Misdiagnosis of bipolar disorder (BD): significant increase in rate of diagnosis has led to concerns about overdiagnosis; speaker reports negating diagnosis of BD as often as he diagnoses BD, but still worries that limited time allotted with patients may result in underdiagnosis; course—patients often enter health care setting with undifferentiated syndromes that endorse full melange of psychopathologic symptoms and domain; those who eventually meet criteria for BD often complain of anxiety and depression early in course of their disorder; although depression typically serves as index presentation of BD, speaker urges physicians to flag anxiety (state or trait) early since it often represents starting point of hypomanic and manic presentation; variability of behaviors and comorbidities associated with early stages of BD may prevent recognition of diagnosis

BD vs unipolar depression (UD): although deterministic markers for BD have not been discovered, collection of probabilistic factors can provide evidence that supports diagnosis; phenomenologic evidence—ataypical symptoms of depression (eg, hyperphagia, hypersonnia) and psychotic features more commonly reported by those with BD; comorbidities—anxiety disorders (more prevalent in BD than in any other diagnosis); substance use disorders; obesity; binge eating; diabetes; migraines; other factors—age of onset; number of episodes; episodes linked to seasons or reproductive life events (in women) more common in BD; family history

Hypomanic symptoms: although BD originally recognized as spectrum disorder, Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) balkanized UD and BD; after DSM-III, hypomanic symptoms considered almost synonymous with BD; however, many individuals with BD and depressive episodes never have manic or hypomanic episodes (instead, they have hypomanic symptoms that fall short of threshold for mania or hypomania); individuals with hypomanic symptoms at increased risk for mania and hypomania, but many never meet full criteria for BD; as such, speaker argues hypomanic symptoms cannot be considered pathognomonic for BD; instead, they should be conceptualized as probabilistic factor in patients with depressive or anxiety-related symptoms

Mixed features: patients rarely display florid mania or depression at same time; study (Goldberg et al, 2009)—majority of individuals with depression had subsyndromal hypomanic symptoms; in contrast, extremely small percentage of individuals fulfilled entire criteria for mania or depression, and relatively few had absolutely no hypomanic symptoms while depressed; predominant hypomanic or elevation symptoms during depression—activation of thought and volition, which manifests as “racing thoughts” and distractibility; increase in speech; impulsivity

Mixed states (DSM-IV-TR): defined as co-occurrence of syndromal mania and depression; numerous studies found majority of patients present with depressive syndrome with subsyndromal hypomania

Mixed features specifier (DSM-5): applies to individuals with depressive episode plus ≥3 criterion items from list of manic symptoms; applies to BD and major depressive disorder (MDD); manic symptoms may coexist with MDD, unlike full manic episodes; excluded manic and depressive features—inomnia; irritability; indecisiveness; distractibility; agitation; anger; clinicians have expressed concern about these exclusions because they represent most commonly encountered mixed features in depressed individuals who fit into BD spectrum; since mixed features often interwoven with depressive episodes associated with BD, clinicians should avoid diagnosing comorbidities if aspects of BD could explain presentation

“With anxious distress” specifier (DSM-5): anxiety increases complexity of illness, may contribute to earlier onset, and has been associated with various outcome measures related to suicidality; common features—feeling “keyed up” or restless; difficulty concentrating; feeling “awful”; fearing loss of control; all evaluations of patients with depression include mixed features, and level of anxiety

DSM-IV-TR conceptualization: categorical (ie, categorical diagnosis of, eg, mania, depression, mixed states); however, because phenotype of BD highly pleomorphic, most patients do not fit neatly into categories

Metabolic issues and BD

Obesity: more common in patients with BD than in general population; 50% of individuals with BD have metabolic syndrome; elevated rates of mortality seen with BD largely attributable

Educational Objectives

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

1. Differentiate bipolar disorder (BD) from unipolar depression and other psychiatric conditions with overlapping symptoms and comorbidities.
2. List changes to the diagnosis and conceptualization of BD under the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.
3. Consider the unique role that inflammation and obesity play in the manifestation of BD, and their potential effects on cognition and disease course.
4. Identify unique characteristics and risks associated with the mixed presentation of BD.
5. Prescribe a medication regimen that maximizes benefits to bipolar depression while minimizing harmful side effects.

