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Practical Approaches in the Management of Bipolar Depression:
Overcoming Challenges and Avoiding Pitfalls

Cover artwork provided by Anne Therese Naylor, a mental health advocate with bipolar disorder.
The Light. *Acrylic on Canvas, 11" x 15".*

Practical Approaches in the Management of Bipolar Depression: Overcoming Challenges and Avoiding Pitfalls

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TARGET AUDIENCE

This activity has been designed to meet the educational needs of family practice physicians involved in the care of patients with bipolar disorder.

STATEMENT OF NEED/ACTIVITY OVERVIEW

In the past 2 decades, the burden of care for psychiatric complaints in primary care—including bipolar depression—has increased considerably. The prevalence of bipolar disorder (BPD) in primary care has been recently estimated to range up to 4.3%, and in studies with broader definitions of the disorder or in populations with higher-than-usual psychiatric disorders, the prevalence has been reported to be up to 11.4%. Even though BPD is seen commonly in primary care, there are still profound disparities in the delivery of care, including underdiagnosis, misdiagnosis, and inappropriate treatments. In the primary care setting, bipolar depression is often misdiagnosed as unipolar depression. Additionally, patients with BPD have many comorbid psychiatric and medical conditions that often go untreated. The results of a needs assessment survey (N=99) of primary care providers reflected the current literature by demonstrating that BPD is frequently misdiagnosed in the primary care setting, and that medical and psychiatric comorbidities of BPD are often underrecognized and undertreated. There is abundant evidence that BPD can be successfully managed in the primary care setting when adequate physician education, collaborative care teams, and patient education are employed. Efficacious and well-tolerated pharmacologic treatments for BPD are available, and evidence-based pharmacotherapy can be optimally managed by the primary care provider. In this activity, experts in BPD discuss the recognition and management of bipolar depression and associated comorbidities in the primary care setting.

EDUCATIONAL OBJECTIVES

After completing this activity, the participant should be better able to:

- Describe the indicators of bipolar disorder among depressed patients
- Accurately differentiate bipolar depression from unipolar depression
- Implement strategies for the recognition and management of medical comorbidities in patients with bipolar disorder
- Recognize and manage metabolic side effects of agents used in the treatment of bipolar disorder
- Describe strategies for management of common psychiatric comorbidities in patients with bipolar disorder
- Integrate treatment of bipolar depression into primary care practice
- Promote a collaborative care team to manage patients with bipolar depression

FACULTY

Larry Culpepper, MD, MPH *(Chairperson)*
Professor of Family Medicine
Boston University School of Medicine
Boston, Massachusetts

J. Sloan Manning, MD
Adjunct Associate Professor
Department of Family Medicine
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina
Co-Director, Mood Disorders Clinic
Moses Cone Family Practice Residency
Greensboro, North Carolina

Roger S. McIntyre, MD, FRCPC
Professor of Psychiatry and Pharmacology
Head, Mood Disorders Psychopharmacology Unit
University Health Network
University of Toronto
Toronto, Ontario

PHYSICIAN CREDIT

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Roger S. McIntyre, MD, FRCPC	*Grants/Research Support:* AstraZeneca, Eli Lilly and Company, H. Lundbeck A/S, Janssen-Ortho Inc., National Alliance for Research on Schizophrenia and Depression (NARSAD), National Institutes of Mental Health (NIMH), Pfizer, Inc., Shire plc, Stanley Medical Research Institute; *Consulting Fees (eg, Ad boards):* AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, France Foundation, GlaxoSmithKline plc, H. Lundbeck A/S, Janssen-Ortho Inc., Merck & Co., Inc., Pfizer, Inc., Organon Pharmaceuticals USA Inc., Shire plc; *Speakers' Bureau:* AstraZeneca, Eli Lilly and Company, H. Lundbeck A/S, Janssen-Ortho Inc., Merck & Co., Inc., Pfizer, Inc.

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Name of Content Manager	Reported Financial Relationship
Matt Groesbeck, MPH – CMEology	No financial relationships to disclose
Rob Lowney – CMEology	No financial relationships to disclose
Rachael Soranno – CMEology	No financial relationships to disclose
Dana Ravyn, PhD, MPH – CMEology	No financial relationships to disclose
Lauren Light, PharmD	No financial relationships to disclose

METHOD OF PARTICIPATION

There are no fees for participating in and receiving credit for this activity. During the period June 2015 through June 2016, participants must (1) read the learning objectives and faculty disclosures, (2) study the educational activity, (3) complete the posttest and evaluation at **http://tinyurl.com/BipolarSuppl**. A statement of credit will be issued only upon completion of an activity evaluation and posttest.

MEDIA

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FEE INFORMATION

There is no fee for this educational activity.

About the Cover Art

Anne Therese Naylor is an award-winning writer, artist, advocate, teacher, and mother of 4 children. She has a bachelor's degree in early childhood education and a master's degree in special education. Anne Therese began writing creative nonfiction in 1987 after her third child was born and was diagnosed with Down syndrome. In 2001, her short story "The Perfect Mother" was awarded a prize in a national writing competition and published in *Cosmopolitan* magazine. In 2005, an unexpected, intense desire to create artwork was accompanied by the advent of bipolar disorder. Her painting *What Lies Beneath* was awarded first prize in the Central Coast Mental Health Art Works Exhibition in 2008. Her book, *Art from Adversity: A Life with Bipolar,* an account of her experience with bipolar disorder, was published in March 2013. Anne Therese is dedicated to raising awareness, challenging stereotypes, and fighting the stigma of mental illness and disability. Cover: *The Light.* Acrylic on Canvas, 11" x 15".

Pathways to the Diagnosis of Bipolar Disorder

Larry Culpepper, MD, MPH

Primary care physicians (PCPs) serve key roles in first contact and ongoing care for patients with bipolar disorder (BPD). Patients with BPD are commonly encountered by PCPs, given a mean lifetime prevalence of 4.4% for any bipolar disorder.[1] Bipolar disorder is characterized by vulnerability to depression and episodic mania (bipolar I) or hypomania (ie, less severe mania; bipolar II) and, in some cases, rapid cycling between states.[2] Unfortunately, BPD is too frequently misdiagnosed as unipolar depression (major depressive disorder [MDD]).[3,4] Depending on the population, between 7% and 52% of patients diagnosed with unipolar depression actually have BPD, which may go unrecognized for 10 years or more from symptom onset to first treatment.[5-9] One study reported that patients were misdiagnosed an average of 3.5 times and had seen 4 physicians before being correctly diagnosed.[10] Thus, there is a substantial need and opportunity to improve the timeliness and accuracy of BPD diagnosis.

Bipolar disorder in primary care

Primary care physicians outnumber psychiatrists 2 to 1 in the United States, and US PCPs provide the majority of mental health care, more than any other specialty.[11,12] Demand for primary care–based psychiatric services continues to escalate. A 2014 study reported that mental health care, including visits resulting in a BPD diagnosis, increased significantly faster in primary care settings than in psychiatric offices.[13] However, difficulty obtaining specialty consultations may limit PCPs' capacity to manage patients with BPD effectively.[14] A 2009 survey of approximately 6600 nonfederal PCPs reported that 66.8% were unable to arrange outpatient mental health services.[14]

Clearly, a more unified approach to primary care delivery is needed to serve patients with multiple conditions, particularly patients with BPD. Fortunately, primary care practice is being redesigned to better serve such patients, including through development of the patient-centered medical home.[15] This multidisciplinary, team-based collaborative care model integrates the efforts of mental and behavioral health personnel to provide counseling, psychotherapy, substance abuse and addiction management, and other services needed by many patients with BPD.[16,17]

The Affordable Care Act (ACA) and the Mental Health Parity and Addiction Equity Act have led to increased coverage and increased demand for coverage. An estimated 62 million people are now obtaining better mental health and substance abuse coverage.[18] In July 2014, the Health Resources and Services Administration (HRSA) began an initiative to prepare for this expected escalation of demand. HRSA awarded $54.6 million in ACA funding to support 221 community health centers across 46 states, Washington, DC, and Puerto Rico to bolster staff and services to serve an additional 450,000 patients.[19] One potential consequence of these developments is that some mental health providers may move to group practices, in part to obtain the practice structure needed to bill for mental health services. However, this move may in turn decrease access to health care in other segments of the community.

Diagnostic and treatment challenges in bipolar disorder

Several reasons may explain the lack of diagnosis and the misdiagnosis of BPD. One survey found that although 28% of patients who were misdiagnosed admitted that they underreported their manic and depressive symptoms, the actual percentage of patients underreporting their symptoms was likely much higher.[10] In addition, 60% of misdiagnosed patients felt that physicians had an inadequate understanding of BPD.[8]

In fact, PCPs acknowledge difficulty in diagnosing BPD. In a 2006 survey evaluating the knowledge, attitudes, and awareness of 102 PCPs, the respondents frequently misiden-

Larry Culpepper, MD, MPH, Professor of Family Medicine, Boston University School of Medicine, Boston, Massachusetts

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Dr. Culpepper discloses that he has received consulting fees (eg, Ad boards) from AstraZeneca; Forest Laboratories, Inc.; H. Lundbeck A/S; Merck & Co., Inc.; Shire plc; Sunovion Pharmaceuticals Inc.; and Takeda Pharmaceutical Company Limited. He has ownership interest/shareholder in M3 (My Mood Monitor) and has received salary from Physician's Postgraduate Press, Inc. Dr. Culpepper receives royalty from/is a patent holder for UpToDate®, Oxford University Press.

tified various symptoms required for the diagnosis of BPD, and 46% indicated that they did not have experience recognizing BPD symptoms.[20] The vast majority (94%) of these PCPs said they would use a brief screening instrument if one were available. Many PCPs also express concern about being unfamiliar with appropriate medications and their adverse effects.[20,21] The National Comorbidity Survey Replication reported that 43.4% of individuals with BPD were treated inappropriately by psychiatrists and 73.1% were treated inappropriately by other medical providers.[22] Inappropriate treatments included administration of an antidepressant without an antimanic agent and antidepressant monotherapy.

In the 2006 survey discussed above, up to one-third of PCPs said that they wished to avoid the complexity of prescribing for BPD patients.[20] More than half considered patients with BPD to be more difficult (60%) and time-consuming (51%) than other patients, and they felt less confident in their ability to manage them (75%). The PCPs also were apt to refer, and two-thirds did so in a timely manner. Overall, a minority of PCPs (6%) prescribed pharmacotherapy.[20] These findings emphasize the need for educational efforts and investment in a more integrated, collaborative partnership between PCPs and psychiatric specialists and allied health personnel, as well as other approaches to improve knowledge, comfort, and skill in managing this complex but treatable condition. Treatment of patients with BPD in primary care settings is feasible, especially given the improved adverse effect profiles of newer psychotropic medications.[2,23]

Consequences of misdiagnosis or nondiagnosis

Morbidity and mortality

Misdiagnosis or nondiagnosis of BPD may not only be inconvenient for a patient, but may also have costly and far-reaching consequences.[24,25] The life expectancy of patients with BPD is 8.5 to 9.0 years shorter than that of the general population.[26,27] Bipolar disorder may increase the risk of developing chronic medical conditions, through biologic as well as behavioral pathways.[27] Early mortality may result primarily from comorbid medical conditions, which may not be adequately diagnosed or treated over long periods. In particular, serious mental illnesses with psychoses, including BPD, have been shown to be an independent risk factor for cardiovascular disease and diabetes.[28,29] Furthermore, depressed patients often have decreased motivation to perform self-care behaviors, exacerbating current diseases and allowing others to develop.[30] Many patients have no access to regular health care but instead present for care only at times of crisis. Suicide also contributes to premature death. The Global Burden of Disease Study 2010 reported that suicide was 5.7 times more likely in patients with BPD compared with the general population.[31] Failure to initiate appropriate therapy in patients with BPD has been associated with increased hospital use and suicide attempts.[32]

Behavioral impairment

A 2011 study reported an association between the number of previous BPD illness episodes and the response to treatment. For the prevention of relapse, patients with 1 to 5 previous episodes were 40% to 60% more likely to benefit from an atypical antipsychotic than those who had >10 previous episodes (for depression, odds ratio [OR] 0.6; 95% confidence interval [CI] 0.4-0.9; for mania, OR 0.4; 95% CI 0.2-0.6).[33] The greater the number of episodes before beginning an effective therapy, the less likely a patient is to respond to treatment.[33-35]

Bipolar disorder can result in behavioral issues that lead to interpersonal difficulty, including anger, abrasive communication, distrust and paranoia, and disrupted family, social, and health care (PCP) relationships. These behaviors may isolate the patient from needed support. In addition, if BPD is misdiagnosed as unipolar depression and antidepressant therapy is erroneously prescribed, a state of mania or hypomania may be induced, potentially with rapid cycling.[36,37] Evidence of antidepressant effectiveness in BPD is weak, and monotherapy with antidepressants is contraindicated.[37] Fewer than half of PCPs are aware that antidepressants can cause potentially deleterious effects.[20] Inappropriate treatment has also been associated with higher hospitalization rates and health care costs.[32,38,39]

Recognizing mania or hypomania

A history of repeated episodes of mania or hypomania is a hallmark of BPD. However, when presenting in primary care, patients with BPD will predominantly exhibit symptoms of depression.[40-42] Such depressive symptoms are a shared feature of BPD and unipolar depression.[40] Although patients with bipolar I or bipolar II typically cycle from mania to depression with periods of euthymia interspersed, they do not usually visit PCPs during manic or hypomanic episodes. When they do present for medical attention during these episodes, it is often through the emergency department. After a manic episode has subsided, they may seek care with a PCP because of the consequences of the episode (eg, sexually transmitted disease, follow-up after an accident).[40] The care of these consequences may be the priority, and the opportunity to investigate the underlying psychopathology that led to the problem may be missed.

