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## CME PSYCHCAST™

### **PRACTICAL MANAGEMENT STRATEGIES FOR ACUTE MANIA AND MIXED EPISODES OF BIPOLAR DISORDER: *TREATMENT GUIDELINES FOR ACUTE MANIC AND MIXED EPISODES OF BIPOLAR DISORDER***

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*Primary Psychiatry* [*Primary Psychiatry* 16:12(12 Suppl 8):12-15].

CME .25

#### **ABSTRACT**

Bipolar disorder is a lifelong condition, which is diagnosed according to corroborative features such as family history, chronobiological sensitivities, treatment outcomes, longitudinal course, and patterns of recurrence. Each illness state is also classified as involving pure mania, hypomania, a mixed episode, a depressed phase, or euthymia. Mixed states are thought to comprise an important subgroup of syndromically ill individuals with bipolar disorder. Several dimensions of psychopathology, including thought-language problems, behavioral disturbances, mood symptoms, and chronobiological changes demand careful evaluation when considering the presentation of a patient with bipolar disorder. Once a comprehensive diagnostic assessment for acute or mixed mania has been completed, it is important to look at an evidence-based data set to guide treatment selection for mood stabilization. Pharmacotherapy is essential to its long-term management of bipolar disorder. Combination therapy, including at least one mood stabilizer, may be necessary to treat acute depression and mania and to further prevent both depressive and manic recurrences. The goal is to minimize frequency, duration, and severity of depressive and manic symptoms with a treatment regimen that is positioned to maximize treatment adherence and minimize side effects. Prevention of mania and maintenance treatment in bipolar disorder is largely routed in the decision to use monotherapy or combination therapy in the treatment regimen. Treatment must also include consideration of comorbidities such as anxiety, substance abuse, cardiovascular disease, and metabolic syndrome, which are pervasive in the bipolar disorder population.

In this Expert Review PsychCast™, Mark A. Frye, MD, reviews treatment guidelines for acute manic and mixed episodes associated with bipolar I disorder as well as the impact of alcohol as an example of drugs of abuse.



This activity is jointly sponsored by the Mount Sinai School of Medicine and MBL Communications, Inc.



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## Acknowledgment of Commercial Support

Funding for this activity has been provided by an educational grant from Bristol-Myers Squibb.

## Activity Review Information

The activity content has been peer-reviewed and approved by

**M. Mehmet Haznedar, MD.**

Review Date: November 30, 2009

## Faculty Affiliation

**Mark A. Frye, MD,** is professor of psychiatry and director of the Mayo Mood Clinic and Research Program in Rochester, Minnesota.

## Faculty Disclosure Policy Statement

It is the policy of the Mount Sinai School of Medicine to ensure objectivity, balance, independence, transparency, and scientific rigor in all CME-sponsored educational activities. All faculty participating in the planning or implementation of a sponsored activity are expected to disclose to the audience any relevant financial relationships and to assist in resolving any conflict of interest that may arise from the relationship. Presenters must also make a meaningful disclosure to the audience of their discussions of unlabeled or unapproved drugs or devices. This information will be available as part of the course material.

## Faculty Affiliations and Disclosures

Dr. Frye is a consultant to Bristol-Myers Squibb, Cephalon, Dainippon, Johnson & Johnson, Medtronic, Ortho McNeil/Janssen, Pfizer, Schering Plough, and Sumitomo; has participated in CME supported activities funded by AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Otsuka, Pfizer, and Schering-Plough; and has received grant support from Pfizer. Dr. Frye's article mentions off-label usages for carbamazepine, clonazepam, clozapine, divalproex, lorazepam, and quetiapine.

CME Course Director James C.-Y. Chou, MD, is associate professor of psychiatry at Mount Sinai School of Medicine in New York City. Dr. Chou has received honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, and Pfizer.

Dr. Haznedar is assistant professor of psychiatry, at Mount Sinai School of Medicine. Dr. Haznedar reports no financial, academic, or other interest in any organization that may pose a conflict of interest.

