

## DIAGNOSIS AND TREATMENT OF THE BIPOLAR SPECTRUM

From 2006 Psychopharmacology Academy, presented by the Neuroscience Education Institute

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**Introduction:** most patients with bipolar disorder present with depression; they spend far more time being depressed than hypomanic, manic, or cycling; because percentage of time bipolar patients spend in hypomanic phase small, often takes many years for correct diagnosis to be made; history important in differentiating bipolar from unipolar depression, and especially important to get history from collateral people because patients in hypomanic phase often “fine with their symptoms ... it’s everybody around them who recognizes how impaired they are”; patient may have little or no insight into his or her own impairment; patients report depression because they feel uncomfortable with it, but they often do not report hypomania because they think it is just “good mood”

**Hypomania:** mood elevation not necessary for hypomania; “you can just have overactivity and be hypomanic”; look for changes in personality (“the person who all of a sudden is making lists and doing this and that ... and then it stops”); when hypomanic, patient may not remember symptoms he or she experienced in depressive phase

**Asking the right questions:** best predictor of bipolar disorder is early age of onset and much time spent being ill; ask about hypomanic symptoms right before or right after depressive episode; ask whether others have mentioned noticing bipolar symptoms in patient; make questions as specific as possible; inquire about overactivity; describe symptoms of mania (patient may not know) and inquire about out-of-character impulsive behaviors

**History:** explore family history, treatment history, and history of medication response (many medications, including antidepressants, can induce hypomania or mania); history of substance of abuse causing switch to mania suggestive of patient’s having bipolar disorder

**Education:** “information sharing is a two-way street”; educate patient and family as to what to expect; ask them to call as soon as they notice any behavior suggestive of bipolar episode; advise them that bipolar disorder is progressive

**Bipolar vs unipolar depression:** in survey of 600 people with bipolar disorder, >33% sought help within first year, but 69% not diagnosed as bipolar; respondents had seen average of 4 physicians, and 33% did not re-

ceive bipolar diagnosis for 10 yr; were they misdiagnosed? or did they have no early symptoms that suggested bipolar disorder?

**Life charting:** provides patient and family with insight into patient’s symptoms; can help patient to determine what stressors trigger bipolar episode, to assess whether illness progressing, and to evaluate treatment response

**Making diagnosis:** many patients with bipolar disorder never have had full-blown manic episode; some have poor recollection of past mood states; many like their hypomania but dislike their depression; *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* says patient must have symptoms for 4 days to make diagnosis, but no data to support that figure (which was arbitrarily determined)

**Monotherapy with lithium:** good evidence to show lithium works in acute phase of mania and hypomania and as maintenance therapy; shown to reduce suicide risk; *disadvantages*—necessity for blood monitoring (although new fingerstick method may be more acceptable to some patients than having blood drawn with needle); narrow therapeutic index; possibility of causing congenital malformations (controversial); possibility that patient taken off lithium (such as parturient) may not respond if it is restarted; *tips for use*—use lowest dose associated with therapeutic response; better tolerated during acute phase than during maintenance; when used for maintenance, consider once-a-day dosing at night (eliminates cognitive dulling); controlled-release formulations may reduce peak blood levels and side effects; generic forms of lithium can be “profoundly different in bioavailability” as well as in side effects; dose usually 300 mg 2 to 3 times/day up to 1800 mg/day; extended-release formulations “a good idea if the insurance company will pay for it”

**Reducing suicide risk and treating acute mania:** lithium and clozapine (Clozaril) only drugs shown to reduce suicide risk; all atypical antipsychotic medications work as monotherapy in acute mania; if lithium started while patient in hospital, atypical antipsychotic probably will need to be started because most insurance companies do not allow long enough inpatient stays for lithium to reach therapeutic levels