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, the following has been disclosed: Dr. McIntyre is on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Janssen Pharmaceuticals, H. Lundbeck A/S, Merck & Co, Pfizer, and Shire; receives grant/research support from AstraZeneca, Eli Lilly, Janssen-Ortho, Lundbeck, Pfizer, and Shire; and is on the Speakers’ Bureaus for AstraZeneca, Eli Lilly and Company, Janssen Pharmaceuticals, H. Lundbeck A/S, Merck & Co, and Pfizer.
to greater prevalence and earlier onset of, e.g., cardiovascular disease, cerebrovascular disease, type 2 diabetes; this phenomenon has led some to conceptualize BD as disorder of premature aging; traits of BD associated with obesity and metabolic abnormalities — chronic depression; recurrences; reports of suicidal ideation and nonlethal self-harm

Mechanistic link between metabolic issues and changes in BD: although medication side effects contribute significantly, many other (nonmutually exclusive) factors may be involved; BD can “metastasize” to body and cause alterations in many systems relevant to, e.g., inflammation, insulin function, mitochondrial function; in many studies, populations with BD show greatest incidence of effects of childhood adversity (powerfully linked to premature mortality, plus many other cardiovascular and metabolic problems); speaker argues link between changes in BD and obesity has strong clinical relevance, since treating and preventing depressive symptoms represents primary challenge in BD; association between obesity and depression, cognitive disruption, and anxiety led to creation of lifestyle management program in speaker’s clinic

Study (Yim et al, 2012): evaluated cognitive function in symptom-free adults with BD; cognitive domains (rather than mood) serve as principle determinant of outcome in schizophrenia, BD, autism, and in many cases of MDD; findings — in adults with BD, increased weight or body mass index and variety of metabolic factors found to decrease some measures of cognition (effect size 0.2-0.4); domains of executive function, learning and memory, processing speed, and attention affected in patients with BD, and greater degree in those with BD plus obesity (particularly, executive function)

Study (Kuswanto et al, 2014): compared patients with first-episode mania plus obesity to those with first-episode mania at healthy weight; group with obesity showed greater incidence of abnormalities in structure, volume, and function of a priori circuits believed to be relevant to cognition

Inflammation: postulated pathway connecting obesity to cognitive issues; study (Reininghaus et al, 2014) — when compared to patients with BD alone or healthy controls, adults with BD plus obesity had highest levels of kynurenine (product of tryptophan associated with high levels of inflammation in brain); increased production of kynurenine shifts tryptophan away from synthesis of serotonin (thought to be relevant in mood, cognition, and impulsivity control); in animal models, injection of kynurenine into brain produces toxicity; in addition, patients with BD plus obesity showed greater evidence of macrophage activation (as indicated by levels of neopterin)

Clinical relevance: patients with BD have greater susceptibility to depression than mania; individuals with BD plus obesity have different biologic illness, compared with those with BD at healthy weight; speaker views this as evidence supporting hypothesis of proinflammatory state

Study (McIntyre et al, 2014): among patients with BD, those who met DSM-5 criteria for mixed features had significantly higher rates of cardiovascular mortality

Prognosis in patients with mixed features: associated with more complex course and outcomes because of increased susceptibility to cardiovascular mortality (primary driver of mortality in populations with BD) and completed suicide, compared with other phenotypes of BD; these susceptibilities can be attributed to confluence of depression and hypomania, which probably represents unique neurohormonal disorder marked by increased risk for abnormalities of hypothalamic-pituitary-adrenal (HPA) axis (i.e., urine of patients with mixed features consistently shows significantly elevated levels of 3-methoxy-4-hydroxyphenylglycol [MPHG]); combination of catecholaminergic dysregulation and HPA abnormalities may have significant effects on heart