## Learning Objectives

At the completion of this activity, participants should be better able to:

- Evaluate individual patient factors along with evidence-based efficacy and safety information of pharmacotherapeutic agents in treatment decision-making.

## Statement of Need and Purpose

Bipolar disorder, a chronic episodic disease that is present in ~5.7 million Americans, is a complicated condition. No single medication or therapy is effective in treating bipolar disorder, and recent evidence suggests that subtypes of the disorder have been underrepresented due to the bipolar spectrum of expression. While the prototypic clinical picture concerns the "classic" bipolar disorder, mixed episodes with incomplete recovery and significant psychosocial impairment are more frequent and comprise up to 40% of acute bipolar hospital admissions. The clinical presentation of these mixed episodes is variable and eludes contemporary classification systems. Patients with mixed episodes tend to have a more severe course of illness compared to those with classic euphoric manias. They have less frequent remissions, higher rates of recurrence, more frequent substance abuse, poorer response to some medications, more extensive comorbidities, and increased potential for suicidality. Despite the available medications, treating mixed states remains a challenge and tends to require more complex treatment. Rational dosing is a problem as many trials do not address dosing questions. In addition, when and how to combine medications has not been studied nor is the issue of which medications should be discontinued during maintenance stages. Treatment ultimately depends on the patient's individual need and his or her psychiatric and medical comorbidities. The presence of a comorbid substance use disorder is associated with significantly lower rates of treatment adherence, higher anxiety disorder comorbidity, more suicide attempts, and poorer outcome, especially in terms of functioning and quality of life. Psychoeducation in combination with efficacious drug therapy may improve outcomes of patients with acute and mixed episodes of bipolar disorder.

## Target Audience

This activity is designed to meet the educational needs of primary care physicians and psychiatrists.

## Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Mount Sinai School of Medicine and MBL Communications, Inc. The Mount Sinai School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.



## Credit Designation

The Mount Sinai School of Medicine designates this educational activity for a maximum of .25 *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

## To Receive Credit for this Activity

Listen to this Expert Panel PsychCast™, reflect on the information presented, and complete the CME posttest and evaluation on pages 5 and 6. To obtain credit, you should score 70% or better. Early submission of this posttest is encouraged. Please submit this posttest by April 30, 2012 to be eligible for credit.

Selected content from this supplement will be available via ePocrates MobileCME in 2010.



# TREATMENT GUIDELINES FOR ACUTE MANIC AND MIXED EPISODES OF BIPOLAR DISORDER

By Mark A. Frye, MD

**SLIDE 1**

*Factors Influencing Choice of Treatment of Mania*

- Characteristics of manic episode
- Need for rapid resolution (promotion of sleep can help)
- Presence of mixed, rapid cycling, or psychotic symptoms
- Medication history
- Presence of comorbidities
- Patient preferences as it relates to current treatment

**SLIDE 2**

*Mood Stabilizers in Acute Mania*

**Advantages**

- Lithium, valproate, carbamazepine effective in acute mania
- Valproate/carbamazepine effective for mixed episodes
- May help with alcohol detoxification/relapse prevention

**Disadvantages**

- Lamotrigine ineffective in acute mania
  - No ability to rapidly load secondary to rash
- Lithium has narrow therapeutic index
- Weight gain and neuroendocrine disturbances

**SLIDE 3**

*Mood Stabilizer Safety and Tolerability<sup>2</sup>*

<i>Lithium</i>	<i>Valproate</i>	<i>Carbamazepine</i>	<i>Lamotrigine</i>
Gastrointestinal	Gastrointestinal	Gastrointestinal	Gastrointestinal
Weight gain	Weight gain	Rash	Rash
Neurotoxicity	Tremor	Neurotoxicity	Headache
Renal toxicity	Hepatotoxicity	Hepatotoxicity	Dizziness
Thyroid toxicity	Thrombocytopenia	Thyroid changes	Pruritis
Hair Loss	Hair Loss	Blood dyscrasias	Dream abnormality
Cardiac toxicity	Pancreatitis	Cardiac toxicity	
Acne, psoriasis	PCOS	Hyponatremia	
Teratogen	Teratogen	Teratogen	Teratogen
	Suicidality (?)	Suicidality (?)	Suicidality (?)