**Estimated time to complete the educational process:**

Review Educational Objectives on page 3  
Take pretest

5 minutes  
10 minutes

Listen to audio program

Review written summary and suggested readings  
Take posttest

60 minutes  
35 minutes  
10 minutes

Acute mania: *ziprasidone*—20-mg dose starts to calm acute agitation within 15 min; does not cause prolonged sedation (patient usually “up and moving in <2 hr ... but not in that aggressive, agitated fashion”); single dose remains effective for 4 hr; *olanzapine*—intramuscular (IM) formulation better than lorazepam for acute agitation; works in as little as 15 to 30 min; efficacy not necessarily dependent on antipsychotic effect; calms patient without excess sedation; initial dose 10 mg IM, except in elderly, in whom dose should be smaller; *quetiapine*—in depressive phase, not much difference between 300-mg dose and 600-mg dose, but in manic phase, many patients need more than 300 mg; *olanzapine-fluoxetine combination (Symbyax)*—better than olanzapine alone

**Dysphoric mania:** loosely defined as score >2 on at least 2 parameters (dysphoric mood, worry, self-reproach, negative self-evaluation, discouragement, suicidal tendencies, fatigue, and loss of interest); in study, overall rate of relapse lower with olanzapine; data good for long-term management with ziprasidone and aripiprazole

**Psychotic symptoms:** study showed that treating physicians estimated that 50% of their patients had psychotic symptoms, but when patients of those physicians asked, 90% reported psychotic symptoms; difference explained by differing definitions of “psychotic”; one definition requires hallucinations and delusions, while another requires only “simple break in reality testing”

**Tolerability of atypical antipsychotic medications:** many patients gain weight on atypical antipsychotic and anticonvulsant drugs, and no way of predicting which patients will have problems; speaker asks whether family member has had good response on some medication and uses that information to select first-line drug; patients discontinue medications for many reasons and need to be educated about compliance; if patient feels well, he or she may think medication no longer needed; advise patient that bipolar disorder not like pneumonia, where medications taken for a while and disease cured, but more like diabetes, where treatment must continue for long term; use psychotherapeutic skills to educate patient and family

**Monotherapy with atypical antipsychotics:** *quetiapine* (Seroquel) has best evidence of efficacy as monotherapy, but other atypical antipsychotics can be used  
**Dosing:** *aripiprazole*—can be dosed as high as 30 mg, but may need to be limited to 5 to 10 mg to avoid activation and akathisia; start with low dose and increase slowly; *olanzapine*—some patients benefit from ≥30 mg; Zydys formulation dissolves in mouth, cannot be spit at people; IM formulation can be started in emergency department, switched to oral or Zydys formulation when patient admitted to hospital; *quetiapine*—at low doses, acts as sedative hypnotic; acute mania can require doses as high as 600 mg; depression may require 300 mg; speaker has used as

high as 1200 mg in patients with substance-induced psychosis or mania; *risperidone*—dose range 2 to 6 mg; can cause elevation of prolactin; best not to use if patient has personal or family history of prolactin-sensitive breast cancer; Risperdal Consta is long-acting depot formulation; *ziprasidone*—dose range 120 to 160 mg; low dose can be extremely activating, and speaker advises raising dose quickly; IM formulation available

**Divalproex:** onset of action occurs within 5 days, especially with oral loading; generic formulations highly variable in side-effect profiles and in bioavailability; starting dose 1000 mg/day, can be increased rapidly; different ethnic groups metabolize divalproex at different rates; slow metabolizers have higher blood levels at lower dose, and rapid metabolizers have opposite; risk for hepatotoxicity greatest in children ≤2 yr of age, decreases in progressively older age groups; if given in pregnancy, may produce neural tube defects in fetus

**Lamotrigine:** efficacious at 200 mg; speaker finds it especially useful in developmentally disabled patients with comorbid psychiatric disorder; helps calm verbal and physical aggressivity; approved for maintenance therapy in bipolar I disorder, and shown to be significantly superior to placebo in preventing recurrence of mood episodes; unclear whether it is as efficacious in managing acute mania; in maintenance therapy in bipolar II, superior to placebo in preventing relapse for 6 mo; speaker finds fewer side effects in patients taking lamotrigine; possible serious side effects include rash that may progress to Stevens-Johnson syndrome and agranulocytosis; therapeutic dose as monotherapy 100 to 200 mg; levels affected by divalproex and other anticonvulsants, and slow titration of lamotrigine necessary