Patients may focus on the current depressive symptoms and may either not recognize or deny manic symptoms. Patients with BPD spend much more time in the depressive phase of the illness compared with mania/hypomania

TABLE 1 Characteristics that may differentiate BPD from unipolar depression[40,42,48]

- Racing thoughts, pressured speech, flight of ideas, inflated self-esteem, irritability, mood lability
- Ability to function with decreased sleep (eg, 2 to 3 hours)
- Early onset of depressive symptoms (eg, during the teenage and early adult years)
- Family history of BPD, which, even if not overtly diagnosed, may be marked by a history of unpredictable behavior and a complicated life (eg, multiple jobs, marriages, relocations, bankruptcies) in first-degree relatives
- Risky behaviors; excessive involvement in pleasurable activities
- Hypersomnia, motor retardation, and suboptimal work functioning
- Paradoxical response to antidepressants, such as mania or hypomania
- Treatment-resistant depression

Abbreviation: BPD, bipolar disorder.

or euthymia; in fact, they spend 30% to 50% of their lives with depressive symptoms.[43,44] When symptoms were measured on a weekly basis over a mean of 13 years of follow-up, patients with bipolar I reported depressive symptoms 3 times more often than manic symptoms and 5 times more often than cycling/mixed symptoms.[42,43] This same measure for patients with bipolar II is startling: they reported depressive symptoms 39 times more often than hypomanic symptoms and 22 times more frequently than cycling/mixed symptoms.[42,43] Furthermore, patients with BPD may experience several depressive episodes and have a diagnosis of MDD well established before they experience their initial manic episode.[45]

Anxiety is a common comorbid psychiatric feature of BPD. Anxiety presentations can make it difficult to address these patients' mental health needs because they may be more likely to avoid seeking treatment or to drop out of treatment.[46] Patients with BPD may present in primary care settings with concerns diagnosed as anxiety, or as anxious depression, with the underlying BPD not recognized.

Patients frequently hesitate to discuss symptoms they consider embarrassing, especially manic or hypomanic symptoms. Many patients also have little insight into the abnormality of their behaviors during manic or hypomanic episodes and minimize or deny the consequences. As a result, recognizing BPD during usual care in primary care settings is difficult. In fact, only 39% of individuals with bipolar I and bipolar II disorders entered treatment during the year of onset; the median delay to initial treatment was 6 years.[47] However, a number of cues and case-finding tools can help PCPs efficiently diagnose patients once BPD is suspected.

Distinguishing bipolar disorder from unipolar depression

The first task for PCPs seeking to improve outcomes for patients with BPD is to increase the early recognition of those likely to have BPD. Although universal screening is not practical, case finding among patients at increased risk is recommended and may be facilitated by the use of several instruments described in the next section. Several red-flag characteristics can be used to identify patients who need further assessment (**TABLE 1**).[40,42,48] Depressive illness itself conveys significantly increased risk of BPD and should lead to inquiry about mania or hypomania before making a diagnosis of MDD. A 2014 study identified 7 risk factors that differentiated BPD from unipolar depression; 4 of these were identifiable at the onset of illness: cyclothymic temperament, family history, young age (<25 years) at onset, and male sex. Additional cues were ≥4 previous depressive episodes, suicide attempts, and substance abuse.[49]

Since the first manic or hypomanic episode may not emerge until after multiple depressive episodes, reevaluation of depressive episodes is indicated, particularly if there are additional red flags. A review of evidence-based guidelines by Connolly and Thase recommends assessment of depressed individuals in primary care to rule out BPD.[50,51]

Diagnostic tools for bipolar disorder

Patients considered to be at risk of BPD based on current behaviors or risk factors require clinical evaluation. Since visit duration in primary care settings is nearly universally constrained to about 12 to 15 minutes, validated questionnaires can be useful to facilitate assessment in a timely manner.[52] They can also help prevent errors due to clinicians' memory lapses, thus increasing the likelihood of obtaining accurate information for assessment and confident diagnosis.

Patients can fill out questionnaires before the visit or in the office with support from office staff. Questionnaires can be repeated with new depressive episodes to assess the possibility of an intercurrent manic or hypomanic episode. Because patients may lack insight into their manic behaviors or may not realize the impact of these behaviors on their

functioning and on others, having a family member complete the same instrument (with the patient's permission) can be helpful in recognizing mania. Such involvement also may open discussion about the condition and help the family to help the patient.

Three instruments have proven useful in the process of diagnosing BPD: the Mood Disorder Questionnaire (MDQ), the Composite International Diagnostic Interview (CIDI), and the My Mood Monitor (M3) test, which can be incorporated into the electronic health record.

Mood Disorder Questionnaire

The MDQ is a brief self-report inventory used as a case-finding instrument. The first question has 13 parts, the second question asks about clustering of symptoms, and an additional question assesses the degree of problematic consequences resulting from the reported behaviors. It usually takes only 5 minutes for a patient to complete the questionnaire. Seven or more "yes" responses suggest BPD. In one study in a primary care practice, an MDQ screening score of 7 or higher yielded a sensitivity of 58% and specificity of 93% for detecting BPD compared with structured clinical interview.[53] Although the MDQ can be a helpful instrument, it is not considered a definitive diagnostic measure and further evaluation is required, including in patients for whom the PCP has a high suspicion but the MDQ is not positive. The MDQ is available at http://www.integration.samhsa.gov/images/res/MDQ.pdf.

Composite International Diagnostic Interview

The CIDI version 3.0 is a clinician-administered instrument that takes roughly 3 minutes to complete.[54] If positive answers are obtained to 2 "stem" and 1 screening question, 9 further questions are asked that identify manic symptoms. As the number of questions answered in the affirmative increases, so too does the likelihood of a positive BPD diagnosis. For example, if 7 or more items are endorsed, the individual is at high risk (>50%) of having BPD. The CIDI 3.0 was found to detect 67% to 96% of true BPD cases in a population-based study.[54] The MDQ, by contrast, found a lower portion of true cases (28%) in a general population sample. The CIDI 3.0 can also be used to help distinguish between bipolar I and bipolar II.[54] The CIDI 3.0 is free and available as part of the STAndards for BipoLar Excellence (STABLE) Resource Toolkit for clinicians at http://www.integration.samhsa.gov/images/res/STABLE_toolkit.pdf.

The M3 test

The M3 is a brief, self-administered test that may indicate unipolar depression, BPD, and anxiety disorders, including post-traumatic stress disorder (PTSD).[55] Because many patients with BPD have other psychiatric comorbidities, such as PTSD, the M3 can be helpful in flagging the full scope of symptomatology requiring diagnostic inquiry. It is available in both English and Spanish for patients to complete online at http://whatsmym3.com. Patients can opt to send the completed M3 scores privately to their PCP, providing valuable information before a visit.

Electronic health records case-finding prompts

At the practice level, integration into existing systems can increase the routine use of case-finding instruments. In a 2012 study, the CIDI was integrated into an electronic health records system. The CIDI module appeared on the screen automatically during the office visit for any patient with a diagnosis of depression. Across 21 primary care sites, the case-finding tool was used in 47.5% of an intervention group (n = 8355), and 2.5% of patients scored at high or very high risk for BPD. Patients in the intervention group were significantly more likely than comparison patients (n = 8799) to receive a new diagnosis of BPD (1.11% vs 0.36%; $P < .01$) and a new prescription for BPD medications (1.85% vs 1.19%; $P < .01$).[50]

Confirming the diagnosis

To confirm the diagnosis of BPD, clinicians must evaluate the relevant symptoms cited in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5).[56] Information from one of the case-finding tools can be used to guide this evaluation. The CIDI 3.0 is particularly valuable because it specifically asks about symptoms constituting the diagnostic criteria. Primary care physicians should inquire about comorbidities such as PTSD or an anxiety disorder, determine the degree and realms of functional impairment, and look for other consequences of disorder-related behaviors. Understanding the severity of symptoms and impairment is the key to differentiating bipolar I and bipolar II. Similarities and differences between manic and hypomanic episodes are shown in **TABLE 2.**[56] In addition to confirming the diagnosis, this information is important for selecting treatment, counseling patients, and motivating patients to adhere to clinical recommendations. Getting another viewpoint of the patient's history from a family member or trusted friend (with the patient's permission) can be very helpful. Requesting medical records from the patient's previous PCP(s) may yield clues to diagnosis or nondiagnosis.

To guide the treatment of depressive episodes, a structured symptom-severity assessment using the M3 or a validated depression screen can be helpful. The initial symptom score can serve as a baseline for comparison with

TABLE 2 DSM-5 criteria for manic or hypomanic episodes[56]

	Manic episode	Hypomanic episode
Core mood characteristics All must be present abnormally and persistently	1. Elevated mood 2. Expansive or irritable mood 3. Increased energy or goal-directed activity	
Core mood duration		
Total duration, days	7 consecutive days (or nearly every day)	4 consecutive days (or nearly every day)
Daily duration	Majority of day	
Behavioral characteristics 3 or more must be present during above period (4 if only irritability is present)	• Inflated self-esteem or grandiosity • Decreased need for sleep (eg, feels rested after only 3 hours of sleep) • More talkative than usual • Flight of ideas or racing thoughts • Distractibility • Increase in goal-directed activity (social, work, school, or sexual) • Excessive risk-taking activities with potential for painful consequences	
Severity causes marked functional impairment	Yes	No
Psychotic symptoms present?	Yes	No

Abbreviation: DSM-5, *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed.

subsequent scores to quantify the patient's response to treatment.[52]

Conclusions

Psychiatric complaints in primary care practice continue to grow more prevalent as patients become better informed about mental illness and behavioral disorders through information campaigns across the range of broadcast and social media. It is incumbent upon PCPs to establish rapport, collect information, correct misinformation, and be prepared to accurately diagnose, initiate treatment, and arrange resources, such as psychiatric consultations. An informed patient assessment can yield the correct diagnosis. Key signs of BPD, including episodes of mania or hypomania, early symptom onset, family history, and unpredictable behavior, help to distinguish BPD from unipolar depression. The MDQ, CIDI, M3, and similar case-finding tools can improve BPD recognition and facilitate timely treatment. New clinical arrangements, such as the patient-centered medical home, may provide additional resources both for diagnosing patients with BPD and engaging them in long-term, integrated care for BPD and medical comorbidities. Primary care physicians are ideally placed to identify BPD, initiate early treatment, encourage sustained treatment, facilitate psychiatric consultations, and manage comorbid conditions to improve the health care and quality of life for these patients.

REFERENCES

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry.* 2005;62(6):593-602.
2. Muzina DJ, Colangelo E, Manning JS, Calabrese JR. Differentiating bipolar disorder from depression in primary care. *Cleve Clin J Med.* 2007;74(2):89, 92, 95-99.
3. Frye MA, Calabrese JR, Reed ML, et al. Use of health care services among persons who screen positive for bipolar disorder. *Psychiatr Serv.* 2005;56(12):1529-1533.
4. Dubovsky SL, Leonard K, Griswold K, et al. Bipolar disorder is common in depressed primary care patients. *Postgrad Med.* 2011;123(5):129-133.
5. Kamat SA, Rajagopalan K, Pethick N, Willey V, Bullano M, Hassan M. Prevalence and humanistic impact of potential misdiagnosis of bipolar disorder among patients with major depressive disorder in a commercially insured population. *J Manag Care Pharm.* 2008;14(7):631-642.
6. Sharma V, Khan M, Smith A. A closer look at treatment resistant depression: is it due to a bipolar diathesis? *J Affect Disord.* 2005;84(2-3):251-257.
7. Ghaemi SN, Boiman EE, Goodwin FK. Diagnosing bipolar disorder and the effect of antidepressants: a naturalistic study. *J Clin Psychiatry.* 2000;61(10):804-808; quiz 809.
8. Vermani M, Marcus M, Katzman MA. Rates of detection of mood and anxiety disorders in primary care: a descriptive, cross-sectional study. *Prim Care Companion CNS Disord.* 2011;13(2).
9. Suppes T, Leverich GS, Keck PE, et al. The Stanley Foundation Bipolar Treatment Outcome Network. II. Demographics and illness characteristics of the first 261 patients. *J Affect Disord.* 2001;67(1-3):45-59.
10. Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the National Depressive and Manic-Depressive Association 2000 survey of individuals with bipolar disorder. *J Clin Psychiatry.* 2003;64(2):161-174.
11. Xierali IM, Tong ST, Petterson SM, Puffer JC, Phillips RL Jr, Bazemore AW. Family physicians are essential for mental health care delivery. *J Am Board Fam Med.* 2013;26(2):114-115.

