BIPOLAR DISORDER/VENOUS THROMBOEMBOLISM
From the Washington Chapter Scientific Meeting 2015:
Fostering Excellence in Internal Medicine, presented by the American College of Physicians

Diagnosis and Management of Bipolar Disorder

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**Challenges in diagnosis and treatment of bipolar disorder (BPD):** difficulty in obtaining adequate history (patients lack insight during manic and depressive phases); lack of diagnostic tests; nonspecific complaints; length of time to diagnosis

**Role of internists:** depends on practice setting, willingness, and interest; expectation of frequent diagnosis or initiation of treatment for major mental illness unreasonable; internists should recognize signs and symptoms of mania and identify safe disposition; be aware of differences between BPD and major depression to allow triage; monitor patients on long-term treatment

**Moods and mood disorders (eg, BPD):** mood — mental experience that includes characteristic emotions, patterns of thought, physical feelings, urge, and behavior; reflection of current context and life experience; version of “up” or “down”; emotions — transient part of mood (emotions last seconds; moods persist for hours, days, or weeks); mood disorder — characterized by fluctuations or persistence of mood that do not reflect external influences

**Definition and diagnosis of BPD:**
- **type I** — diagnosis requires only one manic episode; depressive episode not required; type II — requires hypomanic episode, major depressive episode, and no previous manic episode; types I and II require mood episodes characterized by clear change from baseline, observable to others, and not caused by substance abuse or medical condition; signs and symptoms of mania and hypomania — decreased need for sleep; pressured speech; flight of ideas; distractibility (attention to irrelevant stimuli); agitation; inflated self-esteem; excessive involvement in activities with high potential for negative consequences; hypomanic vs manic episode — only manic episode involves social or occupational impairment or necessity for hospitalization to prevent self-harm; manic episode lasts ≥1 wk; hypomanic episode, ≥4 days; diagnosis of each requires ≥3 of 7 signs and symptoms; psychotic features only in manic episode; patient having manic episode if admission diagnosis at hospital type II BPD

**Bipolar vs major depression:** diagnosis of either requires 5 of 9 symptoms for 2 wk, with depressed mood or anhedonia; depressive episode not required for type I BPD but almost always exists; symptoms of major depression — anhedonia; depressed mood; weight loss or gain; insomnia or hypersomnia; observed psychomotor slowing or agitation; fatigue; feelings of worthlessness or inappropriate guilt; diminished ability to think or concentrate, or indecisiveness; suicidality (recent thoughts about death or killing oneself with or without plan, or suicide attempt) or parasuicidality (eg, cutting)

**Common presentations of BPD:** office setting — episodes of depressed mood most common; next most common, emerging mania and hypomania; emergency department (ED) — full-blown manic and depressive episodes most likely, especially involving attempted suicide or suicidal ideation; manic episodes carry high risk for accidental death or injury; hospitalized patient — manic episodes with accidental injury or depressive episodes with survived suicide attempts most common

**Sleep and BPD:** improvement in sleep useful treatment target (substantially beneficial in short time); all atypical antipsychotic (AAP) drugs effective (eg, olanzapine, quetiapine [Seroquel], risperidone [Risperdal] approved by US Food and Drug Administration [FDA] for management of acute mania and for bipolar maintenance); speaker may prescribe benzodiazepines (BZDs) if patient not sleeping well and mania suspected; diagnosis probably “not BPD” if sleep improves significantly and most mood or anxiety symptoms resolve after 2 days of treatment with BZD

**Determination of safety of patient:** necessary in ED, office-based, and inpatient settings; insight diminished in patients with both depressive and manic episodes; psychotic patient — has delusions (fixed false beliefs); responds to internal stimuli; postures; experiences catatonia and mood lability (intense quickly shifting emotions); suicidal or homicidal thoughts — question patient who does not volunteer such information; may be related to auditory hallucinations or delusional thoughts; determine whether patient agitated; be mindful of own safety (situation can change quickly); when in doubt, transport patient to ED; call police if situation dangerous; move patient to less stimulating environment if situation not dangerous; ED and inpatient settings may use physical restraints, seclusion, and medication (eg, manage agitation with orally disintegrating olanzapine [Zydus] or intramuscular haloperidol [Haldol])

