 25:56-64.

Harris EC, Barraclough B: Suicide as an outcome for mental disorders: a meta-analysis. Br J Psychiatry. 1997;170:205-228.

Hawton K, Sutton L, Haw C, Sinclair J, Harriss L: Suicide and attempted suicide in bipolar disorder: a systematic review of risk factors. J Clin Psychiatry 2005;66:693-704.

Inskip HM, Harris EC, Barraclough B: Lifetime risk for suicide for affective disorder, alcoholism and schizophrenia. Br J Psychiatry. 1998;172:35-7.

Isometsa ET, Henriksson MM, Aro HM, Lonqvist JK: Suicide in bipolar disorder in Finland. Am J Psychiatry. 1994;151:1020-4.

Mann JJ, Apter A, Bertolote J, et al: Suicide prevention strategies: a systematic review. JAMA. 2005;294:2064-2074.

Muller-Oerlinghausen B, Berghofer A, Ahrens B: The antisuicidal and mortality-reducing effect of lithium prophylaxis: consequences for guidelines in clinical psychiatry. Can J Psychiatry., 2003;48:433-9.

Muller-Oerlinghausen B, Felber W, Berghofer A, Lauterbach F, Ahrens B: The impact of lithium long-term medication on suicidal behavior and mortality of bipolar patients. Arch Suic Res., 2005;9:307-319.

Nilsson A: Lithium therapy and suicide risk. J Clin Psychiatry., 1999;60(suppl 2):85-88

Oqendo MA, Chaudhury SR, Mann JJ: Phamacotherapy of suicidal behavior in bipolar disorder. Arch Suicide Res. 2005;9:237-250.

Rucci P, Frank E, Kostelnik B, Fagiolini A, Mallinger AG, Swartz HA, Thase ME, Siegel L, Wilson D, Kupfer DJ: Suicide attempts in patients with bipolar I disorder during acute and maintenance phases of intensive treatment with pharmacotherapy and adjunctive psychotherapy.,Am J Psychiatry. 2002;159:1160-4.

Schou M: The effect of prophylactic lithium treatment on mortality and suicidal behavior: a review for clinicians. J Affect Disord. 1998;50:253-9.

Sharma V: Atypical antipsychotics and suicide in mood and anxiety disorders. Bipolar Disord. 2003;5 Suppl2:48-52.

Tondo L, Isacsson G, Baldessarini R: Suicidal behavior in bipolar disorder: risk and prevention. CNS Drugs. 2003;17:491-511.

Tsai SY, Kou CJ, Chen CC, Lee HC: Risk factors for completed suicide in bipolar disorder. J Clin Psychiatry. 2002;63:469-476

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 I ndividual i n t he C ommunity**—This is particularly a factor with Delusions of Jealousy, Erotomanic Delusions, and Paranoid Idea.
- **Serious p sychiatric illn ess**—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 p revious vi olent s uicide at tempt**—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 patient**s, and

(3) **The efficacy of integrated treatment is still unclear**.

EVIDENCE

	Risk Factor	Sources of Evidence	QE	R
1	History of violence	Harris and Rice, 1997 Thienhaus and Piasecki, 1998 USPSTF, 1996	II-1	B
2	Homicidal ideation, or any ideation of committing harm	Thienhaus and Piasecki, 1998	II-1	B
4	Antisocial personality disorder	Harris and Rice, 1997 Thienhaus and Piasecki, 1998	II-1	B
5	Poor impulse control, inability to delay gratification	Thienhaus and Piasecki, 1998 Kay, Wolkenfeld, Murrill, 1988 Harris and Rice, 1997 USPSTF, 1996	II-1	B
6	Loss of reality testing, with delusional beliefs or command hallucinations	Thienhaus and Piasecki, 1998	II-1	B
7	Feeling controlled by an outside force; Believing that others wish him or her harm Perception of rejection or humiliation at the hands of others	Link, 1999 Thienhaus and Piasecki, 1998	I II-1	A B
10	Frontal Lobe Dysfunction, Head Injury	Hastings, 1997 Krakowski et al., 1999	I	A
11	Being under the influence of substances	Harris and Rice, 1997 Thienhaus and Piasecki, 1998 USPSTF, 1996	II-1	B
12	Availability of drugs, alcohol, or weapons upon release from care	Thienhaus and Piasecki, 1998	II-1	B

QE = Quality of Evidence; R = Recommendation (See Appendix A)

REFERENCES:

Tiet, Q. and B. Mausbach (2007). "Treatments for patients with dual diagnosis: a review." Alcoholism: Clin Exp Res **31**(4): 513-536.

APPENDIX C: CLINICAL QUESTIONS GUIDING THE LITERATURE SEARCH

1. Do mood-stabilizing drugs improve outcomes in patients with a diagnosis of bipolar disorder? Monotherapy vs. Placebo
2. Do mood-stabilizing drugs pose a risk to patients with a diagnosis of bipolar disorder? Monotherapy vs. Placebo
    a. Lithium
    b. Valproate (Depakene, Depakote)
    c. Carbamazepine (Tegretol)
    d. Lamotrigine (Lamictal)
    e. Gabapentin (Neurontin)
    f. Oxcarbazepine (Trileptal)
    g. Topiramate (Topamax)
3. Do atypical antipsychotics improve outcomes in patients with a diagnosis of bipolar disorder **without a comorbid mental health disorder**? Monotherapy vs. Placebo or other drug.
4. Do atypical antipsychotics improve outcomes in patients with a diagnosis of bipolar disorder **with a comorbid mental health disorder**? Monotherapy vs. Placebo or other drug.
5. Do atypical antipsychotics pose a risk to patients **with** a diagnosis of bipolar disorder? Monotherapy vs. Placebo or other drug
    a. aripiprazole (Abilify)
    b. clozapine (Clozaril)
    c. olanzapine (Zyprexa)
    d. quetiapine (Seroquel)
    e. risperidone (Risperdal)
    f. ziprasidone (Zeldox, Geodon)
6. Do antidepressants improve outcomes in patients with a diagnosis of bipolar disorder **without** a comorbid mental health disorder? Monotherapy and combined drug therapy.
7. Do antidepressants improve outcomes in patients with a diagnosis of bipolar disorder **with** a comorbid mental health disorder? Monotherapy and combined drug therapy.
8. Do antidepressants pose a risk to patients with a diagnosis of bipolar disorder? Monotherapy and combined drug therapy.
    a. Monoamine oxidase inhibitors
    b. selective serotonin reuptake inhibitors
    c. bupropion
    d. venlafaxine
9. Do combinations of drugs lead to better outcome of maintenance therapy?
    a. Lithium and antiepileptics
    b. Valproate and Lamotrigine
    c. Combination Antipsychotics & Valproate
    d. Combination Antipsychotics & Lithium
10. Does psychoeducation (includes psychosocial rehabilitation and family education) improve outcomes in patients with a diagnosis of bipolar disorder?
11. Does psychotherapy (includes interpersonal therapy, cognitive behavior therapy, family focused therapy (FFT), group therapy, and social rhythm) improve outcomes in patients with a diagnosis of bipolar disorder?

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 ≤ 150 mEq per day no sooner than every 5 days.	≥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
Antiepilepticss							
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 Maintenance: IM: 25 mg every 2 weeks	>1 >4 weeks	1 – 6 mg 25 – 50 mg every 2 weeks	6 mg 50 mg every 2 weeks	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
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
Tranylcypromine	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 affects 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

APPENDIX F: PARTICIPANTS LIST

Eileen P. Ahearn, MD, PhD
Psychiatrist
Madison VA medical Center
2500 Overlook Terrace
Madison, WI 53705
Phone: (608) 280-7015
Fax: (608) 280-7203
Email: Eileen.ahearn@med.va.gov

George W. Arana, MD
Chief, Mental Health Services Line
Ralph H. Johnson VAMC
Charleston, SC 29401
Phone: (843)789-7316
Email: George.arana@med.va.gov

Aaron Bilow, PharmD
Lackland **AFB,**
San Antonio, TX
Email: aaron.bilow@lackland.af.mil

Carla Cassidy, RN, MSN, NP
Clinical Quality Program Specialist
Department of Veterans Affairs
810 Vermont Avenue
Washington, DC 20032
Phone: (202) 273-6954
Email: Carla.cassidy@hq.med.va.gov

Thomas J. Craig, MD, MPH
Consultant
American Psychiatric Association
6804 Wild Rose Ct
Springfield, VA, 22152
Phone: 703-569-3977
Email: tlc19631@verizon.net

Martha D'Erasmo, MPH
Independent Consultant
4550 North Park Ave, Apt. 505
Chevy Chase, MD 20815
Phone: (301) 654-3152
Email: Marty@hqiinc.com

Rosalie Fishman, RN, MSN, CPHQ
President
Healthcare Quality Informatics, Inc.
15200 Shady Grove Rd, Suite 350
Rockville, MD 20850
Phone: (301) 296-4542

Jennifer Hoblyn, MD, MPH
Director of Inpatient Mental Health,
VA Palo Alto
3801 Miranda Ave Mail Code 118J
Palo Alto, CA 94304
Phone: 650-493-5000 ext 63007
Email: jhoblyn@stanford.edu

Sushma Jani, MD
Psychiatry Consultant
Defense Center of Excellence
10770 Hickory Ridge Road
Columbia, MD 21044
Phone: 410-997-5500
Email: sjani@jhu.edu

Amy M. Kilbourne, PhD, MPH
Associate Professor of Psychiatry,
University of Michigan
National Serious Mental Illness Treatment Research and Evaluation Center (SMITREC) Ann Arbor VA
2215 Fuller Road
Ann Arbor, MI 48105
Phone: 734-845-5046
Email: amykilbo@umich.edu