12. Kessler R, Stafford D. Primary care is the de facto mental health system. In: Kessler R, Stafford D, eds. *Collaborative Medicine Case Studies.* New York, NY: Springer; 2008: 9-21.
13. Olfson M, Kroenke K, Wang S, Blanco C. Trends in office-based mental health care provided by psychiatrists and primary care physicians. *J Clin Psychiatry.* 2014;75(3):247-253.
14. Cunningham PJ. Beyond parity: primary care physicians' perspectives on access to mental health care. *Health Aff (Millwood).* 2009;28(3):w490-501.
15. Dickinson WP, Miller BF. Comprehensiveness and continuity of care and the inseparability of mental and behavioral health from the patient-centered medical home. *Fam Syst Health.* 2010;28(4):348-355.
16. Bauer MS, McBride L, Williford WO, et al. Collaborative care for bipolar disorder: part I. Intervention and implementation in a randomized effectiveness trial. *Psychiatr Serv.* 2006;57(7):927-936.
17. Sylvia LG, Nierenberg AA, Stange JP, Peckham AD, Deckersbach T. Development of an integrated psychosocial treatment to address the medical burden associated with bipolar disorder. *J Psychiatr Pract.* 2011;17(3):224-232.
18. Frank RG, Beronio K, Glied SA. Behavioral health parity and the affordable care act. *J Soc Work Disabil Rehabil.* 2014;13(1-2):31-43.
19. Health Resources and Services Administration, US Department of Health and Human Services. The Affordable Care Act and Health Centers fact sheet. http://bphc.hrsa.gov/about/healthcenterfactsheet.pdf. Accessed December 18, 2014.
20. Stang P, Frank C, Yood MU, Wells K, Burch S, Muma B. Bipolar disorder detection, ascertainment, and treatment: primary care physician knowledge, attitudes, and awareness. *Prim Care Companion J Clin Psychiatry.* 2006;8(3):147-152.
21. Sansone RA, Forbis JS, Sosa T. Primary care perspectives on treating bipolar disorder: a cross-sectional survey. *Prim Care Companion CNS Disord.* 2011;13(2).
22. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey Replication. *Arch Gen Psychiatry.* 2007;64(5):543-552.
23. Ahn YM, Nam JY, Culver JL, Marsh WK, Bonner JC, Ketter TA. Lamotrigine plus quetiapine combination therapy in treatment-resistant bipolar depression. *Ann Clin Psychiatry.* 2011;23(1):17-24.
24. Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RM. The National Depressive and Manic-Depressive Association (DMDA) survey of bipolar members. *J Affect Disord.* 1994;31(4):281-294.
25. McCombs JS, Ahn J, Tencer T, Shi L. The impact of unrecognized bipolar disorders among patients treated for depression with antidepressants in the fee-for-services California Medicaid (Medi-Cal) program: a 6-year retrospective analysis. *J Affect Disord.* 2007;97(1-3):171-179.
26. Crump C, Sundquist K, Winkleby MA, Sundquist J. Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. *JAMA Psychiatry.* 2013;70(9): 931-939.
27. Roshanaei-Moghaddam B, Katon W. Premature mortality from general medical illnesses among persons with bipolar disorder: a review. *Psychiatr Serv.* 2009;60(2): 147-156.
28. Smith DJ, Martin D, McLean G, Langan J, Guthrie B, Mercer SW. Multimorbidity in bipolar disorder and undertreatment of cardiovascular disease: a cross sectional study. *BMC Med.* 2013;11:263.
29. Westman J, Hallgren J, Wahlbeck K, Erlinge D, Alfredsson L, Osby U. Cardiovascular mortality in bipolar disorder: a population-based cohort study in Sweden. *BMJ Open.* 2013;3(4).
30. Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biol Psychiatry.* 2003;54(3):216-226.
31. Ferrari AJ, Norman RE, Freedman G, et al. The burden attributable to mental and substance use disorders as risk factors for suicide: findings from the Global Burden of Disease Study 2010. *PLoS One.* 2014;9(4):e91936.
32. Goldberg JF, Ernst CL. Features associated with the delayed initiation of mood stabilizers at illness onset in bipolar disorder. *J Clin Psychiatry.* 2002;63(11): 985-991.
33. Berk M, Brnabic A, Dodd S, et al. Does stage of illness impact treatment response in bipolar disorder? Empirical treatment data and their implication for the staging model and early intervention. *Bipolar Disord.* 2011;13(1):87-98.
34. Scott J, Paykel E, Morriss R, et al. Cognitive-behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. *Br J Psychiatry.* 2006;188:313-320.
35. Awad AG, Rajagopalan K, Bolge SC, McDonnell DD. Quality of life among bipolar disorder patients misdiagnosed with major depressive disorder. *Prim Care Companion J Clin Psychiatry.* 2007;9(3):195-202.
36. Sussman M, Friedman M, Korn JR, Hassan M, Kim J, Menzin J. The relationship between use of antidepressants and resource utilization among patients with manic or mixed bipolar disorder episodes: findings from a managed care setting. *J Affect Disord.* 2012;138(3):425-432.
37. Pacchiarotti I, Bond DJ, Baldessarini RJ, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am J Psychiatry.* 2013;170(11):1249-1262.
38. Berk M, Malhi GS, Hallam K, et al. Early intervention in bipolar disorders: clinical, biochemical and neuroimaging imperatives. *J Affect Disord.* 2009;114(1-3):1-13.
39. Keck PE Jr, Kessler RC, Ross R. Clinical and economic effects of unrecognized or inadequately treated bipolar disorder. *J Psychiatr Pract.* 2008;14(suppl 2):31-38.
40. Culpepper L. Misdiagnosis of bipolar depression in primary care practices. *J Clin Psychiatry.* 2014;75(3):e05.
41. Carvalho AF, Nunes-Neto PR, Castelo MS, et al. Screening for bipolar depression in family medicine practices: prevalence and clinical correlates. *J Affect Disord.* 2014;162:120-127.
42. Loganathan M, Lohano K, Roberts RJ, Gao Y, El-Mallakh RS. When to suspect bipolar disorder. *J Fam Pract.* 2010;59(12):682-688.
43. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch Gen Psychiatry.* 2003;60(3):261-269.
44. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry.* 2002;59(6):530-537.
45. Baldessarini RJ, Faedda GL, Offidani E, et al. Antidepressant-associated mood-switching and transition from unipolar major depression to bipolar disorder: a review. *J Affect Disord.* 2013;148(1):129-135.
46. Grilo CM, Money R, Barlow DH, et al. Pretreatment patient factors predicting attrition from a multicenter randomized controlled treatment study for panic disorder. *Compr Psychiatry.* 1998;39(6):323-332.
47. Wang PS, Berglund P, Olfson M, Pincus HA, Wells KB, Kessler RC. Failure and delay in initial treatment contact after first onset of mental disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry.* 2005;62(6):603-613.
48. Bowden CL. A different depression: clinical distinctions between bipolar and unipolar depression. *J Affect Disord.* 2005;84(2-3):117-125.
49. Tondo L, Visioli C, Preti A, Baldessarini RJ. Bipolar disorders following initial depression: modeling predictive clinical factors. *J Affect Disord.* 2014;167:44-49.
50. Gill JM, Chen YX, Grimes A, Klinkman MS. Using electronic health record-based tools to screen for bipolar disorder in primary care patients with depression. *J Am Board Fam Med.* 2012;25(3):283-290.
51. Connolly KR, Thase ME. The clinical management of bipolar disorder: a review of evidence-based guidelines. *Prim Care Companion CNS Disord.* 2011;13(4).
52. Abed Faghri NM, Boisvert CM, Faghri S. Understanding the expanding role of primary care physicians (PCPs) to primary psychiatric care physicians (PPCPs): enhancing the assessment and treatment of psychiatric conditions. *Ment Health Fam Med.* 2010;7(1):17-25.
53. Hirschfeld RM, Cass AR, Holt DC, Carlson CA. Screening for bipolar disorder in patients treated for depression in a family medicine clinic. *J Am Board Fam Pract.* 2005;18(4):233-239.
54. Kessler RC, Akiskal HS, Angst J, et al. Validity of the assessment of bipolar spectrum disorders in the WHO CIDI 3.0. *J Affect Disord.* 2006;96(3):259-269.
55. Culpepper L. Does screening for depression in primary care improve outcome? *Curr Psychiatry Rep.* 2012;14(4):345-352.
56. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5.* 5th ed. Arlington, VA: American Psychiatric Association; 2013.

Bipolar Disorder, Bipolar Depression, and Comorbid Illness

J. Sloan Manning, MD

Substantial need exists for the early recognition and treatment of bipolar disorder (BPD) in primary care.[1,2] Bipolar disorder is linked to many other conditions, so its public health impact reaches far beyond the presenting episode of either depression or mania alone.[1] It is a severe, recurring, lifelong, potentially lethal multisystem condition complicated by a multitude of known comorbid conditions, including both psychiatric and physical diagnoses.[3] Unfortunately, the vast majority of these comorbidities may go unrecognized and undertreated in clinical practice.[4]

Bipolar disorder is more than a disturbance of affect and mood.[1] The first and most important step is to accurately differentiate BPD from major depression or other comorbid psychiatric conditions by identifying mania or hypomania in a patient's medical history.[5] Not only must the initial symptoms of BPD be recognized and effectively treated, but prevention of recurrences should be a sustained focus of primary care, the most likely venue for patients to seek psychiatric care.[5,6]

A 2009 systematic review of the literature from 1959 to 2007 reported that, compared with age- and sex-matched control cases in the general population, patients with BPD have a decreased life expectancy because of chronic medical conditions, the pathophysiology of BPD, and lifestyle.[7] The majority of patients with BPD (60%) suffer from one or more comorbid illnesses.[8] When separated into categories, one or more comorbid chronic medical conditions were found in more than 82% of patients with BPD.[9,10] In another study, a comorbid psychiatric diagnosis was reported in 57% of patients with BPD, while 30% had more than one current disorder, primarily anxiety and substance use.[11] Associations with comorbid conditions are frequently reported in bipolar populations, but the reciprocal association is rarely reported.[12]

The interaction between comorbid conditions and BPD progression in depressive or first-episode manic symptoms may be mediated at least in part by inflammatory processes, oxidative stress, apoptosis, and genetic susceptibility in the neurologic, cardiovascular, autoimmune, and other systems.[13-17] We do not yet have discrete biomarkers for BPD, which reinforces the need to improve current methods and accuracy in identifying symptoms, behaviors, histories, and known comorbidities.[16] Unfortunately, many patients with BPD have already accumulated a substantial number of poor prognostic factors for subsequent medical outcomes (eg, childhood traumatic events, family history, early onset of BPD, anxiety disorder, and substance abuse) before being accurately diagnosed with the condition.[18,19] As a result, primary care physicians (PCPs) must be familiar with the clinical features, risk factors, and defining symptomatology of BPD and recognize the potential advantages of integrating primary care and behavioral health for early recognition and intervention.

Treatment of bipolar disorder as a multisystem disorder

Studies characterize BPD as a multisystem, multidimensional disorder.[3] A major feature of BPD is comorbidity or multimorbidity.[20] Both terms describe the array of co-occurring conditions and modifiable risk factors that may be indirectly related to BPD. If left untreated, patients with BPD who have multiple conditions run the risk of relapses and hospitalizations, which impair symptomatic and functional outcomes and lead to higher direct and indirect costs of care than expected from the individual conditions alone.[1,4,21,22] An integrated, collaborative strategy to address multimorbidity has been called for in BPD, but the health care infrastructure has not yet been fully mobilized.[23]

Aggressive, opportunistic screening for comorbid conditions and appropriate management are needed.[24] For medi-

J. Sloan Manning, MD, Adjunct Associate Professor, Department of Family Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; Co-Director, Mood Disorders Clinic, Moses Cone Family Practice Residency, Greensboro, North Carolina

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cal comorbidities, evaluation for hypertension and routine laboratory tests for lipids and hyperglycemia are recommended.[25] A psychiatric referral can be made but, if possible, comorbid issues should be diagnosed and actively managed by the PCP.[5] Simultaneous management may also entail the assistance of an allied health professional, such as a social worker to provide patient education or a caseworker to coordinate care.[6] The emerging model of integrated, collaborative team care may provide a greater range of treatment options in a multidisciplinary environment and better support patients' self-management.[26,27]

Overall, patients with mental illness, compared with those without mental illness, receive lower-quality medical care for a variety of conditions, such as diabetes and cardiovascular disease.[28,29] In one study, patients with a psychiatric diagnosis were less likely to have testing for glycosylated hemoglobin, low-density lipoprotein cholesterol (LDL-C), or eye examinations compared with those who had no psychiatric diagnosis, which implies that patients with BPD may not be receiving screenings for chronic medical disorders.[30] Multiple treatments are often necessary for BPD multimorbidity, and more than half of BPD patients receive 2 or more medications.[31]

Comorbidity related to lifestyle factors

A review of a patient's lifestyle is a significant opportunity to improve the health of all patients, whether at the initial presentation or during follow-up. Several suboptimal lifestyle behaviors and risk factors, including a sedentary lifestyle, tobacco smoking, and obesity, are recognized as being significantly influential in BPD symptom progression and functional impairment.[32] In the 2012 report of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, BPD medical comorbidity was independently associated with smoking and other substance use disorders.[8]

While the foundation of BPD treatment is pharmacotherapy, a healthy diet and physical activity are important whether or not a patient with BPD has underlying cardiovascular risk factors.[33,34] Education about physical activity/exercise, proper nutrition, and wellness is especially needed for patients with BPD. A 2013 review of physical-activity studies in patients with BPD found that suboptimal physical activity was consistently associated with medical comorbidity, social isolation, poor self-efficacy, and lower educational status.[35] However, in a report on a national sample of Veterans Affairs patients, those with BPD were less likely than patients with schizophrenia or no mental illness to report that their provider discussed any nutrition or exercise topic during their office visit. Perhaps it is not surprising, therefore, that patients with BPD, compared with patients without severe mental illness, were more likely to report that they had gained 10 lb in the prior 6 months, had not engaged in walking or strength training, and had poor dietary habits.[36]

Improvements in exercise time, weight, depressive symptoms, and quality of life were reported in patients with BPD who, over 14 weeks, received twelve 60-minute group education sessions on nutrition/weight loss, exercise, and wellness.[37] Another combined nutrition, exercise, and wellness program of cognitive-behavioral therapy for overweight patients with BPD focused on decreasing sugar intake by minimizing or eliminating foods with a high glycemic index. Improvements in cholesterol, triglycerides, body weight, and depressive symptoms were reported, and the participants' stamina tripled over the course of 20 weeks.[38] Such programs can provide an effective method of improving physical and psychiatric outcomes when employed as adjunctive support to ongoing primary care.