**Bipolar depression:** most individuals with BPD in depressed phase more often than manic phase (3 times more prevalent in type I, 40 times more prevalent in type II); criteria for differentiating bipolar from unipolar depression — ≥4 previous depressive episodes; suicidal acts; cyclothymic temperament (ie, mood swings); family history of BPD; substance abuse in context of episode of depression; <25 yr of age at onset; male sex; referral for psychiatric assessment and treatment depends on number of criteria fulfilled

**FDA-approved medications for acute depressive episodes**

1. Distinguish between bipolar depression and unipolar depression
2. Recommend the most appropriate drugs to manage the phases of bipolar disorder
3. Apply best practice advice from the American College of Physicians for patients with suspected pulmonary embolism
4. Implement the American College of Chest Physicians guidelines on duration of anticoagulant therapy

**Educational Objectives**

The goal of this program is to improve the management of bipolar disorder and venous thromboembolism. After hearing and assimilating this program, the clinician will be better able to:

1. Distinguish between bipolar depression and unipolar depression
2. Recommend the most appropriate drugs to manage the phases of bipolar disorder
3. Apply best practice advice from the American College of Physicians for patients with suspected pulmonary embolism
4. Implement the American College of Chest Physicians guidelines on duration of anticoagulant therapy
5. Use the D-dimer test as a guide in decision making about continuation of vitamin K antagonists

**Faculty Disclosure**

In adherence to ACCME Standards for Commercial Support, Audio Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, members of the faculty and planning committee reported nothing to disclose. In his lecture, Dr. Madhavan presents information that is related to the off-label or investigational use of a therapy, product, or device.
Management of Venous Thromboembolism in the Outpatient Setting

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Case 1: 65-yr-old man with hyperlipidemia and otherwise good health presents to clinic with scanty hemoptysis and mild shortness of breath (SOB); history—patient had “bad coughing spell” night before and blood-streaked sputum; denied previous similar episodes; partner recently ill with bronchitis; patient wonders whether he needs antibiotics; SOB has persisted since coughing fit; patient flew from Los Angeles to Spokane 3 days previously; physical examination—notable for blood pressure (BP) 136/92 mm Hg, pulse rate 88 bpm, and O₂ saturation 93% on room air; otherwise normal, including absence of lower-extremity swelling or tenderness; Wells score shows low test probability for deep venous thrombosis (DVT) or pulmonary embolism (PE) because of hemoptysis

Best practice advice on treating patients with suspected DVT or PE (American College of Physicians): D-dimer test has high sensitivity but low specificity (high rate of false-positive results leads to extensive use of computed tomography [CT] and over-diagnosis of PE); advice based not on formal systematic review but on meta-analyses; algorithm—in patient with suspected PE, check pretest probability; if low, apply PE rule-out criteria (PERC); absence of any criteria increases sensitivity to 100%; if any criteria present, perform D-dimer test; PE not ruled out in case patient because of age >50 yr; O₂ saturation 93%, and hemoptysis; if PERC negative, no PE workup indicated; D-dimer test lacks specificity because background levels increase with age (for patients aged >50 yr: threshold level = age × 10 mg/mL); in case patient, D-dimer testing yields 1100 mg/mL (patient 65 yr of age, so threshold 650 mg/mL); if D-dimer test positive, proceed to imaging; important points—D-dimer test lacks specificity, so use PERC for patients with low probability; use age-adjusted D-dimer cutoffs for patients aged >50 yr; consider using D-dimer test for patients with intermediate probability