Joanne E. Ksionzky, RN, CNOR, RNFA
Clinical Practice Guidelines Coordinator
US Army Medical Command Quality Management Division
Evidence-Based Practice Section
Fort Sam Houston, TX 78234
Phone: (210) 221-7104 / DSN 471
Email: joanne.e.ksionzky@amedd.army.mil

Kevin R. Kennedy
CDR, USN
Head, Psychology Department
Naval medical Center, Portsmouth
Portsmouth, VA
Phone: (757) 953-7641
Email: KRKennedy@mar.med.navy.mil

Lauren Marangell, MD
Director Mood Disorder Research
Baylor College of Medicine
6655 Travis St. Suite 560
Houston, TX 77030
Phone: (713) 798-3832 X4
Email: laurenm@bcm.tmc.edu

David Miklowitz, PhD
University of Colorado
Department of Psychology
UCB 345 Boulder, CO 80309
Phone: 303- 492 8575
Email: miklow@psych.colorado.edu

Mary Ramos RN, PhD
Federal Recovery Coordinator
Brooke Army Medical Center
2050 Worth Road, Suite 26
Fort Sam Houston TX 78234
Phone: (210) 916-8852
Email: mary.ramos2@amedd.army.mil

Karen Schoelles, MD SM
Medical Director
Evidence-based Practice Center
ECRI
5200 Butler Pike
Plymouth Meeting, PA 19462
Phone:(610) 825-6000, ext. 5337
Email: kschoelles@ecri.org

Todd. P. Semla, MS, Pharm.D
Clinical Pharmacy Specialist
Department of Veteran Affairs
Pharmacy Benefits management and Strategic Health Group
1st Avenue (building 37, room 139)
Hines, IL 60141
Phone: (708) 786-7976
Email: Todd.semla@med.va.gov

Gary Southwell, PhD
LTC, MS
Chief, Department of Psychology
WRMC Psychology Consultant
Phone: (253) 968-2839
Email: gary.southwell@us.army.mil

David Snyder
Research Analyst
ECRI
5200 Butler Pike
Plymouth Meeting, PA 19462
Phone: (610) 825-6000
Email:dsnyder@ecri.org

Trisha Suppes, MD, PhD
Director, Bipolar Disorders Research Program
Palo Alto Veterans Affairs Health Care System
Department of Psychiatry & Behavioral Sciences
Stanford University School of Medicine
3801 Miranda Ave. (151T)
Palo Alto, CA 94304
Phone:650-493-5000 x62567
Email: tsuppes@stanford.edu

Oded Susskind, MPH
Medical Education Consultant
Brookline MA 02446
Phone: (617) 232-3558
Email: Oded@tiac.net

Alan C. Swann, MD
Department of Psychiatry and Behavioral Sciences
University of Texas - Mental Sciences Institute
1300 Moursund
Houston, TX 77030
Phone: 713-500-2556
Email: alan.c.swann@uth.tmc.edu

Janet Tekell, MD
Interim Chief, Psychiatry Service
VA Ann Arbor healthcare System
University of Michigan
2215 Fuller Road (116A)
Ann Arbor, MI 48105
Phone: (734) 761-7926
Email: jtekell@med.umich.edu

Michael Thase, MD
Department of Psychiatry
Mood and Anxiety Disorders Treatment and Research Program
3535 Market Street
Suite 670
Philadelphia, PA 19104-3309
Phone: 215-746-6680
Email: thase@mail.med.upenn.edu

Randon S. Welton, MD
LtCol, USAF, MC
Military Consultant to the Air Force
Surgeon General, Clinical Psychiatry
Wright Patterson medical Center
4881 Sugar Maple Drive
Wright Patterson AFB OH, 45433
Phone: (937) 257-8722
Email: Randon.welton@wpafb.af.mil

APPENDIX G: BIBLIOGRAPHY

Arora M, Daughton, J. Mania in the medically ill. *Curr Psychiatry Rep 2007; 9*, 232-235.

Badamgarav E, Weingarten SR, Henning JM, Knight K, Hasselblad V, Gano A, ofman J. Effectiveness of disease management programs in depression: A systematic review. Am J Psychiatry 2003;160:2080-90.

Bauer MS, Calabrese J, Dunner DL, Post R, Whybrow PC, Gyulai L, Tay LK, Younkin SR, Bynum D, Lavori P, et al. Multisite data reanalysis of the validity of rapid cycling as a course modifier for bipolar disorder in DSM-IV. Am J Psychiatry 1994;151(4):506-15.

Bauer MS, McBride L, Williford WO, Glick H, Kinosian B, Altshuler L, Beresford T, Kilbourne AM, Sajatovic M. Collaborative care for bipolar disorder: part I. Intervention and implementation in a randomized effectiveness trial. Psychiatr Serv 2006a. Jul 57(7):927-36.

Bauer MS, McBride L, Williford WO, Glick H, Kinosian B, Altshuler L, Beresford T, Kilbourne AM, Sajatovic M: Collaborative Care for Bipolar Disorder: Part II. Impact on Clinical Outcome, Function, and Costs. Psychiatr Serv 2006b; 57:937-45

Bauer MS, McBride L. Structured group psychotherapy for bipolar disorder: The life goals program. New York: Springer; 1996.

Bhagwagar Z, Goodwin GM. Lamotrigine in the treatment of bipolar disorder. Expert Opin Pharmacother 2005; 6: 1401-8.

Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness. JAMA. 2002;288:1775-9

Bottlender R, Rudolf D, Strauss A, Moller H. Mood-stabilizers reduce the risk of developing antidepressant-induced maniform states in acute treatment of bipolar I depressed patients. J Affect Disord 2001 Mar;63(1-3):79-83.

Bouman TK, Niemantsverdriet-van Kampen JG, Ormel J, Slooff CJ. The effectiveness of lithium prophylaxis in bipolar and unipolar depressions and schizo-affective disorders. J Affect Disord 1986;11(3):275-80.

Bowden CL, Grunze H, Mullen J, Brecher M, Paulsson B, Jones M, Vagero M, Svensson K. A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. J Clin Psychiatry 2005 Jan;66(1):111-21.

Bowden CL, Swann AC, Calabrese JR, Rubenfaer LM, Wozniak PJ, Collins MA, Abi-Saab W, Saltarelli M; Depakote ER Mania Study Group. A randomized, placebo-controlled, multicenter study of divalproex sodium extended release in the treatment of acute mania. J Clin Psychiatry 2006 Oct;67(10):1501-10.

Bowden CL, Asnis GM, Ginsberg LD, Bentley B, Leadbetter R, White R. Safety and tolerability of lamotrigine for bipolar disorder. Drug Saf 2004;27(3):173-84.

Bowden CL, Calabrese J R, Sachs G, Yatham L N, Asghar S A, Hompland M, Montgomery P, Earl N, Smoot TM, DeVeaugh-Geiss J; Lamictal 606 Study Group. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. Arch Gen Psychiatry 2003 Apr;60(4):392-400.

Bowden CL, Calabrese JR, Ketter TA, Sachs GS, White RL, Thompson TR. Impact of lamotrigine and lithium on weight in obese and nonobese patients with bipolar I disorder. Am J Psychiatry 2006;163:1199-201.

Bowden CL, Calabrese JR, McElroy SL, Gyulai L, Wassef A, Petty F, Pope HG Jr, Chou JC, Keck PE Jr, Rhodes LJ, Swann AC, Hirschfeld RM, Wozniak PJ. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study. Arch Gen Psychiatry 2000 May;57:481-9.

Bowden CL, Göğüş A, Grunze H, Häggström L, Rybakowski J, Vieta E. A 12-week, open, randomized trial comparing sodium valproate to lithium in patients with bipolar I disorder suffering from a manic episode. Int Clin Psychopharmacol 2008 Sep; 23 9(5):101-8.

Bowden CL, Swann AC, Calabrese JR, Rubenfaer LM, Wozniak PJ, Collins MA, Abi-Saab W, Saltarelli M; Depakote ER Mania Study Group. A randomized, placebo-controlled, multicenter study of divalproex sodium extended release in the treatment of acute mania. J Clin Psychiatry 2006 Oct;67(10):1501-10.

Brodie MJ, Overstall PW, Giorgi L, Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group. Epilepsy Res 1999;37:81-7.

Brooks JO 3rd, Chang HS, Krasnykh O. Metabolic risks in older adults receiving second-generation antipsychotic medication. Curr Psychiatry Rep 2009 Feb;11(1): 33-40.

Brown EB, McElroy SL, Keck PE Jr, Deldar A, Adams DH, Tohen M, Williamson DJ. A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. J Clin Psychiatry 2006 Jul;67(7):1025-33.

Burgess S, Geddes J, Hawton K, Townsend E, Jamison K, Goodwin G. Lithium for maintenance treatment of mood disorders. Cochrane Database Syst Rev 2001;(3):CD003013.

Carney CP, Jones LE. Medical comorbidity in women and men with bipolar disorders: a population-based controlled study. Psychosom Med,2006 *68*, 684-691

Calabrese J, Kimmel S, Woyshville M, Rapport D, Faust C, Thompson P, Meltzer HY. Clozapine for treatment-refractory mania. Am J Psychiatry 1996 Jun 153;(6):759-64.

Calabrese JR, Bowden CL, Sachs G, Yatham LN, Behnke KM, Mehtonen OP, Montgomery P, Ascher J, Paska W, Earl N, DeVeaugh-Geiss J. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. J Lamictal 605 Study Group. Clin Psychiatry 2003 Sep 64(9):1013-24.