Comorbidity related to medical conditions

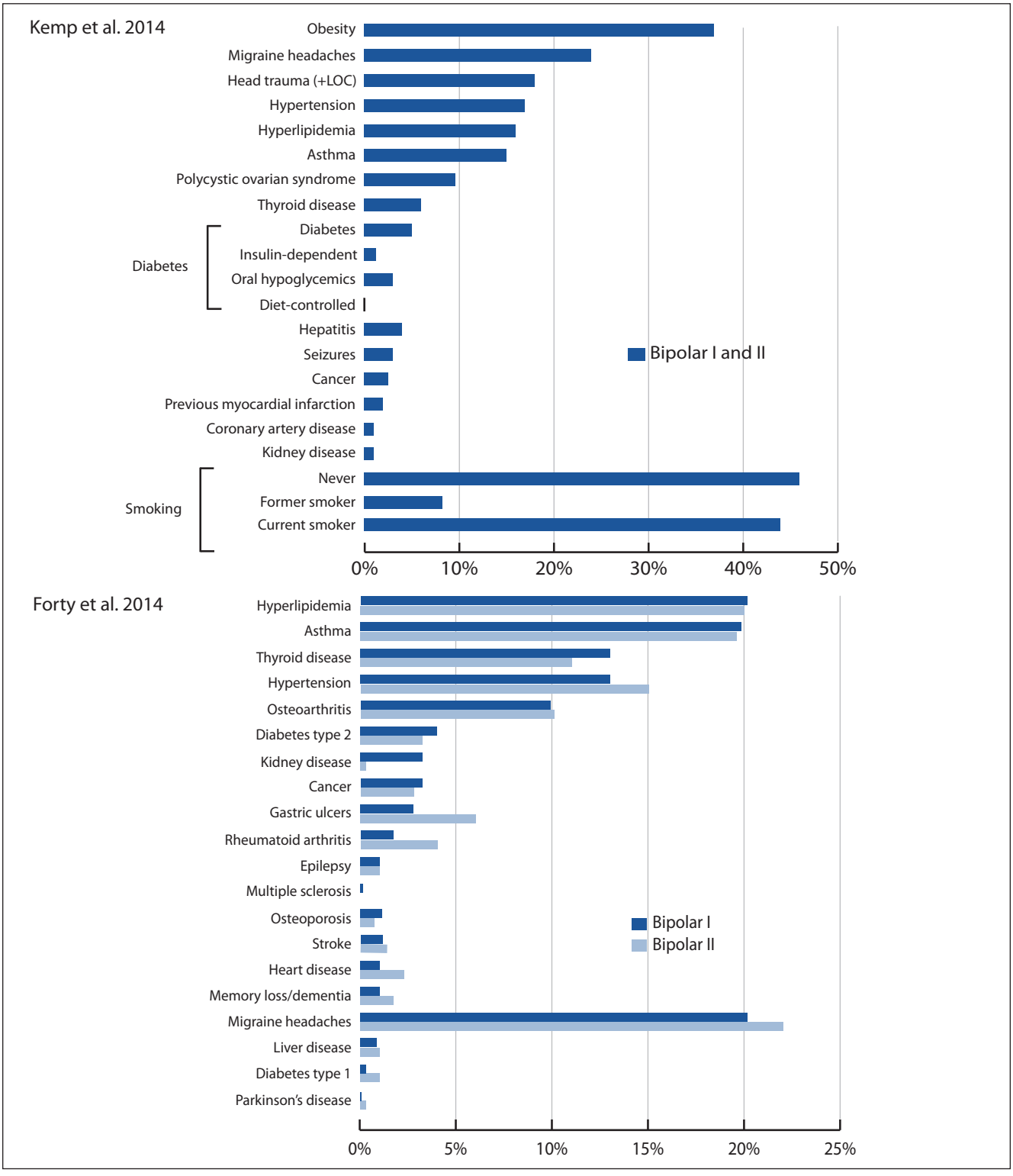
Medical comorbidity has long been considered characteristic of BPD.[8] Although cardiovascular and metabolic issues are the most prevalent in BPD,[4] other body systems should not be overlooked, because neurologic, circadian, and respiratory comorbidities are common. Headache and migraine, sleep disruptions, chronic bronchitis, chronic obstructive pulmonary disease, and asthma have all been reported in patients with BPD more frequently than in individuals without BPD.[10,24,39-41] The **FIGURE** depicts the rates of a number of general medical conditions reported in patients with BPD from 2 different prevalence studies.[9,42]

Cardiovascular risk factors: Diabetes, obesity, and metabolic syndrome

A meta-analysis showed that 37% of patients with BPD had metabolic syndrome, a proportion twice that of the general population.[43] Recent studies have shown that metabolic syndrome is associated with depressive symptomology.[25,44] A review of 17 studies evaluated the mortality rate in patients with BPD compared with matched controls who had other psychiatric illnesses and found cardiovascular diseases to be the most frequent cause of excess mortality.[7] When compared with the general US population, patients with BPD and other severe mental illnesses have 1.5 to 2 times the prevalence of dyslipidemia, hypertension, and obesity and up to 3 times the prevalence of diabetes mellitus.[45,46] Screening for traditional cardiovascular risk factors is warranted in patients with BPD because these risk factors are readily identifiable with established screening approaches and are modifiable.[45]

FIGURE **General medical conditions commonly associated with bipolar disorder[9,42]**

Data from 2 studies published in 2014:
Kemp et al[9]: N = 264, pooled bipolar I (76.9%) and bipolar II (23.1%)
Forty et al[42]: N = 1216, lifetime rates of comorbidities in bipolar I (70.4%) and bipolar II (29.6%)



Abbreviation: LOC, loss of consciousness.

In recent years, obesity has been recognized as an important comorbidity with significant prognostic implications for patients with BPD. Estimates indicate that more than two-thirds of patients with BPD are overweight or obese, a nearly identical finding from 2 recent studies in different US populations (68.5% and 69.0%).[9,47] Rates of obesity, particularly abdominal obesity, are reported to be higher in women with BPD than in men.[48] The synergistic relationship between BPD and obesity is significant for diminished cognitive functioning, greater depressive recurrence, and risk of suicidality.[49]

Management of cardiovascular disease

If cardiovascular risk factors are positively identified, statins may be useful in the treatment of patients with BPD and other psychiatric disorders with these known age-, gender-, and ethnicity-related vulnerabilities. The benefits of statin therapy for primary and secondary prevention have been established.[50] Data suggest that if high LDL-C is not corrected by 3 months of exercise and dietary interventions, a statin could be provided for patients older than 40 years who have a major mental illness, including BPD.[50] After 50 years of age, most patients with BPD who have comorbid diabetes or meet ≥2 criteria for metabolic syndrome should be offered a statin.[50] Further research is needed to establish the benefit of statins in this population for the primary prevention of cardiovascular disease and stroke.[50]

Management of overweight/obesity

In 2013, the American Heart Association, American College of Cardiology, and The Obesity Society updated their joint obesity guidelines for PCPs.[51-53] The structure of the guidelines, based on high-quality evidence, follows the logic of first identifying candidates for intervention by recognizing risks, then advising patients about the risks of unchecked obesity, and then stressing the benefits of weight loss. Only then does the PCP recommend intervention programs, prescribe pharmacotherapy, or refer for bariatric surgery. According to guidance from the US Food and Drug Administration, pharmacologic therapy is approved for patients with a body mass index ≥30 kg/m^2, or ≥27 kg/m^2 if there is an obesity-related comorbidity.[52] As adjuncts to diet and exercise, medications approved for long-term treatment of obesity include orlistat, lorcaserin, phentermine-topiramate, naltrexone-bupropion, and liraglutide.[52] These agents have not been studied specifically in individuals with BPD.

Medications and metabolic disturbances

Certain medications used in the management of BPD are associated with weight gain and/or metabolic side effects.[54] Mood stabilizers and atypical antipsychotics are the major pharmacotherapy classes used for the treatment of BPD. Side effects of mood stabilizers are well documented.[55] Lithium and valproate are associated with moderate weight gain, whereas lamotrigine causes little weight gain.[55] Olanzapine is associated with a higher risk of diabetes, dyslipidemia, and weight gain; quetiapine and risperidone are associated with a moderate risk; and aripiprazole, lurasidone, and ziprasidone are associated with a low risk.[25,55,56]

Comorbidity related to psychiatric conditions

Adequate screening for psychiatric comorbidities is necessary because they complicate the diagnosis and treatment of BPD, potentially worsening its course and prognosis.[57] Several psychiatric comorbidities frequently accompany BPD, including substance use, anxiety disorders, impulse control and personality disorders, eating disorders, attention-deficit hyperactivity disorder, and suicidality.[57-59]

Substance or alcohol use

The prevalence of substance abuse among individuals with BPD is estimated to be 40% to 70%.[60] In a study of patients with BPD and current depression, those with a past or current substance use disorder showed significantly worse functioning and a higher risk of suicide than individuals without such a history.[61] Valproate may have a favorable effect in decreasing the use of alcohol.[62] The second-generation antipsychotic aripiprazole has been shown to reduce drug craving.[63]

Anxiety disorders

Anxiety disorders and BPD may have a close neurologic relationship, but more research is needed to clarify the association and determine optimal treatment.[64] Unfortunately, there are no randomized trials of treatments for comorbid anxiety in patients with BPD, and a review showed that lithium monotherapy or anticonvulsants alone were generally not effective.[57,65] Reductions in anxiety symptomatology associated with BPD or depression may, however, accompany treatment with some atypical antipsychotics and mood stabilizers.[66,67]

Anxiety disorders include panic disorder, social phobia, obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), and post-traumatic stress disorder (PTSD).[64] Comorbid anxiety disorders have been linked to greater illness severity in patients with BPD compared with patients who have BPD but no anxiety disorders.[68] Panic disorder is much more prevalent in patients with bipolar illness than in the general population and is manifest in bipolar mixed states.[64] Obsessive-compulsive disorder is 8 times more prevalent in patients with BPD than in the general population, with a lifetime comorbid rate of 11% to 21%.[68] A 2014 double-

blind, placebo-controlled, randomized clinical trial of topiramate for OCD in patients with BPD reported significantly better efficacy than placebo in ameliorating OCD.[69] Longitudinal studies have shown poor clinical outcomes for patients with both BPD and anxiety, and a correlation has been found between the presence of anxiety symptoms and the duration and severity of depression in patients with BPD.[70-72] A dose-like effect was seen, with more anxiety symptoms correlating to longer depressive morbidity.

There is limited evidence for pharmacologic treatment of comorbid anxiety disorders. It is recommended that psychotherapeutic approaches be tried first, given the lack of compelling efficacy data.[73] Social phobia, panic symptomatology, and PTSD appear most closely associated with impaired time to recovery.[74,75] Cognitive-behavioral therapy has been reported to be effective in patients with BPD, specifically in attenuating OCD, GAD, panic disorder, and PTSD.[76]

Antidepressant use for unipolar depression and anxiety

The use of antidepressants (eg, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors) in combination with mood stabilizers did not show long-term effectiveness of symptomatic benefit in patients with BPD and depression compared with the continued use of mood stabilizers alone.[77] A 2011 meta-analysis also revealed that antidepressants failed to provide a significant clinical response or remission of depressive symptoms in BPD compared with placebo or other standard treatments.[78] Likewise, a meta-analysis performed in 2013 by the International Society for Bipolar Disorders task force reported insufficient evidence of antidepressant effectiveness in combination with mood stabilizers.[79]

Antidepressants, especially venlafaxine and tricyclics, have also been associated with rapid switching to mania or hypomania.[80] Second-generation antipsychotics may offer direct or adjunctive benefits in conjunction with mood stabilizers to protect against bipolar mood switching.[81]

Conclusions

Both medical and psychiatric comorbidities are very common in BPD, and patients should be screened for the detection and management of BPD as well as the conditions themselves. If comorbid conditions are recognized and treated, serious adverse health outcomes may be averted, including substantial morbidity and mortality. Lifestyle interventions are underutilized, and some evidence indicates the efficacy of dietary measures, particularly in tandem with physical activity and wellness programs. Therapies differ with regard to the risk of weight gain, glucose elevation, and dyslipidemia; clinicians should consider metabolic adverse effects in the pharmacologic management of BPD. Anxiety disorders are likely to share similar pathophysiologic origins as BPD, and although this relationship requires clarification, it is clear that comorbid anxiety leads to worse outcomes in patients with BPD. Psychotherapeutic approaches to comorbid anxiety disorders are recommended.