Case (continued): CT angiography of chest shows segmental PE in right lung; patient initially received enoxaparin and transitioned to warfarin; 1 wk later, patient asks how long he has to take “blood thinner”

Guidelines on duration of anticoagulation therapy (American College of Chest Physicians, 2012): patients with uncomplicated venous thromboembolism (VTE) should receive ≥3 mo of anti-coagulation therapy; patients with low or moderate bleeding risk should receive extended anticoagulation therapy

Prolonged Anticoagulation During Eighteen Months vs Placebo After Initial Six-Month Treatment for a First Episode of Idiopathic Pulmonary Embolism (PADIS-PE): randomized clinical trial studied adult patients with first episode of symptomatic uncomplicated VTE treated initially with 6 mo of uninterrupted vitamin K antagonist (VKA) therapy, and then randomized to placebo or continued warfarin therapy for 18 mo; primary outcome—composite of recurrent VTE or major bleeding at 18 mo; findings—rates of combined recurrent VTE plus bleeding significantly lower in group that continued warfarin compared with placebo group; stopping warfarin after 18 mo resulted in increased rate of recurrent VTE; warfarin group had 7 adverse outcomes (placebo group, 26); composite outcome rate 13.5% in warfarin group, 3.5% in placebo group; risk should receive extended anticoagulation therapy

Republished meta-analysis of long-term VKA therapy: showed warfarin highly effective in preventing recurrent VTE (risk reduction ≥80%); found no all-cause mortality benefit

Assessing bleeding risk: HAS-BLED score (hypertension, abnormal renal and/or liver function, stroke, bleeding history, labile international normalized ratios [INRs], elderly, drugs or alcohol) most accurate measure of risk for bleeding; case patient has score of 0 and major bleeding rate ≤1%/yr; should receive anticoagulation therapy indefinitely

Take-home points: anticoagulation highly effective in decreasing risk for recurrent VTE; carries increased but small risk for major bleeding; leads to no measured difference in mortality; strongly consider anticoagulation therapy indefinitely for patients with low risk for bleeding; regularly reevaluate risk-benefit ratio

Case (continued): patient takes warfarin consistently; returns ≥12 mo into treatment for 3-mo follow-up; now aged 66 yr; developed hypertension (takes lisinopril and chlorothalidone); announces inability to continue taking warfarin; HAS-BLED
score 3 (systolic BP 160 mm Hg, labile INR, 66 yr of age), with bleeding rate ≥5%/yr; risk for recurrent VTE first year after stopping anticoagulation therapy ≤10%; long-term risk 5% to 7%/yr

**Decision making about continuation of anticoagulation therapy:** Italian study — involved serial semiquantitative D-dimer measurements in patients aged ≥18 yr with unprovoked VTE and ≥3 mo of anticoagulation; patients with persistently negative D-dimer test (≥50%) who stopped VKA therapy had 25 recurrent VTEs (recurrence rate ≥3%); those with positive D-dimer test (≥50%) who resumed anticoagulation therapy had recurrence rate <1%; *International Society on Thrombosis and Haemostasis* — states patients with annual risk for recurrent VTE of <5% can safely stop warfarin; *Clearview Simplify assay* — point-of-care test with positive or negative D-dimer results; in Canadian study, 97% of patients had negative D-dimer test at outset; rate of dropout high; level of D-dimer in assay too low to risk-stratify or distinguish among patients; rate of recurrence 6.7% (higher in men); *take-home points* — consider D-dimer test to guide decision to stop VKA therapy; cutoff levels poorly defined; use lower level (500 ng/mL); exercise caution in men; start aspirin decision to stop VKA therapy; cutoff levels poorly defined; use lower level (500 ng/mL); exercise caution in men; start aspirin