Calabrese JR, Bowden CL, Sachs GS, Ascher JA, Monaghan E, Rudd GD. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. J Clin Psychiatry 1999 Feb;60(2):79–88.

Calabrese JR, Hirschfeld RM, Frye MA, Reed ML. Impact of depressive symptoms compared with manic symptoms in bipolar disorder: Results of a US community-based sample. J Clin Psychiatry 2004 Nov;65(11):1499-504.

Calabrese JR, Huffman RF, White RL, Edwards S, Thompson TR, Ascher JA, Monaghan ET, Leadbetter RA. Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. Bipolar Disord 2008 Mar;10(2): 323-33.

Calabrese JR, Keck PE Jr, Macfadden W, Minkwitz M, Ketter TA, Weisler RH, Cutler AJ, McCoy R, Wilson E, Mullen J. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry 2005 Jul;162(7):1351-60.

Ceron-Litvoc D, Soares BG, Geddes J, Litvoc J, de Lima MS. Comparison of carbamazepine and lithium in treatment of bipolar disorder: a systematic review of randomized controlled trials. Hum Psychopharmacol 2009 Jan;24(1):19-28.

Chen ST, Altshuler LL, Melnyk KA, Erhart SM, Miller E, Mintz J. Efficacy of lithium vs. valproate in the treatment of mania in the elderly: a retrospective study. J Clin Psychiatry 1999; 60:181-6.

Chengappa KN, Baker RW, Shao L, Yatham LN, Tohen M, Gershon S, Kupfer DJ. Rates of response, euthymia and remission in two placebo-controlled olanzapine trials for bipolar mania. Bipolar Disord 2003;5:1-5.

Ciapparelli A, Dell'Osso L, Bandettini di Poggio A, Carmassi C, Cecconi D, Fenzi, M, Chiavacci MC, Bottai M, Ramacciotti CE, Cassano GB. Clozapine in treatment-resistant patients with schizophrenia, schizoaffective disorder, or psychotic bipolar disorder: a naturalistic, 48-month follow-up study. J Clin Psychiatry 2003; Apr 64(4):451-8.

Ciapparelli A, Dell'Osso L, Pini S, Chiavacci M, Fenzi M, Cassano G. Clozapine for treatment refractory schizophrenia, schizoaffective disorder, and psychotic bipolar disorder: A 24-month naturalistic study. J Clin Psychiatry 2000; 61(5):329-34.

Ciapparelli A, Ducci F, Carmassi C, Carlini M, Paggini R, Catena M, Bottai M, Dell'Osso L. Predictors of response in a sample of treatment-resistant psychotic patients on clozapine. Eur Arch Psychiatry Clin Neurosci 2004 Oct;254(5): 343-6.

Cipriani A, Pretty H, Hawton K, Geddes JR. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. Am J Psychiatry 2005 Oct;162(10):1805-19.

Cipriani A, Rendell J, Geddes J. Olanzapine in long-term treatment for bipolar disorder. Cochrane Database Syst Rev 2009 Jan 21;(1):CD004367.

Clarkin JF, Glick ID, Haas GL, Spencer JH, Lewis AB, Peyser J, Demane N, Good-Ellis M, Harris E, Lestelle V. A randomized clinical trial of inpatient family intervention V. Results for affective disorders. J Affect Disord 1990 Jan;18(1):17-28.

Cochran SD. Preventing medical noncompliance in the outpatient treatment of bipolar affective disorders. J Consult Clin Psychol 1984 Oct;52:873-8.

Colom F, Vieta E, Martinez-Aran A, Reinares M, Beinabarre A, Gasto C. Clinical factors associated with treatment compliance in eurthymic bipolar patients. J Clin Psychiatry 2000 Aug;61(8):549-55.

Colom F, Vieta E, Martinez-Aran A, Reinares M, Goikolea JM, Benabarre A, Torrent C, Comes M, Corbella B, Parramon G, Corominas J. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. Arch Gen Psychiatry 2003Apr;60(4):402-7.

Colom F, Vieta E, Sanchez-Moreno J, Martinez-Aran A, Reinares M, Goikolea JM, Scott J. Stabilizing the stabilizer: group psychoeducation enhances the stability of serum lithium levels. Bipolar Disorders 2005;7(Suppl 5):32-6.

Consensus development conference on antipsychotic drugs and obesity and diabetes. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity Diabetes Care 2004;27:596-601.

Cookson J, Keck PE Jr, Ketter TA, Macfadden W. Number needed to treat and time to response/remission for quetiapine monotherapy efficacy in acute bipolar depression: evidence from a large, randomized, placebo-controlled study. Int Clin Psychopharmacol 2007;22:93-100.

Cullen M, Mitchell P, Brodaty H, Boyce P, Parker G, Hickie I, Wilhelm K. Carbamazepine for treatment-resistant melancholia. J Clin Psychiatry 1991;52:472-6.

Daly JJ, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S. Roose SP, Sackeim HA. ECT in bipolar and unipolar depression: differences in speed of response. Bipolar Disord 2001 Apr;3(2):95-104.

Davenport YB, Ebert MH, Adland ML, Goodwin FK: Couples group therapy as adjunct to lithium maintenance of the manic patient. Am J Orthopsychiatry 1977 Jul;47(3):495-502.

Davis JM, Janicak PG, Hogan DM. Mood stabilizers in the prevention of recurrent affective disorders: a meta-analysis. Acta Psychiatr Scand 1999 Dec;100(6):406-17.

Davis LL, Bartolucci A, Petty F. Divalproex in the treatment of bipolar depression: a placebo-controlled study. J Affect Disord 2005;85(3):259-66.

Depp CA, Jeste, DV. Bipolar disorder in older adults: a critical review. Bipolar Disord 2004;6:343-67.

Dunn KL. Rabins PV. Mania in old age. In: Shulman KI; Tohen M,; Kutcher SP., editors. Mood Disorders Across the Life Span. Wiley-Liss:New York;1996. p. 399-406

Emilien G, Maloteaux JM, Seghers A, Charles G. Lithium compared to valproic acid and carbamazepine in the treatment of mania: a statistical meta-analysis. Eur Neuropsychopharmacol 1996 Aug;6(3):245-52.

Faedda GL, Tondo L, Baldessarini RJ, Suppes T, Tohen M. Outcome after rapid vs gradual discontinuation of lithium treatment in bipolar disorders. Arch Gen Psychiatry 1993 Jun;50(6):448-55.

Fitzgerald RG. Mania as a message: treatment with family therapy and lithium carbonate. Am J Psychother 1972 Oct;26(4);547-54.

Frank E, Kupfer DJ, Thase ME, Mallinger AG, Swartz HA, Fagiolini AM, Grochocinski VJ, Houck P, Scott J, Thompson W, Monk T. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. Arch Gen Psychiatry 2005;62(9):996-1004.

Frye M, Ketter T, Altshuler L, Denicoff K, Dunn R, Kimbrell T, Corá-Locatelli G, Post RM. Clozapine in bipolar disorder: treatment implications for other atypical antipsychotics. J Affect Disord 1998 Mar;48(2-3) 91-104.

Frye MA, Ketter T A, Kimbrell TA, Dunn RT, SpeerAM, Osuch EA, Luckenbaugh DA, Cora-Ocatelli G, Leverich GS, Post RM. A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. J Clin Psychopharmacol 2000 Dec;20(6):607-14.

Gao K, Calabrese JR. Newer treatment studies for bipolar depression. Bipolar Disord 2005 Dec;7(Suppl 5): 13-23.

Gareri P, De Fazio P, De Fazio S, Marigliano N, Ferreri Ibbadu G, De Sarro G. Adverse effects of atypical antipsychotics in the elderly. Drugs Aging 2006;23, 937-56.

Geddes JR, Burgess S, Hawton K, Jamison K, Goodwin GM. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. Am J Psychiatry 2004 Feb;161(2):217-22.

Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. Br J Psychiatry 2009 Jan 194(1):4-9.

Gelenberg AJ, Kane JM, Keller MB, Lavori P, Rosenbaum JF, Cole K, Lavelle J. Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorder. N Engl J Med 1989 Nov 30;321(22):1489-93.

Ghaemi SN, Gilmer WS, Goldberg JF, Zablotsky B, Kemp DE, Kelley ME, Bauer AD, Fleck J, Filkowski MM, Stan VA, Dunn RT. Divalproex in the treatment of acute bipolar depression: a preliminary double-blind, randomized, placebo-controlled pilot study. J Clin Psychiatry 2007 Dec;68(12):1840-4.

Ghaemi SN, Wingo AP, Filkowski MA, Baldessarini RJ. Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks. Acta Psychiatr Scand 2008;118:347-56.

Gijsman HJ, Geddes JR, Rendell JM, Nolen WA, Goodwin GM. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. Am J Psychiatry 2004 Sep;161(9) 1537-47.

Gildengers AG, Whyte EM, Drayer RA, Soreca I, Fagiolini A, Kilbourne AM, Houck PR, Reynolds CF 3rd, Frank E, Kupfer DJ, Mulsant BH. Medical burden in late-life bipolar and major depressive disorders. Am J Geriatr Psychiatry 2008 Mar;16(3):194-200.

Gilman AG, Rall TW, Nies AS, Taylor P (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th ed. New York: Pergamon Press; 1990. 1811p.

Glassman AH, Bigger JT Jr. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. Am J Psychiatry 2001 Nov;158(11):1774-82.