Red boxes indicate boxed warning in prescribing information.  
 (?)=recent alert. PCOS=polycystic ovary syndrome. All mood stabilizers have at least one boxed warning.

**SLIDE 4**

*Atypical Antipsychotics in Acute Mania*

**Advantages**

- As a class, effective in acute and mixed mania
  - Rapid control of acute mania
- In comparison to conventional antipsychotics
  - Less tardive dyskinesia, less acute extrapyramidal symptoms, do not induce depression

**Disadvantages**

- Weight gain, diabetes, activation

**SLIDE 5**

*Conventional Antipsychotics in Acute Mania*

**Advantages**

- Effective for acute mania

**Disadvantages**

- Acute extrapyramidal symptoms
- Tardive dyskinesia, akathisia
- Increased risk of neuroleptic malignant syndrome
- Negative impact on course of illness
  - Increased cycle frequency
  - Increased frequency of major depressive episodes

Dr. Frye is professor of psychiatry and director of the Mayo Mood Clinic and Research Program in Rochester, Minnesota.

Disclosures: Dr. Frye is a consultant to Bristol-Myers Squibb, Cephalon, Dainippon, Johnson & Johnson, Medtronic, Ortho-McNeil/Janssen, Schering Plough, Sumitomo, and Pfizer; has participated in CME supported activities funded by AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Otsuka, Pfizer, and Schering-Plough; and has received grant support from Pfizer. Dr. Frye mentions off-label usages for carbamazepine, clonazepam, clozapine, divalproex, lorazepam, and quetiapine.

**SLIDE 6**

*Antipsychotic Mood Stabilizer Safety and Tolerability<sup>2</sup>*

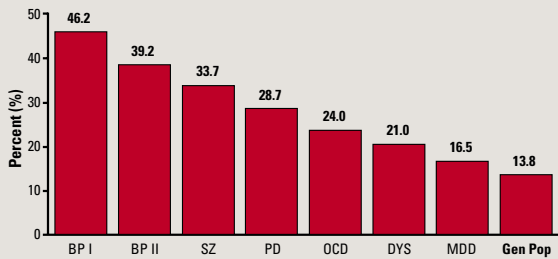
<u>First-Generation</u>	<u>Second-Generation</u>
Depression	Weight gain
Akathisia	Sedation
Acute dystonia	Hyperglycemia, diabetes <sup>†</sup>
Tardive dyskinesia*	Suicidality in age ≤24 <sup>‡</sup>
Weight gain	Akathisia
Sedation	Hyperprolactinemia
Anticholinergic	Cerebrovascular in elderly <sup>§</sup>
Cardiac, Orthostasis	Cardiac, orthostasis
Hyperprolactinemia	Tardive dyskinesia*
Neuroleptic malignant*	Neuroleptic malignant*
Cardiac/pneumonia in older adults*	Cardiac/pneumonia in older adults*

Red boxes indicate boxed warning in prescribing information.

\*Antipsychotic class warning; †Second generation antipsychotic class warning; ‡ Aripiprazole, quetiapine, olanzapine+fluoxetine combination (antidepressant class warning); § Risperidone, olanzapine, aripiprazole. All antipsychotics have at least one boxed warning.

**SLIDE 7**

*Lifetime Prevalence of Alcohol Abuse or Dependence: High Degree of Association With Bipolar Disorder<sup>8</sup>*



BP=bipolar disorder; SZ=schizophrenia; PD=panic disorder; OCD=obsessive-compulsive disorder; DYS=dyslipidemia; MD=major depressive disorder; Gen Pop=general population.