Study (Lin et al, 2014): in some patients with MDD, responsibility to medication may be decreased as function of obesity (for pharmacodynamic reasons beyond simply having larger volume)

Proposed bidirectional links between obesity and BD: speaker argues these links have many implications for pathogenesis of BD and its comorbidities

Treatment and Management of Bipolar Depression

Background: relatively few options available; speaker attributes this to lack of data, plus relative difficulty of getting consistent positive signals in studies of bipolar depression; candidates for new medications have consistently failed to surpass placebo for unknown reasons

Study (Frye et al, 2009): subsyndromal hypomania (most common presentation woven into bipolar depression) associated with increased susceptibility to antidepressant-induced mania or hypomania; despite contraindications, these individuals frequently receive antidepressants

Role of antidepressants in BD: empirical evidence for their role in BD treatment algorithms unavailable; speaker argues they have role as adjunct to other medications (despite overwhelming efficacy); contraindicated in patients with mixed features or rapid cycling; even without treatment, ≈33% of patients with mania develop depression within weeks of resolution of mania (and vice versa); thus, clinicians must be careful to avoid ascribing bliphasic pattern to interventions

Quetiapine: approved for bipolar depression; efficacy demonstrated in 6 studies; however, speaker argues effect size seen in these studies amplified by sedation and somnolence

Lurasidone: approved as add-on to lithium and divalproex, or as monotherapy; shows fairly convincing efficacy in bipolar depression in replicated studies; speaker’s analysis of study data found lurasidone has efficacy in patients with clinically relevant subsyndromal hypomanic symptoms, as well as in those with bipolar depression alone

Lithium: effect size in bipolar depression inferior to effect size in mania, but effect remains positive; particularly recommended for patients with stable episodic BD wherein mania or hypomania precedes depression; lowers rates of dementia and inhibits β-amyloid conversions implicated in Alzheimer disease (AD); elevated risk for AD in patients with multiphase BD negated by lithium

Asenapine: indicated for mania and mixed states (but not for bipolar depression); used off-label for treatment of depressive symptoms (particularly those intertwined with hypomania [most common presentation]); post-hoc data analysis demonstrated efficacy against subsyndromal depressive symptoms in patients with mania (and vice versa)

Adverse events of atypical antipsychotic (AP) medications: algorithm for use of these medications must be informed by potential number of people harmed; olanzapine has fallen out of favor in management of bipolar mania over past several years; because of new data on quetiapine and its effects on weight gain, metabolism, and brain function, speaker argues its role should be reconsidered

Number needed to treat (NNT) and number needed to harm (NNH): olanzapine, fluoxetine, lurasidone, and quetiapine have comparable NNT values; lamotrigine — NNT of 12 to 15 (unimpressive), but shows double-digit NNH values for weight gain, metabolic side effects, sexual dysfunction, and cognitive impairment; recommended for patients with less severe BD who require urgent symptom relief

Typical APs: may increase depressive symptoms

Stimulants: not approved for bipolar depression; safe when used in carefully selected patients; pediatric studies have shown improved outcomes when patients with BD plus attention-deficit/hyperactivity disorder received stimulants; study (McIntyre et al, 2013) — stimulants improved cognition measures and depression in patients with BD; contraindications — rapid cycling; elevation symptoms; must be used as adjunct; modafinil — data suggest efficacy as adjunct; however, negative and failed studies using armodafinil have raised doubts about efficacy
Pramipexole: hints of efficacy seen in small studies (notably with BD type II); study (Burdick et al., 2012) — suggested benefits to cognition in patients with BD

Anti-inflammatory agents: lithium has anti-inflammatory properties; study (Haarman et al., 2015) — imaging study showing significant increase in activated inflammatory cells (microglia) in brains of patients with BD; traditional anti-inflammatory agents — evidence for use in BD insufficient; cyclooxygenase-2 inhibitor failed to surpass placebo but showed hint of benefit to bipolar depression early in illness course; minocycline — seems to stabilize microglia and reverse effects of kynurenine; small open-label studies indicated benefits for depressive symptoms in UP; 2 controlled studies indicated benefits for negative symptoms of schizophrenia; forthcoming study — minocycline yielded improvements in bipolar depression, but only in patients with elevated inflammatory markers and history of childhood trauma; infliximab — subject of speaker’s newest study; tumor necrosis factor-α modulator