Goldberg JF, Garno JL, Leon AC, Kocsis JH, Portera L. Qualitative differences in mixed versus pure mania. Compr Psychatry 2000 Jul-Aug;41(4):237–41.

Goldberg JF, Perlis RH, Ghaemi SN, Calabrese JR, Bowden CL, Wisniewski S, Mikowitz DJ, Sachs GS, Thase ME. Adjunctive antidepressant use and symptomatic recovery among bipolar depressed patients with concomitant manic symptoms: findings from the STEP-BD. Am J Psychiatry 2007;164(9):1348-55.

Goldberg JF, Sacks MH, Kocsis JH. Low-dose lithium augmentation of divalproex in geriatric mania. J Clin Psychiatry 2000 Apr;61(4):304.

Goldsmith DR, Wagstaff AJ, Ibbotson T, Perry CM. Lamotrigine: a review of its use in bipolar disorder. Drugs 2003;63(19): 2029-50.

Goodwin FK, Jamison KR. Manic-Depressive Illness: Second Edition New York, NY: Oxford University Press; 1990. Second edition, 2007.

Goodwin GM, Bowden CL, Calabrese JR, Grunze H, Kasper S, White R, Greene P, Leadbetter R. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. J Clin Psychiatry 2004 Mar;65(3):432-41.

Goodwin GM. Consensus Group of the British Association for Psychopharmacology. Evidence-based guidelines for treating bipolar disorder: recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2003 Jun;17(2):149-73.

Gopal S, Steffens DC, Kramer ML, Olsen MK. Symptomatic remission in patients with bipolar mania: results from a double-blind, placebo-controlled trial of risperidone monotherapy. J Clin Psychiatry 2005 Aug;66(8):1016-20.

Green A, Tohen M, Patel J, Banov M, DuRand C, Berman I, Chang H, Zarate C Jr, Posener J, Lee H, Dawson R, Richards C, Cole JO, Schatzberg AF. Clozapine in the treatment of refractory psychotic mania. Am J Psychiatry 2000 Jun;157(6):982-6.

Grunhaus L, Schreiber S, Dolberg OT, Hirshman S, Dannon PN. Response to ECT in major depression: are there differences between unipolar and bipolar depression? Bipolar Disord 2002;4 Suppl 1:91-3.

Gupta S, Chohan M, Madhusoodanan S. Treatment of acute mania with aripiprazole in an older adult with noted improvement in coexisting Parkinson's Disease. Prim Care Companion J Clin Psychiatry 2004;6 (1):50-1.

Gyulai L, Bowden CL, McElroy SL, Calabrese JR, Petty F, Swann AC, Chou JC, Wassef A, Risch CS, Hirschfeld RM, Nemeroff CB, Keck PE Jr, Evans DL, Wozniak PJ. Maintenance efficacy of divalproex in the prevention of bipolar depression. Neuropsychopharmacology 2003;28:1374-82.

Hewick DS, Newbury P, Hopwood S, Naylor G, Moody J. Age as a factor affecting lithium therapy. Br J Clin Pharmacol 1977; 4: 201-5.

Himmelhoch JM, Neil JF, May SJ, Fuchs CZ, Licata SM. Age, dementia, dyskinesias, and lithium response. Am J Psychiatry 1980;137: 941-5.

Hiremani RM, Thirthalli J, Tharayil BS, Gangadhar BN. Double-blind randomized controlled study comparing short-term efficacy of bifrontal and bitemporal electroconvulsive therapy in acute mania. Bipolar Disord 2008;10:701-7.

Hirschfeld RM, Baker JD, Wozniak P, Tracy K, Sommerville KW. The safety and early efficacy of oral-loaded divalproex versus standard-titration divalproex, lithium, olanzapine, and placebo in the treatment of acute mania associated with bipolar disorder. J Clin Psychiatry 2003 Jul;64(7):841-6.

Hirschfeld RM, Keck PE Jr, Kramer M, Karcher K, Canuso C, Eerdekens M, Grossman F. Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial. Am J Psychiatry 2004 Jun;161(6):1057-65.

Hoblyn J. Bipolar disorder in later life. Older adults presenting with new onset manic symptoms usually have underlying medical or neurologic disorder. Geriatrics 2004;59(6) 41-4.

Hudson-Jessop P, Hughes B, Brinkley N. New for old? Risperidone long-acting injection in older patients. Australas Psychiatry 2007 Dec;15(16):461-4.

Jamison KR, Gerner RH, Goodwin FK. Patient and physician attitudes toward lithium: relationship to compliance. Arch Gen Psychiatry 1979 Jul 20;36(8 Spec No):866-9.

Janicak PG, Davis JM, Preskorn SH, Ayd FJ. In: Principles and Practice of Psychopharmacotherapy. Baltimore: Williams and Wilkins; 1993. p. 224-57.

Jeste DV, Caligiuri MP, Paulsen JS, Heaton RK., Lacro JP, Harris MJ, Bailey A, Fell RL, McAdams LA. Risk of tardive dyskinesia in older patients. A prospective longitudinal study of 266 outpatients. Arch Gen Psychiatry 1995;52:756-65.

Jeste DV, Dolder CR. Treatment of non-schizophrenic disorders: focus on atypical antipsychotics. J Psychiatr Res 2004; 38(1):73-103.

Jeste DV, Rockwell E, Harris MJ, Lohr JB, Lacro J. Conventional vs. newer antipsychotics in elderly patients. Am J Geriatr Psychiatry 1999;7:70-6.

Johnson SL, Miller I. Negative life events and time to recovery from episodes of bipolar disorder. J Abnorm Psychol 1997 Aug;106:449-57.

Johnson SL, Sandrow D, Meyer B, Winters R, Miller I, Solomon D, Keitner G. Increases in manic symptoms following life events involving goal-attainment. J Abnorm Psychol 2000 Nov;109:721-7.

Judd LL, Akiskal HS, Schettl PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, KM. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002 Jun;59(6)530-7.

Juruena MF, Ottoni GL, Machado-Vieira R, Carneiro RM, Weingarthner N, Marquardt AR, Fleig SS, Broilo L, Busnello EA. Bipolar I and II disorder residual symptoms: oxcarbazepine and carbamazepine as add-on treatment to lithium in a double-blind, randomized trial. Prog Neuropsychopharmacol Biol Psychiatry 2009 Feb 1;33(1):94-9.

Justo LP, Soares BG, Calil HM. Family interventions for bipolar disorder. Cochrane Database Syst Rev 2007 Oct 17;(4):CD005167.

Kando JC, Tohen M, Castillo J, Zarate CA Jr. The use of valproate in an elderly population with affective symptoms. J Clin Psychiatry 1996;57:238-40.

Kane JM, Woerner M, Lieberman J. Epidemiological aspects of tardive dyskinesia. Encephale 1988 Sep;14 Spec No:191-4.

Kaplan HI, Sadock BJ. Comprehensive Textbook of Psychiatry VI; Sixth Edition. Baltimore, MD: Williams & Wilkins;1995.

Keck PE Jr, Calabrese JR, McIntyre RS, McQuade RD, Carson WH, Eudicone JM, Carlson BX, Marcus RN, Sanchez R. Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. J Clin Psychiatry 2007;68:1480-91.

Keck PE Jr, Calabrese JR, McQuade RD, Carson WH, Carlson BX, Rollin LM, Marcus RN, Sanchez R;Aripiprazole Study Group. A Randomized double-blind, placebo-controlled 26 week trial of aripiprazole in recently manic patients with bipolar I disorder. J Clin Psych 2006; 67(4):626-37.

Keck PE Jr, Marcus R, Tourkodimitris S, Ali M, Liebeskind A, Saha A, Ingenito G. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. Am J Psychiatry 2003;160(9):1651-8.

Keck PE Jr, Versiani M, Potkin S, West SA, Giller E, Ice K. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. Am J Psychiatry 2003 Apr1;60(4):741-8.

Keck PE, Orsulak PJ, Cutler AJ, Sanchez R, Torbeyns A, Marcus RN, McQuade RD, Carson WH. Aripiprazole monotherapy in the treatment of acute bipolar I mania: A randomized, double-blind, placebo- and lithium-controlled study. J Affect Disord 2009 Jan;112(1-3):36-49.

Kellner MB, Neher F. A first episode of mania after age 80. Can J Psychiatry Oct;36(8):607-8.

Ketter TA, Jones M, Paulsson B. Rates of remission/euthymia with quetiapine monotherapy compared with placebo in patients with acute mania. J Affect Disord 2007;100 Suppl 1:S45-53.

Ketter TA. Monotherapy versus combined treatment with second-generation antipsychotics in bipolar disorder. J Clin Psychiatry 2008;69 Suppl 5:9-15.

Khanna S, Vieta E, Lyons B, Grossman F, Eerdekens M, Kramer M. Risperidone in the treatment of acute mania: double-blind, placebo-controlled study. Br J Psychiatry 2005 Sep;187:229-34.

Kilbourne AM, Post EP, Nossek A, Drill L, Cooley S. Bauer M. Improving general medical care for patients with bipolar disorder: a randomized, controlled pilot study. Psychiatric Services 2008; 59:760-68

Kilbourne AM, Biswas K, Pirraglia PA, Sajatovic M, Williford WO, Bauer MS. Is the collaborative chronic care model effective for patients with bipolar disorder and co-occurring conditions? J Affect Disord. 2009:112:256-61.

Kissling W, Glue P, Medori R, Simpson S. Long-term safety and efficacy of long-acting risperidone in elderly psychotic patients. Hum Psychopharmacol 2007 Dec;22(8):505-13.