**SLIDE 8**

*Evidence-Based Clinical Guidelines<sup>11</sup>*

Bipolar patients with active substance use disorders are routinely excluded from all FDA-controlled trials

In alcohol abuse relapse prevention clinical trials, active symptoms of a mood disorder are exclusionary

Exclusion may be related to difficulties in:

- DSM/ICD criteria for diagnosis
- Lack of hypothesis-driven study design
- Lack of validated assessment tools to reliably quantify patterns of alcohol use

FDA=Food and Drug Administration; DSM=Diagnostic and Statistical Manual of Mental Disorders; ICD=International Classification of Diseases.

**SLIDE 9**

*Bipolar Disorder Diagnosis While Actively Drinking<sup>11</sup>*

Presence of manic, hypomanic, or depressed episode while not drinking (DSM-IV-TR early partial or complete remission)

A manic, hypomanic, or depressed episode that predated the onset of alcohol abuse or dependence

A manic, hypomanic, or depressed episode with high-moderate to severe mood symptoms with current minimal drinking

DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision.

**SLIDE 10**

*Conclusion*

Goal of treatment for acute mania is rapid resolution of symptoms with minimal adverse events

Medications have individual efficacy profiles to consider

- Atypical antipsychotics, anticonvulsants, and lithium are equally effective in acute mania. Patterns of response differ with mixed episodes.
- Combination therapies are most prevalent in clinical settings

Variable safety profiles warrant careful monitoring

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# **PRACTICAL MANAGEMENT STRATEGIES FOR ACUTE MANIA AND MIXED EPISODES OF BIPOLAR DISORDER — TREATMENT GUIDELINES FOR ACUTE MANIC AND MIXED EPISODES OF BIPOLAR DISORDER**

## ***CME QUESTIONS***

- 1. Which factors should be considered when selecting an antimanic treatment?**
  - A. Metabolic syndrome or obesity
  - B. History of pancreatitis
  - C. Blood relative with Bipolar I disorder with robust response to antimanic agent
  - D. All of the above
- 2. Which clinical correlate has not been associated with bipolar disorder and concurrent alcohol use disorders?**
  - A. Lithium response
  - B. Increased suicidality
  - C. Increased mixed presentations
  - D. Earlier onset bipolar illness
- 3. Which drug is not an FDA approved antimanic agent?**
  - A. Carbamazepine
  - B. Asenapine
  - C. Haloperidol
  - D. Aripiprazole
- 4. Which of the mood stabilizers does not have a recent alert for suicidality?**
  - A. Carbamazepine
  - B. Lithium
  - C. Lamotrigine
  - D. Valproate

# REGISTRATION

## APRIL 2010 CME POSTTEST



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**ANSWER FORM**

CME PsychCast™ – Practical Management Strategies for Acute and Mixed Episodes of Bipolar Disorder—*Treatment Guidelines for Acute Manic and Mixed Episodes of Bipolar Disorder*

**TERMINATION DATE:** April 30, 2012

To receive credit, you should score 70% or better (participants will receive certification for their records in approximately 4–6 weeks). Early submission of this posttest is encouraged. Please submit this test by April 1, 2012, to be eligible for credit. If you have any questions about this, or any of our other CME materials, please e-mail CME@mbicommunications.com

*Please circle your answers*

1. A B C D    2. A B C D    3. A B C D    4. A B C D

**EVALUATION SECTION** (please provide the information below and print clearly)

1=Minimally, 5=Completely

1. Please rate how well this CME activity met the stated learning objectives: 1 2 3 4 5
2. Please indicate how well this CME activity met your expectations regarding the following:
 

A. Translating clinical information/trial data to patients I see in my practice	1 2 3 4 5
B. Providing new information	1 2 3 4 5
C. Increased my knowledge and/or skills in delivering patient care	1 2 3 4 5
D. Communicated information in an effective, accessible manner	1 2 3 4 5
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6a. If "yes," what suggestions would you make to improve this activity? \_\_\_\_\_

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