Although challenges remain, both medical and psychiatric comorbid conditions in patients with BPD can be successfully detected, treated, and monitored in the primary care setting. ●

REFERENCES

1. Conus P, Macneil C, McGorry PD. Public health significance of bipolar disorder: implications for early intervention and prevention. *Bipolar Disord.* 2014;16(5):548-556.
2. Brietzke E, Mansur RB, Soczynska JK, Kapczinski F, Bressan RA, McIntyre RS. Towards a multifactorial approach for prediction of bipolar disorder in at risk populations. *J Affect Disord.* 2012;140(1):82-91.
3. Leboyer M, Soreca I, Scott J, et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? *J Affect Disord.* 2012;141(1):1-10.
4. Fagiolini A, Goracci A. The effects of undertreated chronic medical illnesses in patients with severe mental disorders. *J Clin Psychiatry.* 2009;70 (suppl 3):22-29.
5. Culpepper L. The diagnosis and treatment of bipolar disorder: decision-making in primary care. *Prim Care Companion CNS Disord.* 2014;16(3).
6. Cerimele JM, Chan YF, Chwastiak LA, Avery M, Katon W, Unutzer J. Bipolar disorder in primary care: clinical characteristics of 740 primary care patients with bipolar disorder. *Psychiatr Serv.* 2014;65(8):1041-1046.
7. Roshanaei-Moghaddam B, Katon W. Premature mortality from general medical illnesses among persons with bipolar disorder: a review. *Psychiatr Serv.* 2009;60(2): 147-156.
8. Magalhaes PV, Kapczinski F, Nierenberg AA, et al. Illness burden and medical comorbidity in the Systematic Treatment Enhancement Program for Bipolar Disorder. *Acta Psychiatr Scand.* 2012;125(4):303-308.
9. Kemp DE, Sylvia LG, Calabrese JR, et al. General medical burden in bipolar disorder: findings from the LiTMUS comparative effectiveness trial. *Acta Psychiatr Scand.* 2014;129(1):24-34.
10. Kilbourne AM, Cornelius JR, Han X, et al. Burden of general medical conditions among individuals with bipolar disorder. *Bipolar Disord.* 2004;6(5):368-373.
11. Bauer MS, Altshuler L, Evans DR, Beresford T, Williford WO, Hauger R. Prevalence and distinct correlates of anxiety, substance, and combined comorbidity in a multisite public sector sample with bipolar disorder. *J Affect Disord.* 2005;85(3):301-315.
12. McIntyre RS, Soczynska JK, Beyer JL, et al. Medical comorbidity in bipolar disorder: reprioritizing unmet needs. *Curr Opin Psychiatry.* 2007;20(4):406-416.
13. Noto MN, de Souza Noto C, de Jesus DR, et al. Recognition of bipolar disorder type I before the first manic episode: challenges and developments. *Expert Rev Neurother.* 2013;13(7):795-806; quiz 807.
14. Brown NC, Andreazza AC, Young LT. An updated meta-analysis of oxidative stress markers in bipolar disorder. *Psychiatry Res.* 2014;218(1-2):61-68.
15. Berk M, Berk L, Dodd S, et al. Stage managing bipolar disorder. *Bipolar Disord.* 2014;16(5):471-477.
16. Frey BN, Andreazza AC, Houenou J, et al. Biomarkers in bipolar disorder: a positional paper from the International Society for Bipolar Disorders Biomarkers Task Force. *Aust N Z J Psychiatry.* 2013;47(4):321-332.
17. Perugi G, Quaranta G, Belletti S, et al. General medical conditions in 347 bipolar disorder patients: clinical correlates of metabolic and autoimmune-allergic diseases. *J Affect Disord.* 2015;170:95-103.
18. Post RM, Altshuler LL, Leverich GS, et al. Illness progression as a function of independent and accumulating poor prognosis factors in outpatients with bipolar disorder in the United States. *Prim Care Compan CNS Disord.* 2014;16:19-26.
19. Post RM, Altshuler L, Leverich GS, et al. Relationship of clinical course of illness variables to medical comorbidities in 900 adult outpatients with bipolar disorder. *Compr Psychiatry.* 2015;56:21-28.
20. Smith DJ, Martin D, McLean G, Langan J, Guthrie B, Mercer SW. Multimorbidity in bipolar disorder and undertreatment of cardiovascular disease: a cross sectional study. *BMC Med.* 2013;11:263.
21. Scott J, Leboyer M. Consequences of delayed diagnosis of bipolar disorders. *Encephale.* 2011;37(suppl 3):S173-175.
22. Keck PE Jr, Kessler RC, Ross R. Clinical and economic effects of unrecognized or inadequately treated bipolar disorder. *J Psychiatr Pract.* 2008;14(suppl 2):31-38.
23. Culpepper L. Does screening for depression in primary care improve outcome? *Curr*

Psychiatry Rep. 2012;14(4):345-352.
24. 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(8):1140-1144.
25. McElroy SL, Keck PE Jr. Metabolic syndrome in bipolar disorder: a review with a focus on bipolar depression. *J Clin Psychiatry.* 2014;75(1):46-61.
26. Woltmann E, Grogan-Kaylor A, Perron B, Georges H, Kilbourne AM, Bauer MS. Comparative effectiveness of collaborative chronic care models for mental health conditions across primary, specialty, and behavioral health care settings: systematic review and meta-analysis. *Am J Psychiatry.* 2012;169(8):790-804.
27. Cerimele JM, Ratzliff A, Sexton JM. Collaborative care for a patient with bipolar disorder in primary care: a case example. *Gen Hosp Psychiatry.* 2015;37(2):144-146.
28. Frayne SM, Halanych JH, Miller DR, et al. Disparities in diabetes care: impact of mental illness. *Arch Intern Med.* 2005;165(22):2631-2638.
29. Hippisley-Cox J, Parker C, Coupland C, Vinogradova Y. Inequalities in the primary care of patients with coronary heart disease and serious mental health problems: a cross-sectional study. *Heart.* 2007;93(10):1256-1262.
30. Leung GY, Zhang J, Lin WC, Clark RE. Behavioral health disorders and adherence to measures of diabetes care quality. *Am J Manag Care.* 2011;17(2):144-150.
31. Ventimiglia J, Kalali AH, McIntyre R. Treatment of bipolar disorder. *Psychiatry (Edgmont).* 2009;6(10):12-14.
32. Cerimele JM, Katon WJ. Associations between health risk behaviors and symptoms of schizophrenia and bipolar disorder: a systematic review. *Gen Hosp Psychiatry.* 2013;35(1):16-22.
33. Reininghaus EZ, Lackner N, Fellendorf FT, et al. Weight cycling in bipolar disorder. *J Affect Disord.* 2015;171:33-38.
34. Ruel G, Shi Z, Zhen S, et al. Association between nutrition and the evolution of multimorbidity: the importance of fruits and vegetables and whole grain products. *Clin Nutr.* 2014;33(3):513-520.
35. Vancampfort D, Correll CU, Probst M, et al. A review of physical activity correlates in patients with bipolar disorder. *J Affect Disord.* 2013;145(3):285-291.
36. Kilbourne AM, Rofey DL, McCarthy JF, Post EP, Welsh D, Blow FC. Nutrition and exercise behavior among patients with bipolar disorder. *Bipolar Disord.* 2007;9(5):443-452.
37. Sylvia LG, Nierenberg AA, Stange JP, Peckham AD, Deckersbach T. Development of an integrated psychosocial treatment to address the medical burden associated with bipolar disorder. *J Psychiatr Pract.* 2011;17(3):224-232.
38. Sylvia LG, Salcedo S, Bernstein EE, Baek JH, Nierenberg AA, Deckersbach T. Nutrition, exercise, and wellness treatment in bipolar disorder: proof of concept for a consolidated intervention. *Int J Bipolar Disord.* 2013;1(1):24.
39. Dilsaver SC, Benazzi F, Oedegaard KJ, Fasmer OB, Akiskal HS. Is a family history of bipolar disorder a risk factor for migraine among affectively ill patients? *Psychopathology.* 2009;42(2):119-123.
40. Soreca I, Buttenfield JA, Hall MH, Kupfer DJ. Screening for obstructive sleep apnea in patients with bipolar I disorder: comparison between subjective and objective measures. *Bipolar Disord.* 2015;17(3):345-348.
41. Alonso J, de Jonge P, Lim CC, et al. Association between mental disorders and subsequent adult onset asthma. *J Psychiatr Res.* 2014;59:179-188.
42. Forty L, Ulanova A, Jones L, et al. Comorbid medical illness in bipolar disorder. *Br J Psychiatry.* 2014;205(6):465-472.
43. Vancampfort D, Vansteelandt K, Correll CU, et al. Metabolic syndrome and metabolic abnormalities in bipolar disorder: a meta-analysis of prevalence rates and moderators. *Am J Psychiatry.* 2013;170(3):265-274.
44. McIntyre RS, Rasgon NL, Kemp DE, et al. Metabolic syndrome and major depressive disorder: co-occurrence and pathophysiologic overlap. *Curr Diab Rep.* 2009;9(1):51-59.
45. Newcomer JW, Hennekens CH. Severe mental illness and risk of cardiovascular disease. *JAMA.* 2007;298(15):1794-1796.
46. McIntyre RS, Konarski JZ, Misener VL, Kennedy SH. Bipolar disorder and diabetes mellitus: epidemiology, etiology, and treatment implications. *Ann Clin Psychiatry.* 2005;17(2):83-93.
47. Depp CA, Strassnig M, Mausbach BT, et al. Association of obesity and treated hypertension and diabetes with cognitive ability in bipolar disorder and schizophrenia. *Bipolar Disord.* 2014;16(4):422-431.
48. Baskaran A, Cha DS, Powell AM, Jalil D, McIntyre RS. Sex differences in rates of obesity in bipolar disorder: postulated mechanisms. *Bipolar Disord.* 2014;16(1):83-92.
49. Liu CS, Carvalho AF, Mansur RB, McIntyre RS. Obesity and bipolar disorder: synergistic neurotoxic effects? *Adv Ther.* 2013;30(11):987-1006.
50. Andrade C. Primary prevention of cardiovascular events in patients with major mental illness: a possible role for statins. *Bipolar Disord.* 2013;15(8):813-823.
51. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol.* 2014;63(25 pt B):2985-3023.
52. Kushner RF. Weight loss strategies for treatment of obesity. *Prog Cardiovasc Dis.* 2014;56(4):465-472.
53. Kushner RF, Ryan DH. Assessment and lifestyle management of patients with obesity: clinical recommendations from systematic reviews. *JAMA.* 2014;312(9):943-952.
54. Nihalani N, Schwartz TL, Siddiqui UA, Megna JL. Weight gain, obesity, and psychotropic prescribing. *J Obes.* 2011;2011:893629.
55. Kemp DE. Managing the side effects associated with commonly used treatments for bipolar depression. *J Affect Disord.* 2014;169(suppl 1):S34-S44.
56. The Medical Letter. February 21, 2011 (Issue 1358). Available at: http://secure.medicalletter.org/. Accessed February 3, 2015.
57. Singh JB, Zarate CA Jr. Pharmacological treatment of psychiatric comorbidity in bipolar disorder: a review of controlled trials. *Bipolar Disord.* 2006;8(6):696-709.
58. Valtonen H, Suominen K, Mantere O, Leppamaki S, Arvilommi P, Isometsa ET. Suicidal ideation and attempts in bipolar I and II disorders. *J Clin Psychiatry.* 2005;66(11):1456-1462.
59. McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *Am J Psychiatry.* 2001;158(3):420-426.
60. Ostacher MJ, Sachs GS. Update on bipolar disorder and substance abuse: recent findings and treatment strategies. *J Clin Psychiatry.* 2006;67(9):e10.
61. Ostacher MJ, Perlis RH, Nierenberg AA, et al. Impact of substance use disorders on recovery from episodes of depression in bipolar disorder patients: prospective data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry.* 2010;167(3):289-297.
62. Salloum IM, Cornelius JR, Daley DC, Kirisci L, Himmelhoch JM, Thase ME. Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism: a double-blind placebo-controlled study. *Arch Gen Psychiatry.* 2005;62(1):37-45.
63. Brown ES, Jeffress J, Liggin JD, Garza M, Beard L. Switching outpatients with bipolar or schizoaffective disorders and substance abuse from their current antipsychotic to aripiprazole. *J Clin Psychiatry.* 2005;66(6):756-760.
64. Vazquez GH, Baldessarini RJ, Tondo L. Co-occurrence of anxiety and bipolar disorders: clinical and therapeutic overview. *Depress Anxiety.* 2014;31(3):196-206.
65. Keck PE Jr, Strawn JR, McElroy SL. Pharmacologic treatment considerations in co-occurring bipolar and anxiety disorders. *J Clin Psychiatry.* 2006;67(suppl 1):8-15.
66. Sheehan DV, Harnett-Sheehan K, Hidalgo RB, et al. Randomized, placebo-controlled trial of quetiapine XR and divalproex ER monotherapies in the treatment of the anxious bipolar patient. *J Affect Disord.* 2013;145(1):83-94.
67. Loebel A, Cucchiaro J, Silva R, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry.* 2014;171(2):160-168.
68. Amerio A, Odone A, Liapis CC, Ghaemi SN. Diagnostic validity of comorbid bipolar disorder and obsessive-compulsive disorder: a systematic review. *Acta Psychiatr Scand.* 2014;129(5):343-358.
69. Sahraian A, Bigdeli M, Ghanizadeh A, Akhondzadeh S. Topiramate as an adjuvant treatment for obsessive compulsive symptoms in patients with bipolar disorder: a randomized double blind placebo controlled clinical trial. *J Affect Disord.* 2014;166:201-205.
70. Goes FS. The importance of anxiety states in bipolar disorder. *Curr Psychiatry Rep.* 2015;17(2):540.
71. Coryell W, Solomon DA, Fiedorowicz JG, Endicott J, Schettler PJ, Judd LL. Anxiety and outcome in bipolar disorder. *Am J Psychiatry.* 2009;166(11):1238-1243.
72. Coryell W, Fiedorowicz JG, Solomon D, Leon AC, Rice JP, Keller MB. Effects of anxiety on the long-term course of depressive disorders. *Br J Psychiatry.* 2012;200(3):210-215.
73. Rakofsky JJ, Dunlop BW. Treating nonspecific anxiety and anxiety disorders in patients with bipolar disorder: a review. *J Clin Psychiatry.* 2011;72(1):81-90.
74. Feske U, Frank E, Mallinger AG, et al. Anxiety as a correlate of response to the acute treatment of bipolar I disorder. *Am J Psychiatry.* 2000;157(6):956-962.
75. 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):500-508.
76. Provencher MD, Hawke LD, Thienot E. Psychotherapies for comorbid anxiety in bipolar spectrum disorders. *J Affect Disord.* 2011;133(3):371-380.
77. Ghaemi SN, Ostacher MM, El-Mallakh RS, et al. Antidepressant discontinuation in bipolar depression: a Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) randomized clinical trial of long-term effectiveness and safety. *J Clin Psychiatry.* 2010;71(4):372-380.
78. Sidor MM, MacQueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. *J Clin Psychiatry.* 2011;72(2):156-167.
79. Pacchiarotti I, Bond DJ, Baldessarini RJ, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am J Psychiatry.* 2013;170(11):1249-1262.
80. Post RM, Altshuler LL, Leverich GS, et al. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. *Br J Psychiatry.* 2006;189:124-131.
81. Vieta E, Angst J, Reed C, Bertsch J, Haro JM. Predictors of switching from mania to depression in a large observational study across Europe (EMBLEM). *J Affect Disord.* 2009;118(1-3):118-123.