Kruger SR, Sarkar R, Pietsch R, Hasenclever D, Braunig Pl. Levetiracetam as monotherapy or add-on to valproate in the treatment of acute mania-a randomized open-label study. Psychopharmacology (Berl) 2008 Jun;198(2):297-9.

Kushner SF, Khan A, Lane R, Olson WH. Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials. Bipolar Disord 2006 8(1):15-27.

Lam DH, Hayward P, Watkins ER, Wright K, Sham P. Relapse prevention in patients with bipolar disorder: cognitive therapy outcome after 2 years. Am J Psychiatry 2005 Feb;162:324-9.

Lam DH, Watkins ER, Hayward P, Bright J, Wright K, Kerr N, Parr-Davis G, Sham P. A randomized controlled study of cognitive therapy of relapse prevention for bipolar affective disorder: outcome of the first year. Arch Gen Psychiatry 2003 Feb;60:145-52.

Lanctot K L, Best TS, Mittmann N, Liu BA, Oh PI, Einarson TR, Naranjo CA. Efficacy and safety of neuroleptics in behavioral disorders associated with dementia. J Clin Psychiatry 1998 Oct;59(10); 550-61.

Lasser RA, Bossie CA, Zhu Y, Gharabawi G, Eerdekens M, Davidson M. Efficacy and safety of long-acting risperidone in elderly patients with schizophrenia and schizoaffective disorder. Int J Geriatr Psychiatry 2004;19: 898-905.

Lepkifker E, Iancu I, Horesh N, Strous RD, Kotler M. Lithium therapy for unipolar and bipolar depression among the middle-aged and older adult patient subpopulation. Depress Anxiety 2007;24(8):571-6.

Licht RW, Vestergaard P, Brodersen A. Long –term outcome of patients with bipolar disorder commenced on lithium prphylaxsis during hospitalization: a complete 15-year register-based follow-up. Bipolar Disord 2008;10:79-86.

Licht RW. Lithium in the treatment of acute mania. In Bauer M; Grof P; Muller-Oerlinghausen B, editors. Lithium in Neuropsychiatry--the Comprehensive Guide. London: Informa Healthcare; p. 59-72.

Macritchie K, Geddes JR, Scott J, Haslam D, de Lima M, Goodwin G. Valproate for acute mood episodes in bipolar disorder. Cochrane Database Syst Rev 2003;(1):CD004052.

Madhusoodanan S, Brenner R, Alcantra A. Clinical experience with quetiapine in elderly patients with psychotic disorders. J Geriatr Psychiatry Neurol 2000;13:28-32.

Madhusoodanan S, Brenner R, Araujo L, Abaza A. Efficacy of risperidone treatment for psychoses associated with schizophrenia, schizoaffective disorder, bipolar disorder, or senile dementia in 11 geriatric patients: a case series. J Clin Psychiatry 1995; 56:514-8.

Maj M, Pirozzi R, Magliano L. Nonresponse to reinstituted lithium prophylaxis in previously responsive bipolar patients: prevalence and predictors. Am J Psychiatry 1995 Dec;152(12):1810-1.

Malkoff-Schwartz S, Frank E, Anderson B, Sherrill JT, Siegel L, Patterson D, Kupfer DJ. Stressful life events and social rhythm disruption in the onset of manic and depressive bipolar episodes: a preliminary investigation. Arch Gen Psychiatry 1998;55:702-7.

Malkoff-Schwartz S, Frank E, Anderson BP, Hlastala SA, Luther JF, Sherrill JT, Houck PR, Kupfer DJ. Social rhythm disruption and stressful life events in the onset of bipolar and unipolar episodes. Psychol Med 2000 Sep;30:1005-16.

Management of Major Depressive Disorder. Washington, DC: VA/DoD Evidence-Based Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs, and Health Affairs, Department of Defense, 2008. Office of Quality and Performance publication 10Q-CPG/MDD-08 Available from:
http://www.healthquality.va.gov/Major_Depressive_Disorder_MDD_Clinical_Practice_Guideline.asp

Management of Substance Use Disorder in the Primary Care Setting. Washington, DC: VA/DoD Evidence-Based Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs, and Health Affairs, Department of Defense, 2009. Office of Quality and Performance publication 10Q-CPG/SUD-09
http://www.healthquality.va.gov/Substance_Use_Disorder_SUD.asp

Marder SR, Essock SM, Miller AL, Buchanan RW, Casey DE, Davis JM, Kane JM, Lieberman JA, Schooler NR, Covell N, Stroup S, Weissman EM, Wirshing DA, Hall CS, Pogach L, Pi-Sunyer X, Bigger JT Jr, Friedman A, Kleinberg D, Yevich SJ, Davis B, Shon S. Physical health monitoring of patients with schizophrenia. Am J Psychiatry 2004 Aug;161(8):1334-49.

Martínez-Arán A, Vieta E, Reinares M, Colom F, Torrent C, Sánchez-Moreno J, Benabarre A, Goikolea JM, Comes M, Salamero M. Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. Am J Psychiatry 2004 Feb;161(2):262-70.

McDonald WM, Wermager J. Pharmacologic treatment of geriatric mania. Curr Psychiatry Rep 2002 Feb 4(1): 43-50.

McElroy SL, Bowden CL, Collins MA, Wozniak PJ, Keck PE Jr, Calabrese JR. Relationship of open acute mania treatment to blinded maintenance outcome in bipolar I disorder. J Affect Disord 2008 Apr;107:127–33.

McElroy SL, Young AH, Carlsson A. A double-blind, placebo-controlled study with acute and continutation phase of quetiapine and paroxetine in adults with bipolar depression (EMBOLDEN II). Bipolar Disord 2008 10;(Suppl):1-59.

McFarland BH, Miller MR, Straumfjord A. Valproate use in the older manic patient. J Clin Psychiatry 1990;51:479-81.

McIntyre RS, Brecher M, Paulsson B, Huizar K, Mullen J. Quetiapine vs haloperidol as monotherapy for bipolar mania – a 12 week, double-blind, randomized, parallel-group, placebo-controlled trial. Eur Neropsychopharmacol 2005;15(5):573-85.

McIntyre RS, Soczynska JK. Beyer JL, Woldeyohannes HO, Law CW, Miranda A. Medical comorbidity in bipolar disorder: re-prioritizing unmet needs. Curr Opin 2007; 20, 29 406-416.

McIntyre RS, Konarski JZ, Soczynska JK et al. Medical comorbidity in bipolar disorder: implications for functional outcomes and health service utilization. Psychiatr Serv 2006; 57: 1140–1144.

Meehan K, Zhang F, David S, Tohen M, Janicak P, Small J, Koch M, Rizk R, Walker D, Tran P, Breier A. A double-blind, randomized comparison of the efficacy and safety of intramuscular injects of olanzapine, lorazepam, or placebo in treating acutely agitated patients diagnosed with bipolar mania. J Clin Pscyhopharm 2001 Aug;2(194):389-97.

Miklowitz DJ, George EL, Richards JA, Simoneau TL, Suddath RL. A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. Arch Gen Psychiatry 2003 Sep;60(9):904-12.

Miklowitz DJ, Goldstein MJ. Behavioral family treatment for patients with bipolar affective disorder. Behav Modif 1990 Oct;14(4):457-89.

Miklowitz DJ, Otto MW, Frank E, Reilly-Harrington NA, Kogan J N, Sachs GS, Thase ME, Calabrese JR, Marangell LB, Ostacher MJ, Patel J, Thomas MR, Araga M, Gonzalez JM, Wisniewski SR. Intensive psychosocial intervention enhances functioning in patients with bipolar depression: results from a 9-month randomized controlled trial. Am J Psychiatry 2007 Sep;164(9):1340-7.

Miklowitz DJ, Otto MW. New psychosocial interventions for bipolar disorder: a review of literature and introduction of the Systematic Treatment Enhancement Program. J Cogn Psychother 2006;20(2):215-30.

Miklowitz DJ, Richards JA, George EL, Suddath RL, Frank E, Powell K, Sacher JS. Integrated family and individual therapy for bipolar disorder: results of a treatment development study. J Clin Psychiatry 2003;64:182-91.

Miklowitz DJ. Adjunctive psychotherapy for bipolar disorder: state of the evidence. Am J Psychiatry 2008 Nov165(11):1408-19.

Miller IW, Keitner GI, Ryan CE, Uebelacker LA, Johnson SL, Solomon DA. Family treatment for bipolar disorder: family impairment by treatment interactions. J Clin Psychiatry 2008 May;69(5):732-40.

Miller IW, Solomon DA, Ryan CE, Keitner GI. Does adjunctive family therapy enhance recovery from bipolar I mood episodes? J Affect Disord 2004;82(3):431-6.

Mitchell PB, Ball JR, Best JA, Gould BM, Malhi GS, Riley GJ, Wilson IG. The management of bipolar disorder in general practice. Med J Aust 2006;184(11):566-70.

Monk TH, Flaherty JF, Frank E, Hoskinson K, Kupfer DJ. The social rhythm metric: an instrument to quantify daily rhythms of life. J Nerv Ment Dis 1990;178:120-6.

Mordecai DJ, Sheikh JI, Glick ID. Divalproex for the treatment of geriatric bipolar disorder. Int J Geriatr Psychiatry 1999;14:494-6.

Muller-Oerlinghausen B, Muser-Causemann B, Volk J. Suicides and parasuicides in a high-risk patient group on and off lithium long-term medication. J Affect Disord 1992 Aug 25(4):261-9.

Murray N, Hopwood S, Balfour DJ, Ogston S, Hewick DS. The influence of age on lithium efficacy and side-effects in out-patients. Psychol Med 1983;13(1):53-60.