**Medication combinations:** choose medications that have different modes of action to obtain benefits of both; combinations that have not been studied but are rational include lithium and carbamazepine and aripiprazole and lamotrigine

Evidence-based combinations: lithium with any atypical antipsychotic, especially olanzapine, risperidone, or *quetiapine*; divalproex with any atypical antipsychotic, especially olanzapine, risperidone, or *quetiapine*; olanzapine-fluoxetine combination

**Instruments for measuring:** magnitude of effect for above combinations may differ with different instruments, but all instruments agree combinations better than placebo

**Guidelines for combining divalproex and lamotrigine:** divalproex inhibits metabolism of lamotrigine, necessitating reduction in lamotrigine dose (ultimate dose should be ≈50% of that of lamotrigine as monotherapy); if divalproex stopped, remember to increase dose of lamotrigine

**Multidrug therapy:** generally the rule in bipolar disorder; some patients may need up to 5 medications; medications can be combined rationally if they have different mechanisms of action

### Educational Objectives

The goal of this program is to educate the listener about the diagnosis and treatment of the bipolar spectrum. After hearing and assimilating this program, the clinician will be better able to:

1. Explain why bipolar illness is considered to be a spectrum disease.
2. Ask the right questions to elicit a diagnosis of bipolar disorder.
3. Discuss which medications have been shown to reduce suicide risk in patients with bipolar disorder.
4. Describe the best medications for monotherapy in bipolar disorder.
5. Discuss the best medication combinations for treating bipolar disorder.

### Discussed on This Program

Aripiprazole [Abilify]	Lorazepam [Ativan, Lorazepam Intensol]
Carbamazepine [Carbatrol, Eptol, Tegretol]	Olanzapine [Zyprexa]
Clozapine [Clozaril, FazaClo]	Olanzapine and fluoxetine HCl [Symbyax]
Haloperidol [Haldol]	Quetiapine fumarate [Seroquel]
Lamotrigine [Lamictal]	Risperidone [Risperdal]
Lithium (several formulations and trade names)	Valproic acid [Depacon, Depakene, Depakote]
	Ziprasidone HCl [Geodon]

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### Suggested Reading

**Altamura AC:** Bipolar spectrum and drug addiction. *J Affect Disord* Oct 4, 2006 [Epub ahead of print]; **Bahk WM et al:** Topiramate and divalproex in combination with risperidone for acute mania: a randomized open-label study. *Prog Neuropsychopharmacol Biol Psychiatry* 29:115, 2005; **Benazzi F:** The continuum/spectrum concept of mood disorders: is mixed depression the basic link? *Eur Arch Psychiatry Clin Neurosci* Sep 7, 2006 [Epub ahead of print]; **Bowden CL:** Atypical antipsychotic augmentation of mood stabilizer therapy in bipolar disorder. *J Clin Psychiatry* 66(Suppl 3):12, 2005; **Brugue E, Vieta E:** Atypical antipsychotics in bipolar depression: Neurobiological basis and clinical implications. *Prog Neuropsychopharmacol Biol Psychiatry* Jul 27, 2006 [Epub ahead of print]; **Chengappa KN, Suppes T, Berk M:** Treatment of bipolar mania with atypical antipsychotics. *Expert Rev Neurother* 4(6 Suppl 2):S17, 2004; **Cipriani A, Rendell JM, Geddes JR:** Haloperidol alone or in combination for acute mania. *Cochrane Database Syst Rev* 3:CD004362, 2006; **Corya SA et al:** A 24-week open-label extension study of olanzapine-fluoxetine combination and olanzapine monotherapy in the treatment of bipolar depression. *J Clin Psychiatry* 67:798, 2006; **Dando TM, Keating GM:** Spotlight on quetiapine in acute mania and depression associated with bipolar disorder. *CNS Drugs* 20:429, 2006; **Gonzalez-Pinto A et al:** Suicidal risk in bipolar I disorder patients and adherence to long-term lithium treatment. *Bipolar Disord* 8:618, 2006; **Houston JP et al:** Reduced suicidal ideation in bipolar I disorder mixed-episode patients in a placebo-controlled trial of olanzapine combined with lithium or divalproex. *J Clin Psychiatry* 67:1246, 2006; **Keck PE Jr:** Long-term management strategies to achieve optimal function in patients with bipolar disorder. *J Clin Psychiatry* 67(Suppl 9):19, 2006; **Lin D, Mok H, Yatham LN:** Polytherapy in bipolar disorder. *CNS Drugs* 20:29, 2006; **Nasrallah HA, Ketter TA, Kalali AH:** Carbamazepine and valproate for the treatment of bipolar disorder: a review of the literature. *J Affect Disord* 95:69, 2006; **Nguyen LN, Guthrie SK:** Risperidone treatment of bipolar mania. *Ann Pharmacother* 40:674, 2006; **Patel NC, Keck PE Jr:** Ziprasidone: efficacy and safety in patients with bipolar disorder. *Expert Rev Neurother* 6:1129, 2006; **Schatzberg AF:** Employing pharmacologic treatment of bipolar disorder to greatest effect. *J Clin Psychiatry* 65(Suppl 15):15, 2004; **Surja AA, Tamas RL, El-Mallakh RS:** Antipsychotic medications in the treatment of bipolar disorder. *Curr Drug Targets* 7:1217, 2006; **Thase ME:** Bipolar depression: issues in diagnosis and treatment. *Harv Rev Psychiatry* 13:257, 2005; **Tohen M et al:** Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. *Br J Psychiatry* 184:337, 2004; **Vieta E:** Maintenance therapy for bipolar disorder: current and future management options. *Expert Rev Neurother* 4(6 Suppl 2):S35, 2004; **Yatham LN:** Atypical antipsychotics for bipolar disorder. *Psychiatr Clin North Am* 28:325, 2005.