**VTE and CA:** *early review* — at baseline, ≥1 in 20 patients with unprovoked VTE had occult CA; prevalence increased to ≥1 in 10 at 12 mo; *more recent data* — show prevalence half that of earlier studies; *recent study in New England Journal of Medicine* — primary outcome confirmed CA missed by initial screening but detected by end of follow-up; patients had no chest CT; ≥4% had new diagnosis of CA; rate of missed CAs not statistically different; no significant differences found in mean time to CA diagnosis, overall mortality, or CA-related mortality; *individuals with unprovoked VTE* — in large case series, ≥10% of patients found to have CA had prostate CA (screening appropriate); *take-home points* — routine CT of abdomen and pelvis probably not useful; investigate symptoms; continue standard screening, including for prostate CA

**Suggested Reading**


**Acknowledgments**

Drs. Madhavan and Hollon were recorded at the Washington Chapter Scientific Meeting: Fostering Excellence in Internal Medicine, held November 5-7, 2015, in Seattle, WA, and presented by the American College of Physicians. For information about upcoming CME activities from the American College of Physicians, please visit www.acponline.org. The Audio Digest Foundation thanks the speakers and the sponsor for their cooperation in the production of this program.
1. The diagnosis of type II bipolar disorder (BPD) requires which of the following?
   (A) Episodes of both hypomania and major depression with no previous history of mania **
   (B) Episodes of both hypomania and major depression with at least one previous episode of mania
   (C) A history of mania without a depressive episode

2. All of the following clinical factors are useful in differentiating patients with bipolar depression from those with unipolar depression, EXCEPT:
   (A) Family history of BPD
   (B) Marital status **
   (C) Suicidal acts
   (D) Mood swings

3. Lurasidone is approved by the US Food and Drug Administration for:
   (A) Treatment of acute mania
   (B) Treatment of bipolar depression **
   (C) Maintenance therapy
   (D) All the above

4. Which of the following agents has been shown to reduce suicidality in patients with bipolar depression?
   (A) Lithium **
   (B) Quetiapine
   (C) Lamotrigine
   (D) Lurasidone

5. Which of the following agents can cause rare but serious rashes and thus needs careful titration?
   (A) Quetiapine
   (B) Olanzapine
   (C) Lamotrigine **
   (D) Lurasidone

6. A patient has signs and symptoms suggestive of pulmonary embolism (PE), and her assessment indicates that she has a low pretest probability. Which of the following is the next step in her management?
   (A) Apply PE rule-out criteria **
   (B) Perform a D-dimer test
   (C) Obtain imaging
   (D) Continued observation without further testing

7. The American College of Chest Physicians guidelines recommend that patients with unprovoked venous thromboembolism (VTE) receive anticoagulation therapy:
   (A) For ≥3 mo
   (B) For ≥6 mo
   (C) For ≥9 mo
   (D) Indefinitely

8. All of the following are findings of the Prolonged Anticoagulation During Eighteen Months vs Placebo After Initial Six-Month Treatment for a First Episode of Idiopathic Pulmonary Embolism (PADIS-PE) trial, EXCEPT:
   (A) Rates of combined recurrent VTE and bleeding were lower in the group with continued warfarin therapy compared with the placebo group
   (B) Stopping warfarin after 18 mo resulted in an increased rate of VTE
   (C) Benefits of warfarin continued after discontinuation **
   (D) Principal risk factor for recurrent VTE is previous deep venous thrombosis or PE

9. The International Society on Thrombosis and Haemostasis states that it is safe to stop warfarin therapy if the patient’s annual risk for recurrent VTE is:
   (A) <1% **
   (B) <3%
   (C) <5%
   (D) <7%

10. Which of the following is the recommended screening for cancer in patients with unprovoked VTE?
    (A) Routine computed tomography of the abdomen and pelvis
    (B) Standard screening only
    (C) Advanced imaging studies of the abdomen, including magnetic resonance imaging

Answers to Audio Digest Internal Medicine Volume 63, Issue 23: 1-C, 2-A, 3-C, 4-B, 5-D, 6-C, 7-D, 8-B, 9-D, 10-A