Namjoshi MA, Risser R, Shi L, Tohen M, Breier A. Quality of life assessment in patients with bipolar disorder treated with olanzapine added to lithium or valproic acid. J Affect Disord 2004 Sep;81(3):223-9.

Nasrallah HA, White T, Nasrallah AT. Lower mortality in geriatric patients receiving risperidone and olanzapine versus haloperidol: preliminary analysis of retrospective data. Am J Geriatr Psychiatry 2004;12:437-9.

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]

Nemeroff CB, Evans DL, Gyulai L, Sachs GS, Bowden CL, Gergel IP, Oakes R, Pitts CD. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. Am J Psychiatry 2001 Jun;158(6):906-12.

Nicolato R, Romano-Silva MA, Correa H, dos Santos RR, Teixeira AL. Stuporous catatonia in an elderly bipolar patient: response to olanzapine. Aust N Z J Psychiatry 2006 May 40(5):498.

Niedermier JA, Nasrallah HA. Clinical correlates of response to valproate in geriatric inpatients. Ann Clin Psychiatry 1998;10:165-8.

Nilsson A. Mortality in recurrent mood disorders during periods on and off lithium. A complete population study in 362 patients. Pharmacopsychiatry 1995 Jan;28(1):8-13.

Niufan G, Tohen M, Qiuqing A, Fude Y, Pope E, McElroy H, Ming L, Gaohua W, Xinbao Z, Huichun L, Liang S. Olanzapine versus lithium in the acute treatment of bipolar mania: a double-blind, randomized, controlled trial. J Affect Disord 2008;105(1-3):101–8.

Noaghiul S, Narayan M, Nelson JC. Divalproex treatment of mania in elderly patients. Am J Geriatr Psychiatry 1998; 6:257-62.

Norton JW, Quarles E. Intravenous valproate in neuropsychiatry. Pharmacotherapy. 2000 Jan;20(1):88-92.

Ogilvie AD, Morant N, Goodwin GM. The burden on informal caregivers of people with bipolar disorder. Bipolar Disord 2005;7 Suppl 1:25-32.

Oshima A, Higuchi T. Treatment guidelines for geriatric mood disorders. Psychiatry Clin Neurosci 1999;53 Suppl:S55-9.

Pande AC, Crockatt JG, bJanney CA, Werth JL, Tsaroucha G. Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. Gabapentin Bipolar Disorder Study Group. BipolarDisord 2000 Sep;2(3 Pt 2):249- 55.

Peet M. Peters S. Drug-induced mania. *Drug Saf 1995; 12,* 146-153

Perlis RH, Baker RW, Zarate CA Jr, Brown EB, Schuh LM, Jamal HH, Tohen M. Olanzapine versus risperidone in the treatment of manic or mixed States in bipolar I disorder: a randomized, double-blind trial. J Clin Psychiatry 2006; 67:1747-53.

Poolsup N, Li Wan Po A, de Oliveira IR. Systematic overview of lithium treatment in acute mania. J Clin Pharm Ther 2000;25(2):139-56.

Post RM, Altshuler LL, Leverich GS, Frye MA, Nolen WA, Kupka RW, Suppes T, McElroy S, Keck PE, Denicoff KD, Grunze H, Walden J, Kitchen CM, Mintz J. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. Br J Psychiatry 2006;189:124-31.

Post RM, Baldassano CF, Perlis RH, Ginsberg DL. Treatment of bipolar depression. CNS Spectr 2003 Dec;8(12):1-10.

Post RM, Calabrese JR, Bipolar depression: the role of atypical antipsychotics. Expert Rev Neurother 2004 Nov;4(6 Suppl 2):S27-33.

Potkin SG, Keck PE Jr, Segal S, Ice K, English P. Ziprasidone in acute bipolar mania: a 21-day randomized, double-blind, placebo-controlled replication trial. J Clin Psychopharmacol 2005 Aug;25(4):301-10.

Puryear LJ, Kunik ME, Workman R Jr. Tolerability of divalproex sodium in elderly psychiatric patients with mixed diagnoses. J Geriatr Psychiatry Neurol 1995;8:234-7.

Rea MM, Tompson M, Miklowitz DJ, Goldstein MJ, Hwang S, Mintz, J. Family focused treatment vs. individual treatment for bipolar disorder: results of a randomized clinical trial. J Cons Clin Psychol 2003 Jun;71(3):482-92.

Revicki DA, Paramore LC, Sommerville KW, Swann AC, Zajecka JM. Divalproex sodium versus olanzapine in the treatment of acute mania in bipolar disorder: health-related quality of life and medical cost outcomes. J Clin Psychiatry 2003 Mar;64(3):288-94.

Rhodes LJ. Maintenance ECT replaced with lamotrigine. Am J Psychiatry 2000 Dec;157(12):2058.

Risinger RC, Risby ED, Risch, SC. Safety and efficacy of divalproex sodium in elderly bipolar patients. J Clin Psychiatry 1994;55(5):215.

Robillard M, Conn DK. Lamotrigine use in geriatric patients with bipolar depression. Can J Psychiatry 2002; 47:767-70.

Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. Biol Psychiatry 1998 Jul 15;44(2):77-87.

Rosenbaum, Arana, Hyman, Labbate, Fava; Handbook of Psychiatric Drug Therapy, 5th Edition. Philadelphia: Lippincott, Williams &Wilkins; 2005.

Sachs G, Chengappa KN, Suppes T, Mullen JA, Brecher M, Devine NA, Sweitzer DE. Quetiapine with lithium or divalproex for the treatment of bipolar mania: a randomized, double-blind, placebo-controlled study. Bipolar Disord 2004;6(3):213-23.

Sachs G, Sanchez R, Marcus R, Stock E, McQuade R, Carson W, Abou-Gharbia N, Impellizzeri C, Kaplita S, Rollin L, Iwamoto T. Aripiprazole Study Group. Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. J Psychopharmacol 2006;20:536-46.

Sachs GS, Grossman F, Ghaemi S N, Okamoto A, Bowden CL. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebocontrolled comparison of efficacy and safety. Am J Psychiatry 2002 Jul;159:1146-54.

Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, Friedman ES, Bowden CL, Fossey MD, Ostacher MJ, Ketter TA, Patel J, Hauser P, Rapport D, Martinez JM, Allen MH, Miklowitz DJ, Otto MW, Dennehy EB, Thase ME. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med 2007;356:1711-22.

Sachs GS, Thase ME. Bipolar disorder therapeutics: maintenance treatment. Biol Psychiatry 2000;48:573-81.

Sackeim HA, Prudic J, Fuller R, Keilp J, Lavori PW, Olfson M. The cognitive effects of electroconvulsive therapy in community settings. Neuropsychopharmacology 2007 Jan;32(1):244- 54.

Sajatovic M, Blow FC, Ignacio RV, Kales, HC. Age-related modifiers of clinical presentation and health service use among veterans with bipolar disorder. Psychiatr Serv 2004;55:1014-21.

Sajatovic M, Blow FC, Ignacio RV. Psychiatric comorbidity in older adults with bipolar disorder. Int J Geriatr Psychiatry 2006;21;582-7.

Sajatovic M, Calabrese JR, Mullen J. Quetiapine for the treatment of bipolar mania in older adults. Bipolar Disord 2008;10:662-71.

Sajatovic M, Coconcea N, Ignacio RV, Blow FC, Hays RW, Cassidy KA Meyer WJ. Aripiprazole therapy in 20 older adults with bipolar disorder: a 12-week, open-label trial. J Clin Psychiatry 2008;69;41-6.

Sajatovic M, Davies MA, Ganocy SJ, Bauer MS, Cassidy KA, Hays RW, Safavi R, Blow FC, Calabrese JR. A comparison of the life goals program and treatment as usual for individuals with bipolar disorder. Psychiatr Serv. 2009;60:1182-9.

Sajatovic M, Davies M, Hrouda DR. Enhancement of treatment adherence among patients with bipolar disorder. Psychiatr Serv 2004;55(3):264-9.

Sajatovic M, Gyulai L, Calabrese JR, Thompson TR, Wilson BG, White R, Evoniuk G. Maintenance treatment outcomes in older patients with bipolar I disorder. Am J Geriatr Psychiatry 2005 Apr;13(4):305-11.

Sajatovic M, Ignacio RV, West JA, Cassidy KA, Safavi R, Kilbourne AM, Blow FC. Predictors of nonadherence among individuals with bipolar disorder receiving treatment in a community mental health clinic. Compr Psychiatry 2009 Mar-Apr;50(2):100-7.

Sajatovic M. Treatment of bipolar disorder in older adults. Int J Geriatr Psychiatry 2002 Sep;17(9):865-73.

Samuels S, Fang, M. Olanzapine may cause delirium in geriatric patients. J Clin Psychiatry 2004;65:582-3.

Sanderson DR. Use of mood stabilizers by hospitalized geriatric patients with bipolar disorder. Psychiatr Serv 1998;49:1145-7.

Schneider A, Wilcox CS. Divalproate augmentation in lithium-resistant rapid cycling mania in four geriatric patients. J Affect Disord 1998;47:201-5.

Schneier HA, Kahn D. Selective response to carbamazepine in a case of organic mood disorder. J Clin Psychiatry 1990;51:485.

Schou M, Amdisen A. Lithium and pregnancy. 3. Lithium ingestion by children breast-fed by women on lithium treatment. Br Med J 1973 Apr 21;2(5859):137-8.