Antioxidants: include N-acetyl cysteine and ketamine; safety not yet established; efficacy has not been replicated

Study (Ahmed et al., 2013): included 144 patients with BD who underwent bariatric surgery; patients lost 85% of excess body weight; safe and well tolerated; destabilizations did not occur, and many patients had improved outcomes

Meta-analysis (Dierckx et al., 2012): electroconvulsive therapy (ECT) found significantly superior to medication in patients with bipolar depression

Manual-based strategies: critical to functional recovery; associated with positive outcomes when combined with lifestyle changes, diet, and chronic disease management in coordinated and accountable care program

Florida Medicaid medication therapy protocol (2014): level 1a — quetiapine, lurasidone, or either as adjunct to lithium or divalproex; speaker expresses concern about adding divalproex to quetiapine because of increase in risks for weight gain and diabetes; level 1b — olanzapine plus fluoxetine; level 2 — lithium and lamotrigine (separately or in combination); level 3 — ECT; level 4 — repetitive transcranial magnetic stimulation (results underwhelming, but this may reflect lack of refinement in study parameters); pramipexole; modafinil; stimulants; adjunctive use of antidepressants

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Suggested Reading


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TREATING BIPOLAR DEPRESSION: PRACTICAL CONSIDERATIONS

1. Compared to patients with unipolar depression, patients with bipolar depression (BD) are more likely to report and exhibit symptoms consistent with which of the following?
   (A) Melancholic or typical depression
   (B) Atypical depression
   (C) Dysthymia

2. What percentage of patients with BD also have metabolic syndrome?
   (A) 65%  (B) 50%  (C) 30%  (D) 15%

3. Which of these domains of cognitive function is particularly affected in patients with obesity and BD, relative to patients with BD who are at a healthy weight?
   (A) Executive function
   (B) Leaning and memory
   (C) Processing speed
   (D) Attention

4. Increased inflammation in the brains of patients with BD results in increased production of kynurenine, which is believed to shift vital precursors away from the synthesis of:
   (A) γ-Aminobutyric acid
   (B) Glutamate
   (C) Dopamine
   (D) Serotonin

5. Which of the following is the primary driver of mortality in populations with bipolar disorder?
   (A) Completed suicide
   (B) Substance abuse
   (C) Cardiovascular mortality
   (D) Cerebrovascular mortality

6. Which of the following medications has demonstrated efficacy in patients with bipolar depression plus clinically relevant subsyndromal hypomanic symptoms?
   (A) Quetiapine
   (B) Lurasidone
   (C) Asenapine
   (D) Olanzapine

7. Which of the following has been shown to negate the increased risk for Alzheimer disease associated with BD?
   (A) Lithium
   (B) Lamotrigine
   (C) Modafinil
   (D) Pramipexole

8. Because of its inferior efficacy but relatively benign side effects, which of the following medications is recommended for patients with less severe forms of bipolar disorder who require urgent relief from their symptoms?
   (A) Lithium
   (B) Lamotrigine
   (C) Asenapine
   (D) Minocycline

9. There is evidence that _______ can stabilize microglia and reverse the effects of kynurenine, but may only show efficacy in patients with increased inflammatory markers or a history of childhood trauma.
   (A) Armodafinil
   (B) Pramipexole
   (C) Minocycline
   (D) Infliximab

10. Which of the following neuromodulating treatments has shown significant superiority over medications in patients with bipolar depression?
    (A) Electroconvulsive therapy
    (B) Repetitive transcranial magnetic stimulation
    (C) Vagus nerve stimulation
    (D) Deep brain stimulation

Answers to Audio Digest Psychiatry Volume 44, Issue 17: 1-C, 2-C, 3-A, 4-D, 5-A, 6-C, 7-A, 8-C, 9-C, 10-C