### Faculty Disclosure

In adherence to ACCME guidelines, the Audio-Digest Foundation requests all lecturers to disclose any significant financial relationship with the manufacturer or provider of any commercial product or service discussed. For this issue, Dr. Swift reported nothing to disclose.

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On a Test and Evaluation form, complete Pretest section **before** listening and Posttest section **after** listening.

1. Patients with bipolar disorder report their episodes of \_\_\_\_\_, but they usually do not report episodes of \_\_\_\_\_.  
(A) Hypomania; depression (B) Depression; hypomania
2. Which of the following may be predictive of bipolar disorder when the patient presents in a depressed state?  
(A) Early age of onset (C) High proportion of time spent ill  
(B) Slow abatement of symptoms (D) A and C
3. In bipolar disorder, many medications, including \_\_\_\_\_, can trigger a hypomanic or manic episode.  
(A) Antidepressant medications (C) Antihypertensive medications  
(B) Corticosteroids (D) All the above
4. In a survey of 600 people with bipolar disorder, \_\_\_\_\_ did not receive the diagnosis of bipolar disorder for 10 yr.  
(A) 1% (B) 33% (C) Half
5. The patient who has overactivity without a mood disorder probably does not have bipolar disorder.  
(A) True (B) False
6. The only medications shown to reduce suicide risk in bipolar patients are lithium and:  
(A) Clozapine (B) Olanzapine (C) Ziprasidone (D) Divalproex
7. In treating acute agitation, the intramuscular formulation of \_\_\_\_\_ was shown to be better than lorazepam.  
(A) Ziprasidone (B) Quetiapine (C) Risperidone (D) Olanzapine
8. Which of the following has the best evidence of efficacy as monotherapy in bipolar disorder?  
(A) Ziprasidone (B) Quetiapine (C) Risperidone (D) Olanzapine
9. Generic formulations of divalproex are highly variable in:  
(A) Bioavailability (B) Side-effect profiles (C) A and B
10. Divalproex inhibits the metabolism of lamotrigine, necessitating an ultimate 50% \_\_\_\_\_ in the lamotrigine dose.  
(A) Increase (B) Decrease

Answers to Audio-Digest Psychiatry Volume 35, Issue 22: 1-C, 2-D, 3-C, 4-A, 5-B, 6-D, 7-B, 8-B, 9-C, 10-D

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