Scott J, Gutierrez MJ. The current status of psychological treatments in bipolar disorders: a systematic review of relapse prevention. Bipolar Disord 2004 Dec;6(6):498-503.

Scott J, Paykel E, Morriss R, Bentall R, Kinderman P, Johnson T, Abbott R, Hayhurst H. Cognitive behaviour therapy for severe and recurrent bipolar disorders: a randomised controlled trial. Br J Psychiatry 2006 Apr;188:313-20.

Seemuller F, Forsthoff A, Dittmann S, Born C, Bernhard B, Severus WE, Grunze H. The safety and tolerability of atypical antipsychotics in bipolar disorder. Expert Opin Drug Saf 2005 Sep;4(5):849-68.

Sharma V, Persad E, Mazmanian D, Karunaratne, K. Treatment of rapid cycling bipolar disorder with combination therapy of valproate and lithium. Can J Psychiatry 1993;38:137-9.

Shi L, Schuh LM, Trzepacz PT, Huang LX, Namjoshi MA, Tohen M. Improvement of Positive and Negative Syndrome Scale cognitive score associated with olanzapine treatment of acute mania. Curr Med Res Opin 2004 Sep;20(9):1371-6.

Shulman KI, Rochon P, Sykora K, Anderson G, Mamdani M, Bronskill S, Tran CT. Changing prescription patterns for lithium and valproic acid in old age: shifting practice without evidence. BMJ 2003;326: 960-1.

Shulman R W, Singh A, Shulman KI. Treatment of elderly institutionalized bipolar patients with clozapine. Psychopharmacol Bull 1997;33:113-8.

Sikdar S, Kulhara P, Avasthi A, Singh, H. Combined chlorpromazine and electroconvulsive therapy in mania. Br J Psychiatry1994 Jun;164(6): 806-10.

Simon GE, Ludman EJ, Bauer MS, Unutzer J, Operskalski B. Long-term effectiveness and cost of a systematic care program for bipolar disorder. Arch Gen Psychiatry 2006;63(5):500-8.

Simon GE, Ludman EJ, Unutzer J, Bauer MS, Operskalski B, Rutter C. Randomized trial of a population-based care program for people with bipolar disorder. Psychol Med 2005 Jan;35(1):13-24.

Simoneau TL, Miklowitz DJ, Richards JA, Saleem R, George EL. Bipolar disorder and family communication: Effects of a psychoeducational treatment program. J Abnorm Psychol 1999 Nov;108(4):588-97.

Small JG, Klapper MH, Kellams JJ, Miller MJ, Milstein V, Sharpley PH, Small IF. Electroconvulsive treatment compared with lithium in the management of manic states. Arch Gen Psychiatry1988 Aug 45;(8):727-32.

Smulevich AB, Khanna S, Eerdekens M, Karcher K, Kramer M, Grossman F. Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol. Eur Neuropsychopharmacol 2005 Jan;15(1):75-84.

Steele A, Maruyama N, Galynker I. Psychiatric symptoms in caregivers of patients with bipolar disorder: a review. J Affect Disord 2010 Feb;121(1-2):10-21.

Stone K. Mania in the elderly. Br J Psychiatry 1989 Aug;155:220-4.

Suppes T, Baldessarini RJ, Faedda GL, Tohen M. Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. Arch Gen Psychiatry 1991;48(12):1082-8.

Suppes T, Baldessarini RJ, Faedda GL, Tondo GL, Tohen M. Discontinuation of maintenance treatment in bipolar disorder: risks and implications. Harv Rev Psychiatry 1993 Sep-Oct;1(3):131-44.

Suppes T, Brown E, Schuh LM, Baker RW, Tohen M. Rapid versus non-rapid cycling as a predictor of response to olanzapine and divalproex sodium for bipolar mania and maintenance of remission: post hoc analyses of 47-week data. J Affect Disord 2005 Dec;89(1-3):69-77.

Suppes T, Dennehy EB, Hirschfeld RM, Altshuler LL, Bowden C, Calabrese J, Crismon ML, Ketter TA, Sachs G, Swann AC. The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar disorder. J Clin Psychiatry 2005 Jul;66(7):870-86

Suppes T, Hirschfeld RM, Vieta E, Raines S, Paulsson B. Quetiapine for the treatment of bipolar II depression: analysis of data from two randomized, double-blind, placebo-controlled studies. World J Biol Psychiatry 2008;9(3):198-211.

Suppes T, Kelly DI, Hynan LS, Snow DE, Sureddi S, Foster B, Curley E. Comparison of two anticonvulsants in a randomized, single-blind treatment of hypomanic symptoms in patients with bipolar disorder. Aust N Z J Psychiatry 2007 May 41(5):397-402.

Suppes T, Marangell LB, Bernstein I, Kelly D, Fischer EG, Zboyan HA, Snow DE, Martinez M, Al Jurdi R, Shivakumar G, Sureddi S, Gonzalez R. A single blind comparison of lithium and lamotrigine for the treatment of bipolar II depression. J Affect Disord 2008 Dec;111(2-3):334–43.

Suppes T, Vieta E, Liu S, Brecher M, Paulsson B; Trial 127 Investigators. Maintenance treatment for patients with bipolar I disorder: results from a North American study of quetiapine in combination with lithium or divalproex (trial 127). Am J Psychiatry 2009 Apr;166(4):476-88.

Suppes T, Webb A, Paul B, Carmody T, Kraemer H, Rush A. Clinical outcome in a randomized 1-year trial of clozapine versus treatment as usual for patients with treatment-resistant illness and a history of mani. Am J Psychiatry 1999;156(8):1164-9.

Swann AC, Bowden CL, Morris D, Calabrese JR, Petty F, Small J, Dilsaver SC, Davis JM. Depression during mania: treatment response to lithium or divalproex. Arch Gen Psychiatry 199; Jan;54(1):37-42

Tariot PN, Salzman C, Yeung PP, Pultz J, Rak IW. Long-Term use of quetiapine in elderly patients with psychotic disorders. Clin Ther 2000; 22:1068-84.

Thase M. Maintenance therapy for bipolar disorder. J Clin Psychiatry 2008 Nov6;69(11):e32

Thase ME, Jonas A, Khan A, Bowden CL, Wu X, McQuade RD, Carson WH, Marcus RN, Owen R. Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. J Clin Psychopharmacol 2008;28:13-20.

Thase ME, Macfadden W, Weisler RH, Chang W, Paulsson B, Khan A, Calabrese JR; BOLDER II Study Group. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo- controlled study (the BOLDER II study). J Clin Psychopharmacol 2006;26(6):600-9.

Timell AM. Thioridazine: re-evaluating the risk/benefit equation. Ann Clin Psychiatry 2000;12:147-51.

Tohen M, Ketter, TA, Zarate CA, Suppes T, Frye M, Altshuler L, Zajecka J, Schuh LM, Risser RC, Brown E, Baker RW. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. Am J Psychiatry 2003b Jul;160(7):1263-71.

Tohen M, Baker RW, Altshuler LL, Zarate CA, Suppes T, Ketter TA, Milton DR, Risser R, Gilmore JA, Breier A, Tollefson GA. Olanzapine versus divalproex in the treatment of acute mania. Am J Psychiatry 2002;159:1011-7.

Tohen M, Bowden CL, Smulevich AB, Bergstrom R, Quinlan T, Osuntokun O, Wang WV, Oliff HS, Martenyi F, Kryzhanovskaya LA, Greil W. Olanzapine plus carbamazepine v. carbamazepine alone in treating manic episodes. Br J Psychiatry 2008;192:135-43.

Tohen M, Calabrese JR, Sachs GS, Banov MD, Detke HC, Risser R, Baker RW, Chou JC, Bowden CL. Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. Am J Psychiatry 2006;163:247-56.

Tohen M, Chengappa KN, Suppes T, Baker RW, Zarate CA, Bowden CL, Sachs GS, Kupfer DJ, Ghaemi SN, Feldman PD, Risser RC, Evans AR, Calabrese JR. Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v mood stabiliser alone. Br J Psychiatry 2004 Apr;184:337-45.

Tohen M, Chengappa KN, Suppes T, Zarate CA Jr, Calabrese JR, Bowden CL, Sachs GS, Kupfer DJ, Baker RW, Risser RC, Keeter EL, Feldman PD, Tollefson GD, Breier A. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. Arch Gen Psychiatry 2002;59:62-9.

Tohen M, Goldberg JF, Gonzalez-Pinto Arrillaga AM, Azorin JM, Vieta E, Hardy-Bayle MC, Lawson WB, Emsley RA, Zhang F, Baker RW, Risser RC, Namjoshi MA, Evans AR, Breier A. A 12-week, double-blind comparison of olanzapine vs haloperidol in the treatment of acute mania. Arch Gen Psychiatry 2003a Dec;60(12):1218-26.

Tohen M, Greil W, Calabrese JR, Sachs GS, Yatham LN, Oerlinghausen BM, Koukopoulos A, Cassano GB, Grunze H, Licht RW, Dell'Osso L, Evans AR, Risser R, Baker RW, Crane H, Dossenbach MR, Bowden CL. Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. Am J Psychiatry 2005 Jul;162(7):1281-90.

Tohen M, Jacobs TG, Grundy SL McElroy SL, Banov MC, Janicak PG, Sanger T, Risser R, Zhang F, Toma V, Francis J, Tollefson GD, Breier A. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzipine HGGW Study Group. Arch Gen Psychiatry 2000;57(9):841-9.