Evidence-Based Treatment of Bipolar Disorder, Bipolar Depression, and Mixed Features

Roger S. McIntyre, MD, FRCPC

Bipolar disorder (BPD) is commonly encountered in the primary care setting. The high rate of misdiagnosis of BPD highlights the need for timely and accurate diagnosis and initiation of evidence-based treatments to avoid progression of untreated disease.[1-5] Timely recognition is often challenging because the early presentation of BPD is nonspecific, involving a confluence of mood, anxiety, and cognitive symptoms, and often manifests at the subthreshold level.[3,4,6-8] Establishing an accurate diagnosis and implementing guideline-concordant care offer the opportunity for improved health outcomes in patients with BPD.

Primary care providers (PCPs) are ideally positioned to initiate pharmacologic and psychosocial treatment as part of an integrated, accountable care plan for BPD once a diagnosis has been accurately established.[9] When BPD is diagnosed in the primary care setting, optimal pharmacologic and nonpharmacologic treatment is achievable.[10-12] Early recognition is important. If BPD progresses untreated, a response to treatment becomes less likely, and more complex therapeutic management is required to achieve sustained improvement.[13,14]

The goals of BPD treatment are to stabilize symptoms, prevent relapse, and optimize function (**TABLE 1**).[15] Increasingly, BPD is conceptualized as a chronic disease, as evidenced by the enduring subsyndromal symptoms, sleep difficulties, cognitive dysfunction, psychiatric and medical comorbidity, as well as clinically significant mood reactivity. Clinicians planning care pathways for individuals with BPD must anticipate this long-term course.

Roger S. McIntyre, MD, FRCPC, Professor of Psychiatry and Pharmacology, Head, Mood Disorders Psychopharmacology Unit, University Health Network, University of Toronto, Toronto, Ontario

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Pharmacotherapy for bipolar disorder: General principles

Prescribing trends and polypharmacy

Replicated evidence indicates that antidepressant prescription in BPD is common. However, antidepressants are not indicated for patients with BPD because of their lack of proven efficacy in registration trials as well as the possibility of mood destabilization in subsets of individuals with BPD.[16] A 2009 study reported that while 71% of patients with BPD were prescribed an atypical antipsychotic and 53% received a mood stabilizer, 30% received an antidepressant.[17] The complexity of BPD often invites the need for complex polypharmacy regimens integrated with patient education and psychosocial treatments in an integrated and accountable management plan.[17]

Number needed to treat and number needed to harm

For any treatment strategy, whether monotherapy or combination therapy, the practitioner must carefully consider efficacy, tolerability, and safety as treatment is tailored for every individual.[18-21] The number needed to treat (NNT) and the number needed to harm (NNH) are practical aids for treatment decisions.[22-25] The NNT describes the efficacy of a given treatment by quantifying the number of patients who would have to be treated to achieve a single desired outcome, with lower numbers preferred (ie, <10).[24] The NNH describes the number of patients exposed who are expected to yield an additional adverse event. A high NNH is desirable, preferably >10.[24] **TABLE 2** summarizes the NNT and NNH of pharmacologic options for the treatment of bipolar depression and mania.[26,27]

TABLE 1 Goals of treatment for bipolar disorder[15]

Goal	Description
Stabilize	The primary goal is stabilizing mood disturbance • Mania and/or • Depression
Prevent	Once stability is achieved, relapse prevention is the goal • Encourage adherence and proactivity, including patients' symptom tracking • Mobilize family and social support
Maximize function	Maximize function (family, social, work) over the long term • Reassess treatment goals • Mobilize nonpharmacologic therapies to address dysfunctional cognitive and behavioral patterns

Assessing response to treatment

The response to treatment should be a routine assessment priority that may be systematized with the electronic medical record and the use of measurement tools to capture symptoms and functioning from both the patient's and provider's perspectives. The Young Mania Rating Scale and the Montgomery-Asberg Depression Rating Scale are widely used clinician-rated scales for assessing symptom severity.[28,29]

Several factors may influence the likelihood of responding to treatment, including (but not limited to) the type of illness (bipolar I or bipolar II), number of prior episodes, existence of comorbidity, and phase as well as stage of treatment. For example, patients with 1 to 5 prior depression episodes are 60% more likely to respond to treatment compared with patients with >10 previous episodes (odds ratio [OR] 1.6; 95% confidence interval [CI] 1.02-2.40).[2] When formulating the overall treatment strategy, the PCP should anticipate the multidimensionality of the illness and assess comorbidity before initiating any treatment.

Monotherapy treatment in bipolar disorder

Reviewing the extant literature for monotherapy in BPD is beyond the scope of this article. Nevertheless, clinicians should aim to use monotherapy whenever feasible to reduce the potential for medicine-related complications (including adverse effects and drug-drug interactions) and be cautious when considering combination therapy.[30] A 2012 study found that monotherapy was associated with fewer adverse effects and lower discontinuation rates compared with combination therapy.[31] Efficacy of monotherapy for acute bipolar depression has been demonstrated in a meta-analysis for olanzapine-fluoxetine combination (OFC), quetiapine, and lurasidone.[22] For relapse prevention, lithium monotherapy has been reported to be superior to divalproex monotherapy.[32] Lamotrigine is approved by the Food and Drug Administration (FDA) for BPD maintenance treatment as monotherapy.[26] There is inadequate research supporting the use of antidepressant monotherapy in acute BPD depression, and it is generally discouraged in the treatment of BPD as it can lead to switching to mania.[33,34]

Combination therapy in bipolar disorder

The following is a brief review of key elements in combination therapy for BPD. Combination therapy may be necessary when monotherapy is insufficient to fully treat acute and breakthrough episodes during maintenance. A meta-analysis of combination therapy concluded that an antipsychotic plus lithium is superior to lithium monotherapy for acute mania.[35] For relapse prevention, lithium plus divalproex has also been shown to be superior to divalproex monotherapy.[32] A placebo-controlled trial demonstrated that quetiapine plus lithium or divalproex was superior to a mood stabilizer alone for prevention of manic and depressive recurrences regardless of the type of index episode.[36] Separate randomized clinical trials of the combination of ziprasidone or olanzapine plus a mood stabilizer compared to a mood stabilizer alone demonstrated a relapse rate in favor of the combination.[37,38] Treatment with lurasidone adjunctive to lithium or divalproex significantly improved depressive symptoms compared with a mood stabilizer alone.[39]

Adverse effects, tolerability, and adherence

A timely and accurate diagnosis, followed by initiation of pharmacotherapy, is the foundation of treatment for BPD. It is important to identify treatments that are well tolerated and likely to be accepted so that patients with BPD will adhere to the treatment for optimal outcomes.[40] Adverse effects of mood stabilizers and/or various atypical antipsychotic agents have been reported in specific domains, including antihistaminergic (sedation, weight gain), anticholiner-

TABLE 2 Pharmacologic treatment options for bipolar disorder[26,27]

Agent	Starting dose	Target dose	NNT	NNH
Acute depression				
Lurasidone	20 mg once daily	20 to 120 mg once daily	5	15
Olanzapine-fluoxetine (OFC)	3 mg/25 mg to 6 mg/25 mg once daily in the evening	6 mg/25 mg to 12 mg/50 mg	4	6
Quetiapine	50 mg once daily at bedtime	300 mg once daily at bedtime	6	5
Acute mania				
Carbamazepine	200 mg twice daily	200 mg once daily to 800 mg twice daily	4	6
Divalproex	IR: 750 mg daily in divided doses ER: 25 mg/kg once daily	IR: 60 mg/kg daily ER: 60 mg/kg daily	7	7
Lithium*	300 to 900 mg 1 to 2 times daily; titrate to serum level of 0.6 to 1.5 mEq/L	900 to 1800 mg per day	4	27
Aripiprazole*	10 to 15 mg once daily if adjunctive therapy 15 mg once daily if monotherapy	15 to 30 mg once daily	5	9
Asenapine	5 mg sublingual twice daily if adjunctive therapy 10 mg sublingual twice daily if monotherapy	10 mg sublingual twice daily	8	11
Olanzapine*	10 mg once daily if adjunctive therapy 10 to 15 mg once daily if monotherapy	5 to 20 mg once daily	5	5
Quetiapine*	XR: 300 mg once daily IR: 50 mg twice daily	400 to 800 mg per day (XR once daily or IR twice daily)	6	9
Risperidone	2 to 3 mg/day	1 to 6 mg per day	4	5
Ziprasidone*	40 mg twice daily	40 to 80 mg twice daily	7	5

ER, extended release; IR, immediate release; NNH, number needed to harm for specific adverse effect compared with placebo (higher is better); NNT, number needed to treat for response compared with placebo (lower is better); XR, extended release.

*Approved for bipolar maintenance; quetiapine (XR and IR) and ziprasidone are approved for maintenance only as adjunctive therapy.

gic (dry mouth, constipation), alpha-1 blockade (dizziness, orthostasis), dopamine antagonism (hyperprolactinemia, psychomotor slowing, extrapyramidal symptoms [EPS]), and increased serotonergic effect (sexual dysfunction).[41] Time to recurrence of depressive episodes has been reported to be significantly shorter in obese versus nonobese patients, so weight-loss measures are advised in these patients, as is the consideration of using BPD pharmacotherapies known to have fewer metabolic side effects.[18,42-44]

Features of BPD that influence treatment decisions

Cognition

Bipolar disorder is a complex disorder that usually presents with one or more comorbid conditions. Altered cognition, impaired attention, difficulties with communication, and related behavior patterns can be barriers to a patient's interaction with the health care system and may affect both readiness for treatment and adherence, and ultimately affect the quality of treatment. Cognitive impairment has also been found to be associated with some comorbid conditions. For instance, a 2012 study of BPD patients found greater cognitive impairment in overweight or obese patients (body mass index [BMI] ≥25.0 kg/m^2; n=48) compared with normal-weight patients (BMI 18.5 to 24.9 kg/m^2; n=19), particularly in the domains of attention, psychomotor processing, and overall verbal fluency.[45] In addition, a meta-analysis reported that patients with bipolar II had significantly lower cognitive performance than healthy controls and at nearly the same severity as bipolar I.[46]

Mixed features

One of the more heterogeneous clinical presentations of BPD is the phenomenon of mixed mood states. Mixed states or mixed

features are conceptualized as the co-occurrence of manic and depressive symptoms. Mixed features during a depressive episode appear to be very common. For example, in a study of 1380 patients experiencing an index episode of bipolar depression, 54% had subsyndromal mania.[47] The recent designation of mixed features in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) recognizes subsyndromal depressive symptoms while manic, or subsyndromal manic symptoms while depressed. For example, a patient with mixed features can meet the full criteria for a manic episode and have only a minimum of 3 of the symptoms of a major depressive episode.[48] Conversely, he or she may meet all the criteria for major depressive disorder and have 3 or more of the symptoms of mania or hypomania.[48]

Patients with a mixed presentation may have a suboptimal response to pharmacotherapy compared with those presenting with a manic or depressive episode, and these patients have an increased risk of subsequent affective episodes.[49] The principal challenge of treating these patients is to simultaneously address both manic and depressive symptoms. There are currently no evidence-based guidelines to specifically address the treatment of patients falling into the category of DSM-defined mixed features. For patients with mixed symptoms during mania, atypical antipsychotics and divalproex are effective.[50] The evidence base is larger for the use of atypical antipsychotics in mixed states, for which they have demonstrated mitigation of manic and depressive symptoms. Divalproex also is capable of mitigating manic/hypomanic as well as depressive symptoms in adults with mixed mania and mixed hypomania.[51-53] However, there is an absence of replicated evidence documenting antidepressant effects with divalproex in large placebo-controlled trials. Patients with BPD and mixed features should not be treated with antidepressant monotherapy because of a risk of greater mania severity or switching to mania.[54]

Pharmacologic treatment options

The following provides a brief summary of the pharmacologic agents used in the treatment of BPD.

Antidepressants

No antidepressant is FDA approved for BPD as monotherapy. Of note, fluoxetine in combination with olanzapine is approved. Antidepressants are used in up to 30% of bipolar treatment regimens, as reported by the SDI/Verispan's Prescription Drug and Diagnosis Audit prescribing database from 3100 office-based US physicians across 29 specialties.[17] Antidepressants are problematic in the treatment of BPD depression because of their lack of efficacy and variability of outcomes, including multiple medication treatment failures and treatment resistance. A meta-analysis reported that augmentation with an antidepressant does not improve response rates or remissions beyond the effects of mood stabilizers alone.[55]

The risk-benefit profile for the use of antidepressant medications in patients with BPD is controversial. The International Society for Bipolar Disorders evaluated the evidence base for efficacy and safety of antidepressant medications in BPD.[33] The society concluded that there was insufficient evidence to endorse the use of antidepressants, but acknowledged that individual patients may benefit from antidepressants. Selective serotonin reuptake inhibitors and bupropion may be less likely to induce manic switching than tricyclic/tetracyclic antidepressants or serotonin-norepinephrine reuptake inhibitors.[33]

Mood stabilizers and anticonvulsants

Lithium and selected anticonvulsants are possible therapeutic options for the treatment of BPD, but lithium and anticonvulsants are not approved for bipolar depression.[56-60] Lamotrigine is approved as maintenance therapy for the prevention of mood episodes (mania, depression, hypomania, and mixed episodes).[61]

Lithium. Lithium is an important pharmacotherapy for regulation of mood in patients with BPD and it decreases the risk of suicide in these patients. The antisuicide effect of lithium is purported to act in part by decreasing aggression and impulsivity.[62] Lithium is approved for mania and for maintenance only (not for mixed features).[63] Both lithium monotherapy and lithium plus divalproex in combination have been shown to be more effective than divalproex monotherapy to prevent BPD relapse.[32] Common and mild adverse effects include tremor, fatigue, lethargy, dry mouth, dehydration, polyuria, weight gain, and gastrointestinal effects.[63]

Divalproex. Divalproex is approved for the treatment of mania only and is not approved for mixed features or maintenance treatment.[64] Divalproex plus lamotrigine was found to be superior to lamotrigine monotherapy for depressive symptoms.[65] For prevention of relapse, divalproex plus lithium achieved a sustained benefit lasting up to 2 years as compared with divalproex monotherapy (hazard ratio 0.59; 95% CI 0.42-0.83; $P = .0023$).[32] Adjunctive use of divalproex with an atypical antipsychotic may be effective for depression in some patients.[39] Common adverse effects include nausea, weight gain, and, less commonly, metabolic and menstrual irregularities.[66,67] Because of the risk of neural tube defects and other teratogenic effects, women of childbearing potential should use divalproex only when essential.[64]

Lamotrigine. Lamotrigine is approved for BPD maintenance only and is not approved for acute mania or depression.[61] Two randomized controlled trials indicated that

lamotrigine was superior to placebo in the maintenance and prevention of depressive symptoms in patients with BPD.[68,69] In double-blind, placebo-controlled studies of acute bipolar depression, however, lamotrigine showed inadequate efficacy as demonstrated by a double-digit NNT (eg, >10).[70,71] Common and mild adverse effects of lamotrigine include headache, fatigue, ataxia, skin rash, nausea, and vomiting, and limited evidence suggests that it could contribute to weight loss.[61]

Carbamazepine. Carbamazepine is approved for acute mania or mixed episodes, but not for BPD maintenance. Carbamazepine has been found to be more effective in patients with nonclassic features such as mood-incongruent delusions, which may suggest a broader spectrum of activity.[72,73] For the first 6 months of a 2003 trial in untreated patients with BPD, carbamazepine was narrowly more effective than lithium in preventing relapses, although at 2 years significance shifted in favor of lithium over carbamazepine.[74] More recently, 2 double-blind, randomized, placebo-controlled trials showed that carbamazepine extended-release capsules were efficacious in the treatment of acute mania in patients experiencing mania or mixed episodes.[75,76] Common and mild adverse effects include drowsiness, headache, anxiety, memory problems, diarrhea, constipation, heartburn, and dry mouth. As do many other anticonvulsants, carbamazepine has teratogenic effects.[77]

Atypical antipsychotics

Atypical antipsychotics are effective for BPD in the manic/hypomanic, depressive, and maintenance phases, but only 3 have been FDA approved for bipolar depression. The approved agents differ markedly in terms of tolerability and safety. Certain antipsychotics have a propensity for metabolic disruption, including weight gain. All 3 antipsychotics that are FDA approved for bipolar depression (olanzapine-fluoxetine, quetiapine, and lurasidone) have reasonably low NNT values, as determined from randomized, placebo-controlled trials and meta-analyses (**TABLE 2**).[23,26,27] Atypical antipsychotics approved for bipolar depression are comparable in terms of NNT (efficacy) but differ in terms of NNH (tolerability).[26,27] A number of atypical antipsychotics have also been approved for acute mania as monotherapy or adjunctive treatment (**TABLE 2**).

Olanzapine-fluoxetine. OFC has been FDA approved for bipolar depression based on replicated placebo-controlled studies.[78-80] A long-term follow-up trial in 2009 reported superiority of OFC to lamotrigine for both depressive and manic symptoms.[79] Common adverse effects include sedation, hypersomnolence, and weight gain (NNH = 6) and, less commonly, a risk of EPS.[27] In a systematic review of randomized trials, olanzapine was associated with a mean weight gain of 5.0 kg.[81]

Quetiapine. Quetiapine monotherapy was approved after demonstrating efficacy in acute bipolar depression, as supported by several large randomized trials of the immediate-release formulation and the extended-release formulation.[82-86] Common adverse effects associated with quetiapine are sedation (NNH = 5), weight gain, and, less commonly, EPS.[27]

Lurasidone. Lurasidone was FDA approved in 2013 as monotherapy or as an adjunct to lithium or divalproex for patients with bipolar depression. Evidence of efficacy was supported in 2 randomized clinical trials, 1 for adjunctive therapy[39] and a 6-week monotherapy trial.[39,87] Adverse effects of lurasidone include nausea, somnolence, tremor, akathisia (NNH = 15), and insomnia.[25] Metabolic adverse effects have been reported to be minimal in terms of weight gain, lipid abnormalities, and measures of glycemic control.[44,88]

Nonpharmacologic treatments

Nonpharmacologic interventions consisting of both psychosocial and lifestyle strategies should be integrated into the overall treatment of bipolar depression. Psychosocial interventions that have been used successfully in bipolar depression as adjuncts to pharmacotherapy include cognitive-behavioral therapy, patient education, and family-focused therapies.[89-95] Some evidence shows that these interventions are associated with greater symptom stability, fewer relapses, and longer time to relapse.[96]

Multidimensional, collaborative, and measurement-based care improves health outcomes for patients with BPD.[16,97-101] Referral to a psychiatrist, psychologist, psychotherapist, or social worker can provide the patient a full range of psychological therapy if needed, but initial and ongoing patient education efforts can occur at the PCP visit, thereby reinforcing prior and subsequent psychiatric care and psychosocial support.[102,103] Primary care providers may have different roles depending on the practice setting (eg, primary care medical homes may be integrated with psychiatric support as opposed to independent practices). They should attempt to engage in a partnership with sources of psychiatric care to aid in the monitoring of symptoms and the long-term management of medical comorbidities.

Primary care providers should promote lifestyle management for patients with BPD, focusing on exercise and wellness, particularly for patients at increased cardiometabolic risk.[40,104-106] Studies suggest that physical activity yields neurocognitive benefits, including an antidepressant and anxiolytic effect.[107-109] Lack of physical activity in patients with BPD is pervasive and can have negative effects.

Conclusions

Bipolar depression is frequently encountered in the primary care setting. Timely and accurate diagnosis and appropriate treatment, informed by FDA-approved treatments, can have a substantial impact for the patient with BPD. Treatment selection for acute symptomatic management should anticipate the long-term course of the illness. Against this background, consideration of both short-term and long-term adverse events is essential.

Mood stabilizers and atypical antipsychotics should be considered as the primary evidence-based treatment choices because of demonstrated efficacy and tolerability. Antidepressant monotherapy should be avoided wherever possible because of lack of efficacy in bipolar depression and the increased risk of triggering manic symptoms. OFC, quetiapine, and lurasidone are indicated for bipolar depression and have single-digit NNTs. Metabolic adverse effects and clinical weight gain have been documented with some atypical antipsychotics as shown by a low NNH, and these effects may be a concern for some patients. Whenever possible, patient education interventions should be integrated into the treatment paradigm.

Bipolar disorder can be a debilitating condition, and delayed recognition and treatment can have adverse clinical, functional, and economic outcomes. The PCP can prevent the unnecessary prolongation of BPD symptoms through prompt diagnosis and management of patients with this recognizable and treatable disorder. ●

REFERENCES

1. Conus P, Macneil C, McGorry PD. Public health significance of bipolar disorder: implications for early intervention and prevention. *Bipolar Disord.* 2014;16(5):548-556.
2. Berk M, Brnabic A, Dodd S, et al. Does stage of illness impact treatment response in bipolar disorder? Empirical treatment data and their implication for the staging model and early intervention. *Bipolar Disord.* 2011;13(1):87-98.
3. Smith DJ, Griffiths E, Kelly M, Hood K, Craddock N, Simpson SA. Unrecognised bipolar disorder in primary care patients with depression. *Br J Psychiatry.* 2011;199(1):49-56.
4. Keck PE Jr, Kessler RC, Ross R. Clinical and economic effects of unrecognized or inadequately treated bipolar disorder. *J Psychiatr Pract.* 2008;14(suppl 2):31-38.
5. Berk M, Hallam K, Lucas N, et al. Early intervention in bipolar disorders: opportunities and pitfalls. *Med J Aust.* 2007;187(7 suppl):S11-14.
6. Hoertel N, Le Strat Y, Angst J, Dubertret C. Subthreshold bipolar disorder in a US national representative sample: prevalence, correlates and perspectives for psychiatric nosography. *J Affect Disord.* 2013;146(3):338-347.
7. Angst J, Gamma A, Benazzi F, Ajdacic V, Eich D, Rossler W. Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. *J Affect Disord.* 2003;73(1-2):133-146.
8. Martino DJ, Samame C, Ibanez A, Strejilevich SA. Neurocognitive functioning in the premorbid stage and in the first episode of bipolar disorder: a systematic review. *Psychiatry Res.* 2015;226(1):23-30.
9. Xierali IM, Tong ST, Petterson SM, Puffer JC, Phillips RL Jr, Bazemore AW. Family physicians are essential for mental health care delivery. *J Am Board Fam Med.* 2013;26(2):114-115.
10. Sansone RA, Forbis JS, Sosa T. Primary care perspectives on treating bipolar disorder: a cross-sectional survey. *Prim Care Companion CNS Disord.* 2011;13(2).
11. Sansone RA, Sansone LA. Managing bipolar disorder in the primary care setting: a perspective for mental health professionals. *Innov Clin Neurosci.* 2011;8(10):10-13.
12. Kaye NS. A primary care approach to bipolar disorder. *Adv Stud Med.* 2006;6(6A):S442-S458.
13. Berk M, Malhi GS, Hallam K, et al. Early intervention in bipolar disorders: clinical, biochemical and neuroimaging imperatives. *J Affect Disord.* 2009;114(1-3):1-13.
14. Wang PS, Berglund P, Olfson M, Pincus HA, Wells KB, Kessler RC. Failure and delay in initial treatment contact after first onset of mental disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry.* 2005;62(6):603-613.
15. Agency for Healthcare Research and Quality. Evidence-based practice center systematic review protocol: treatment for bipolar disorder. 2014:1-25.
16. Yatham LN, Kennedy SH, Parikh SV, 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 2013. *Bipolar Disord.* 2013;15(1):1-44.
17. Ventimiglia J, Kalali AH, McIntyre R. Treatment of bipolar disorder. *Psychiatry (Edgmont).* 2009;6(10):12-14.
18. Ketter TA. Strategies for monitoring outcomes in patients with bipolar disorder. *Prim Care Companion J Clin Psychiatry.* 2010;12(suppl 1):10-16.
19. Peh AL. Safety monitoring of patients on atypical antipsychotics. *Qual Saf Health Care.* 2008;17(6):469-472.
20. Kilbourne AM, Post EP, Bauer MS, et al. Therapeutic drug and cardiovascular disease risk monitoring in patients with bipolar disorder. *J Affect Disord.* 2007;102(1-3):145-151.
21. Mojtabai R, Olfson M. National trends in psychotropic medication polypharmacy in office-based psychiatry. *Arch Gen Psychiatry.* 2010;67(1):26-36.
22. Selle V, Schalkwijk S, Vazquez GH, Baldessarini RJ. Treatments for acute bipolar depression: meta-analyses of placebo-controlled, monotherapy trials of anticonvulsants, lithium and antipsychotics. *Pharmacopsychiatry.* 2014;47(2):43-52.
23. Citrome L, Ketter TA, Cucchiaro J, Loebel A. Clinical assessment of lurasidone benefit and risk in the treatment of bipolar I depression using number needed to treat, number needed to harm, and likelihood to be helped or harmed. *J Affect Disord.* 2014;155:20-27.
24. Citrome L, Ketter TA. When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. *Int J Clin Pract.* 2013;67(5):407-411.
25. Ketter TA, Citrome L, Wang PW, Culver JL, Srivastava S. Treatments for bipolar disorder: can number needed to treat/harm help inform clinical decisions? *Acta Psychiatr Scand.* 2011;123(3):175-189.
26. Ketter TA, Miller S, Dell'Osso B, Calabrese JR, Frye MA, Citrome L. Balancing benefits and harms of treatments for acute bipolar depression. *J Affect Disord.* 2014;169(suppl 1):S24-S33.
27. Srivastava S, Ketter TA. Clinical relevance of treatments for acute bipolar disorder: balancing therapeutic and adverse effects. *Clin Ther.* 2011;33(12):B40-48.
28. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry.* 1978;133:429-435.
29. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* 1979;134:382-389.
30. Ketter TA. Treating bipolar disorder: monotherapy versus combination therapy. *J Clin Psychiatry.* 2009;70(2):e42.
31. Geoffroy PA, Etain B, Henry C, Bellivier F. Combination therapy for manic phases: a critical review of a common practice. *CNS Neurosci Ther.* 2012;18(12):957-964.
32. Geddes JR, Goodwin GM, Rendell J, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. *Lancet.* 2010;375(9712):385-395.
33. Pacchiarotti I, Bond DJ, Baldessarini RJ, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am J Psychiatry.* 2013;170(11):1249-1262.
34. McIntyre RS, Konarski JZ, Yatham LN. Comorbidity in bipolar disorder: a framework for rational treatment selection. *Hum Psychopharmacol.* 2004;19(6):369-386.
35. Buoli M, Serati M, Altamura AC. Is the combination of a mood stabilizer plus an antipsychotic more effective than monotherapies in long-term treatment of bipolar disorder? A systematic review. *J Affect Disord.* 2014;152-154:12-18.
36. Suppes T, Vieta E, Liu S, Brecher M, Paulsson B. 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;166(4):476-488.
37. Bowden CL, Vieta E, Ice KS, Schwartz JH, Wang PP, Versavel M. Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. *J Clin Psychiatry.* 2010;71(2):130-137.
38. Tohen M, Chengappa KN, Suppes T, et al. Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. *Br J Psychiatry.* 2004;184:337-345.
39. Loebel A, Cucchiaro J, Silva R, et al. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry.* 2014;171(2):169-177.
40. Culpepper L. The diagnosis and treatment of bipolar disorder: decision-making in primary care. *Prim Care Companion CNS Disord.* 2014;16(3).
41. Young SL, Taylor M, Lawrie SM. "First do no harm." A systematic review of the prevalence and management of antipsychotic adverse effects. *J Psychopharmacol.* 2015;29(4):353-362.
42. Fagiolini A, Kupfer DJ, Houck PR, Novick DM, Frank E. Obesity as a correlate of outcome in patients with bipolar I disorder. *Am J Psychiatry.* 2003;160(1):112-117.
43. De Hert M, Cohen D, Bobes J, et al. Physical illness in patients with severe mental

disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. *World Psychiatry.* 2011;10(2):138-151.
44. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet.* 2013;382(9896):951-962.
45. Yim CY, Soczynska JK, Kennedy SH, Woldeyohannes HO, Brietzke E, McIntyre RS. The effect of overweight/obesity on cognitive function in euthymic individuals with bipolar disorder. *Eur Psychiatry.* 2012;27(3):223-228.
46. Bora E, Yucel M, Pantelis C, Berk M. Meta-analytic review of neurocognition in bipolar II disorder. *Acta Psychiatr Scand.* 2011;123(3):165-174.
47. Goldberg JF, Perlis RH, Bowden CL, et al. Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD. *Am J Psychiatry.* 2009;166(2):173-181.
48. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5.* 5th ed. Arlington, VA: American Psychiatric Association; 2013.
49. Hu J, Mansur R, McIntyre RS. Mixed specifier for bipolar mania and depression: highlights of DSM-5 changes and implications for diagnosis and treatment in primary care. *Prim Care Companion CNS Disord.* 2014;16(2).
50. McIntyre RS, Yoon J. Efficacy of antimanic treatments in mixed states. *Bipolar Disord.* 2012;(14 suppl 2):22-36.
51. Bowden C, Gogus A, Grunze H, Haggstrom 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;23(5):254-262.
52. Bowden CL, Mosolov S, Hranov L, et al. Efficacy of valproate versus lithium in mania or mixed mania: a randomized, open 12-week trial. *Int Clin Psychopharmacol.* 2010;25(2):60-67.
53. Muzina DJ, Gao K, Kemp DE, et al. Acute efficacy of divalproex sodium versus placebo in mood stabilizer-naive bipolar I or II depression: a double-blind, randomized, placebo-controlled trial. *J Clin Psychiatry.* 2011;72(6):813-819.
54. McInerney SJ, Kennedy SH. Review of evidence for use of antidepressants in bipolar depression. *Prim Care Companion CNS Disord.* 2014;16(5).
55. Sidor MM, MacQueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. *J Clin Psychiatry.* 2011;72(2):156-167.
56. Bauer M, Ritter P, Grunze H, Pfennig A. Treatment options for acute depression in bipolar disorder. *Bipolar Disord.* 2012;(14 suppl 2):37-50.
57. Grunze HC. Anticonvulsants in bipolar disorder. *J Ment Health.* 2010;19(2):127-141.
58. Schneck CD. Treatment of rapid-cycling bipolar disorder. *J Clin Psychiatry.* 2006;(67 suppl 11):22-27.
59. McIntyre RS, Mancini DA, Lin P, Jordan J. Treating bipolar disorder: evidence-based guidelines for family medicine. *Can Fam Physician.* 2004;50:388-394.
60. Denicoff KD, Smith-Jackson EE, Disney ER, Ali SO, Leverich GS, Post RM. Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. *J Clin Psychiatry.* 1997;58(11):470-478.
61. Lamictal (lamotrigine) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2014.
62. Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ.* 2013;346:f3646.
63. Eskalith (lithium carbonate) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2003.
64. Depakote (divalproex sodium) [package insert]. North Chicago, IL: AbbVie, Inc; 2015.
65. Bowden CL, Singh V, Weisler R, et al. Lamotrigine vs lamotrigine plus divalproex in randomized, placebo-controlled maintenance treatment for bipolar depression. *Acta Psychiatr Scand.* 2012;126(5):342-350.
66. Segura-Bruna N, Rodriguez-Campello A, Puente V, Roquer J. Valproate-induced hyperammonemic encephalopathy. *Acta Neurol Scand.* 2006;114(1):1-7.
67. McIntyre RS, Mancini DA, McCann S, Srinivasan J, Kennedy SH. Valproate, bipolar disorder and polycystic ovarian syndrome. *Bipolar Disord.* 2003;5(1):28-35.
68. Calabrese JR, Bowden CL, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry.* 2003;64(9):1013-1024.
69. Bowden CL, Calabrese JR, Sachs G, et al. 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;60(4):392-400.
70. 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;194(1):4-9.
71. Calabrese JR, Huffman RF, White RL, et al. Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. *Bipolar Disord.* 2008;10(2):323-333.
72. Kleindienst N, Greil W. Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: results of the MAP study. *Neuropsychobiology.* 2000(42 suppl 1):2-10.
73. Greil W, Kleindienst N, Erazo N, Muller-Oerlinghausen B. Differential response to lithium and carbamazepine in the prophylaxis of bipolar disorder. *J Clin Psychopharmacol.* 1998;18(6):455-460.
74. Hartong EG, Moleman P, Hoogduin CA, Broekman TG, Nolen WA; LitCar Group. Prophylactic efficacy of lithium versus carbamazepine in treatment-naive bipolar patients. *J Clin Psychiatry.* 2003;64(2):144-151.
75. Weisler RH, Kalali AH, Ketter TA. 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;65(4):478-484.
76. Weisler RH, Keck PE Jr, 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;66(3):323-330.
77. Equetro (carbamazepine) [package insert]. Parsippany, NJ: Validus Pharmaceuticals, LLC; 2012.
78. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry.* 2003;60(11):1079-1088.
79. Brown E, Dunner DL, McElroy SL, et al. Olanzapine/fluoxetine combination vs lamotrigine in the 6-month treatment of bipolar I depression. *Int J Neuropsychopharmacol.* 2009;12(6):773-782.
80. Brown EB, McElroy SL, Keck PE Jr, et al. A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. *J Clin Psychiatry.* 2006;67(7):1025-1033.
81. Parsons B, Allison DB, Loebel A, et al. Weight effects associated with antipsychotics: a comprehensive database analysis. *Schizophr Res.* 2009;110(1-3):103-110.
82. Calabrese JR, Keck PE Jr, Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry.* 2005;162(7):1351-1360.
83. Thase ME, Macfadden W, Weisler RH, et al. 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):600-609.
84. McElroy SL, Weisler RH, Chang W, et al. A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). *J Clin Psychiatry.* 2010;71(2):163-174.
85. Young AH, McElroy SL, Bauer M, et al. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry.* 2010;71(2):150-162.
86. Suppes T, Datto C, Minkwitz M, Nordenhem A, Walker C, Darko D. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. *J Affect Disord.* 2010;121(1-2):106-115.
87. Loebel A, Cucchiaro J, Silva R, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry.* 2014;171(2):160-168.
88. De Hert M, Yu W, Detraux J, Sweers K, van Winkel R, Correll CU. Body weight and metabolic adverse effects of asenapine, iloperidone, lurasidone and paliperidone in the treatment of schizophrenia and bipolar disorder: a systematic review and exploratory meta-analysis. *CNS Drugs.* 2012;26(9):733-759.
89. Scott J, Paykel E, Morriss R, et al. Cognitive-behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. *Br J Psychiatry.* 2006;188:313-320.
90. Colom F. Keeping therapies simple: psychoeducation in the prevention of relapse in affective disorders. *Br J Psychiatry.* 2011;198(5):338-340.
91. Colom F. The evolution of psychoeducation for bipolar disorder: from lithium clinics to integrative psychoeducation. *World Psychiatry.* 2014;13(1):90-92.
92. Colom F, Lam D. Psychoeducation: improving outcomes in bipolar disorder. *Eur Psychiatry.* 2005;20(5-6):359-364.
93. Colom F, Reinares M, Pacchiarotti I, et al. Has number of previous episodes any effect on response to group psychoeducation in bipolar patients? A 5-year follow-up post hoc analysis. *Acta Neuropsychiatr.* 2010;22(2):50-53.
94. Colom F, Vieta E, Sanchez-Moreno J, et al. Psychoeducation for bipolar II disorder: an exploratory, 5-year outcome subanalysis. *J Affect Disord.* 2009;112(1-3):30-35.
95. 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;60(9):904-912.
96. Stafford N, Colom F. Purpose and effectiveness of psychoeducation in patients with bipolar disorder in a bipolar clinic setting. *Acta Psychiatr Scand Suppl.* 2013(442):11-18.
97. Susman JL. Improving outcomes in patients with bipolar disorder through establishing an effective treatment team. *Prim Care Companion J Clin Psychiatry.* 2010;12(suppl 1):30-34.
98. Billsborough J, Mailey P, Hicks A, et al. 'Listen, empower us and take action now!': reflexive-collaborative exploration of support needs in bipolar disorder when 'going up' and 'going down.' *J Ment Health.* 2014;23(1):9-14.
99. Reilly S, Planner C, Gask L, et al. Collaborative care approaches for people with severe mental illness. *Cochrane Database Syst Rev.* 2013;11:CD009531.
100. Vannoy SD, Mauer B, Kern J, et al. A learning collaborative of CMHCs and CHCs to support integration of behavioral health and general medical care. *Psychiatr Serv.* 2011;62(7):753-758.
101. 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 cooccurring conditions? *J Affect Disord.* 2009;112(1-3):256-261.

102. Connolly KR, Thase ME. The clinical management of bipolar disorder: a review of evidence-based guidelines. *Prim Care Companion CNS Disord.* 2011;13(4).
103. Podawiltz A. A review of current bipolar disorder treatment guidelines. *J Clin Psychiatry.* 2012;73(3):e12.
104. Sylvia LG, Nierenberg AA, Stange JP, Peckham AD, Deckersbach T. Development of an integrated psychosocial treatment to address the medical burden associated with bipolar disorder. *J Psychiatr Pract.* 2011;17(3):224-232.
105. Sylvia LG, Salcedo S, Bernstein EE, Baek JH, Nierenberg AA, Deckersbach T. Nutrition, exercise, and wellness treatment in bipolar disorder: proof of concept for a consolidated intervention. *Int J Bipolar Disord.* 2013;1(1):24.
106. Bauer MS, McBride L, Williford WO, et al. Collaborative care for bipolar disorder: part II. Impact on clinical outcome, function, and costs. *Psychiatr Serv.* 2006;57(7):937-945.
107. Sylvia LG, Ametrano RM, Nierenberg AA. Exercise treatment for bipolar disorder: potential mechanisms of action mediated through increased neurogenesis and decreased allostatic load. *Psychother Psychosom.* 2010;79(2):87-96.
108. Kucyi A, Alsuwaidan MT, Liauw SS, McIntyre RS. Aerobic physical exercise as a possible treatment for neurocognitive dysfunction in bipolar disorder. *Postgrad Med.* 2010;122(6):107-116.
109. Ng F, Dodd S, Berk M. The effects of physical activity in the acute treatment of bipolar disorder: a pilot study. *J Affect Disord.* 2007;101(1-3):259-262.

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