Tohen M, Sanger TM, McElroy SL, Tollefson GD, Chengappa KN, Daniel DG, Petty F, Centorrino F, Wang R, Grundy SL, Greaney MG, Jacobs TG, David SR, Toma V. Olanzapine versus

placebo in the treatment of acute mania. Olanzapine HGEH Study Group. Am J Psychiatry 1999;156(5):702-9.

Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden,C, Mitchell PB, Centorrino F, Risser R, Baker RW, Evans AR, Beymer K, Dube S, Tollefson GD, Breier A. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry 2003c Nov 60;1079-88.

Tohen M, Vieta E, Goodwin GM, Sun B, Amsterdam JD, Banov M, Shekhar A, Aaronson ST, Bardenstein L, Grecu-Gabos I, Tochilov V, Prelipceanu D, Oliff HS, Kryzhanovskaya L, Bowden C. Olanzapine versus divalproex versus placebo in the treatment of mild to moderate mania: a randomized, 12-week, double-blind study. J Clin Psychiatry 2008;69(11):1776-89.

Tohen M, Zhang F, Taylor CC, Burns P, Zarate C, Sanger T, Tollefson G. A meta-analysis of the use of typical antipsychotic agents in bipolar disorder. J Affect Disord 2001 Jun;65(1):85-93.

Tohen M. Olanzapine versus placebo in acute mania: treatment responses in subgroups. J Clin Psychopharmacol 2003 Aug;23(4):370-6.

Tunnessen WW Jr, Hertz CG. Toxic effects of lithium in newborn infants: a commentary. J Pediatr 1972 Oct;81(4):804-7.

van der Loos ML, Mulder PG, Hartong EG, Blom MB, Vergouwen AC, de Keyzer HJ, Notten PJ, Luteijn ML, Timmermans MA, Vieta E, Nolen WA; LamLit Study Group. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. J Clin Psychiatry 2009 Feb;70(2):223-31.

van der Velde CD. Effectiveness of lithium carbonate in the treatment of manic-depressive illness. Am J Psychiatry 1970; 127: 345-51.

van Gent EM, Zwart FM. Psychoeducation of partners of bipolar-manic patients. J Affect Disord 1991 Jan; 21(1):15-8.

Van Gerpen MW, Johnson JE, Winstead DK. Mania in the geriatric patient population: a review of the literature. Am J Geriatr Psychiatry 1999;7:188-202.

Vasudev K K, Macritchie, Geddes J, Watson S, Young A. Topiramate for acute affective episodes in bipolar disorder. Cochrane Database Syst rev 2006 Jan 25;(1):CD003384.

Vieta E, Bourin M, Sanchez R, Marcus R, Stock E, McQuade R, Carson W, Abou-Gharbia N, Swanink R, Iwamoto T. Effectiveness of aripiprazole v. haloperidol in acute bipolar mania: double-blind, randomised, comparative 12-week trial. Br J Psychiatry 2005 Sep;187:235-42.

Vieta E, Calabrese JR, Goikolea JM, Raines S, Macfadden W. Quetiapine monotherapy in the treatment of patients with bipolar I or II depression and a rapid-cycling disease course: a randomized, double-blind, placebo-controlled study. Bipolar Disord 2007;9:413-25.

Vieta E, Calabrese JR, Hennen J, Colom F, Martinez-Aran A, Sanchez-Moreno J, Yatham LN, Tohen M, Baldessarini RJ. Comparison of rapid-cycling and non-rapid-cycling bipolar I manic patients during treatment with olanzapine: analysis of pooled data. J Clin Psychiatry 2004 Oct;65(10):1420-8.

Vieta E, Martinez-Aran A, Goikolea JM, Torrent C, Colom F, Benabarre A, Reinares M. A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers. J Clin Psychiatry2002 Jun;63:508-12.

Vieta E, Mullen J, Brecher M, Paulsson B, Jones M. Quetiapine monotherapy for mania associated with bipolar disorder: combined analysis of two international, double-blind, randomised, placebo-controlled studies. Curr Med Res Opin 2005 Jun;21(6):923-34.

Vieta E, Ramey T, Keller D, English P, Loebel A, Miceli J. Ziprasidone in the treatment of acute mania: a 12-week, placebo-controlled, haloperidol-referenced study. J Psychopharmacol 2008 Dec 12.

Vieta E, Rosa A. Evolving trends in the long-term treatment of bipolar disorder. World J Biol Psychiatry 2007;8(1): 4-11.

Vieta E, Suppes T, Eggens I, Persson I, Paulsson B, Brecher M. Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). J Affect Disord 2008;109:251-63.

Vieta E, T'joen C, McQuade RD, Carson WH Jr, Marcus RN, Sanchez R, Owen R, Nameche L. Efficacy of adjunctive aripiprazole to either valproate or lithium in bipolar mania patients partially nonresponsive to valproate/lithium monotherapy: A placebo-controlled study. Am J Psychiatry 2008 Oct;165(10):1316-25.

Vornik LA, Brown ES. Management of comorbid bipolar disorder and substance abuse. J Clin Psychiatry. 2006;67 Suppl 7:24-30.

Wagner EH, Austin BT, Von korff M. Organizing care for patients with chronic illness. Milbank Q. 1996;74:511-544.

Wagner KD, Kowatch RA, Emslie GJ, Findling RL, WilensTE, McCague K, D'Souza J, Wamil A, Lehman RB, Berv D, Linden D. A double-blind, randomized, placebo-controlled trial of oxcarbazepine in the treatment of bipolar disorder in children and adolescents. Am J Psychiatry 2006 Jul 16;(7):1179-86.

Wehr TA, Goodwin FK. Can antidepressants cause mania and worsen the course of affective illness? Am J Psychiatry 1987;144(11):1403-11.

Weisler RH, Calabrese JR, Thase ME, Arvekvist R, Stening G, Paulsson B, Suppes T. Efficacy of quetiapine monotherapy for the treatment of depressive episodes in bipolar I disorder: a post hoc analysis of combined results from 2 double-blind, randomized, placebo-controlled studies. 2008 J Clin Psychiatry 69, 769-82.

Weisler RH, Kalali AH, Ketter TA; SPD417 Study Group. A multicenter, randomized, double-blind, placebo-controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes. J Clin Psychiatry 2004 Apr;65(4):478-84.

Weisler RH, Keck PE, Swann AC, Cutler AJ, Ketter TA, Kalali AH. Extended-release carbamazepine capsules as monotherapy for acute mania in bipolar disorder: a multicenter, randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2005 Mar;66(3):323-30.

Weisman MM, Markowitz J, Klerman GL. Comprehensive Guide to Interpersonal Psychotherapy. New York: Basic Books; 2000.

Wilson KC, Mottram PG, Vassilas CA. Psychotherapeutic treatments for older depressed people. Cochrane Database Syst Rev 2008 Jan 23;(1):CD004853.

Yatham LN, Grossman F, Augustyns I, Vieta E, Ravindran A. Mood stabilisers plus risperidone or placebo in the treatment of acute mania. International, double-blind, randomised controlled trial. Br J Psychiatry 2003 Feb;182:141-7

Yatham LN, Kennedy SH, O'Donovan C, MacQueen G, McIntyre RS, Sharma V, Ravindran A, Young LT, Young AH, Alda M, Milev R, Vieta E, Calabrese JR, Berk M, Ha K, Kapczinski F. 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 Disord 2009;11:225-55.

Yatham LN, Paulsson B, Mullen J, Vagero AM. Quetiapine versus placebo in combination with lithium or divalproex for the treatment of bipolar mania. Erratum in: J Clin Psychopharmacol 2005 Feb;25(1):103. J Clin Psychopharmacol. 2004 Apr;25(2):201.

Yatham LN, Paulsson B, Mullen J, Vagero AM. Quetiapine versus placebo in combination with lithium or divalproex for the treatment of bipolar mania. J Clin Psychopharmacol 2004 Dec;24(6):599-606.

Young AH, Oren DA, Lowry A, MsQuade RD, Marcus RN, carson WH, Spiller NH, Torbeyns AF, Sanchez R. Aripiprazole monotherapy in acute mania: 12-week ransomised placebo- and haloperidol-controlled study. Br J Psychaitry 2009;194:40-48.

Young RC, Klerman GL. Mania in late life: focus on age at onset. Am J Psychiatry 1992;149:867-76.

Young RC, Geriatric mania. Clin Geriatr Med. 1992 May;8(2):387-99.

Young RC, Bipolar disorder in older persons: perspectives and new findings. 2005 Am J Geriatr Psychiatry 2005;13:265-7.

Yumru M, Eren Ozen M, Savas HA, Selek S. Long-acting injectable risperidone for control of agitation in dementia. J Clin Psychiatry 2006; 67:1651-2.

Zajecka JM, Weisler R, Sachs G, Swann AC, Wozniak P, Sommerville KW. A comparison of the efficacy, safety, and tolerability of divalproex sodium and olanzapine in the treatment of bipolar disorder. J Clin Psychiatry 2002 Dec;63(12):1148-55

Zarate C, Tohen M, Baldessarini R J. Clozapine in severe mood disorders. J Clin Psychiatry 1995 Sep; 56 (9): 411-17.

Zaretsky A, Lancee W, Miller C, Harris A, Parikh SV. Is cognitive-behavioural therapy more effective than psychoeducation in bipolar disorder? Can J Psychiatry 2008 Jul;53(7):441-8.

Zaretsky AE, Rizvi S, Parikh SV. How well do psychosocial interventions work in bipolar disorder? Can J Psychiatry 2007 Jan 52(1);14-21.

Zornberg GL, Pope HG Jr. Treatment of depression in bipolar disorder: new directions for research. J Clin Psychopharmaco 1993 Dec13;(6):397-08.