Bipolar disorder is a chronic, relapsing illness characterized by recurrent episodes of manic or depressive symptoms, with intervening periods that are relatively (but not fully) symptom-free. Onset usually occurs in adolescence or early adulthood, although onset later in life is also possible. Bipolar disorder has a lifelong impact on patients' overall health status, quality of life, and functioning.

This disorder has 2 major types—bipolar disorder I and bipolar disorder II. Bipolar disorder I is defined by episodes of depression and the presence of mania, whereas bipolar disorder II is characterized by episodes of depression and hypomania. Therefore, the main distinction between the 2 types is the severity of manic symptoms: full mania causes severe functional impairment, can include symptoms of psychosis, and often requires hospitalization; hypomania, by contrast, is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization.

Longitudinal studies show that patients with bipolar disorder of either type experience symptomatic depression at least 3 times more frequently than symptomatic mania or hypomania (Figure 1). The lifetime prevalence of bipolar disorder in adults is reported to be approximately 4%, and its management was estimated to cost the US healthcare system in 2009 $150 billion in combined direct and indirect costs.
Bipolar disorder has an enormous economic impact on the US healthcare system. The estimated total direct cost of bipolar disorder (including inpatient costs, outpatient costs, pharmaceuticals, and community care) in the United States in 2009 was $30.7 billion. In addition, the adverse impact of bipolar disorder on functioning and quality of life translates to a substantial total indirect healthcare cost resulting from the loss of employment, loss of productivity, sick leave, and uncompensated care that is estimated at more than $120 billion annually.

From a managed care perspective, bipolar disorder is among the most costly of all mental health conditions. In a major study of commercial insurance claims data from 1996 of almost 1.7 million individuals, although only 3% of patients with a mental health claim were identified with bipolar disorder, these patients accounted for 12.4% of the total plan expenditures. High cost was driven largely by a disproportionate rate of inpatient admissions for bipolar disorder versus all other behavioral health claimants (39.1% vs 4.5%, respectively), resulting in a cost of $1.80 for inpatient care per every dollar of outpatient treatment cost.

Another large study of healthcare utilization and costs from 2004 to 2007 compared 122 patients with bipolar disorder with patients with other psychiatric conditions, including 1290 patients with depression, 2770 with asthma, 1759 with coronary artery disease, and 1418 with diabetes. The patients with bipolar disorder had higher adjusted mean costs per member per month (approximately $1700) than all other groups, including depression (approximately $1300), with the exception of patients who had both diabetes and coronary artery disease (with approximately $2000 per member per month).

Despite the advent of lithium therapy more than 60 years ago, the introduction of other pharmacotherapies and the development of disease-specific behavioral approaches, and a generally greater awareness of bipolar disorder, treatment outcomes remain less satisfactory than the outcomes for major depressive disorder; treatment outcomes remain less satisfactory than the outcomes for major depressive disorder (MDD) in all sectors of the US healthcare system, including...
managed care. This represents a challenge and an opportunity for managed care to focus on this disorder to improve outcomes and to reduce healthcare costs.

This review article presents the clinical evidence supporting best practice for the diagnosis and treatment of bipolar disorder. The review highlights what little is known about the most effective ways to address specific clinical challenges in caring for patients with bipolar disorder and identifies recent research that documents innovative approaches to improving the effectiveness of care in this setting.

### Study Selection Methodology

Studies were selected for inclusion in this review based on a comprehensive literature search initially using MEDLINE/PubMed and Google Scholar, and was restricted to the years 1994 to the present. The search terms included “bipolar disorder,” “mania,” “bipolar depression,” “mood stabilizer,” “atypical antipsychotics,” and “antidepressants.” For the sections on diagnosis, treatment, and key challenges, articles were selected for inclusion from the extensive literature based on the clinical judgment of the author, using the conventional criteria of relevance, importance, and robustness of data. In selecting studies for inclusion, a broad representation of topics was sought, while limiting the total number of references on any given topic; high-quality, recent reviews of major topics were included to supplement the primary studies.

### Diagnosis

A diagnosis of bipolar disorder is obvious when a patient presents with florid mania but is challenging when the initial presentation includes depressive symptoms; studies generally report that 50% or more of patients initially present with depression.\(^1,17-20\) Primarily because unipolar depression (ie, MDD) is more common than bipolar depression, and because bipolar depression lacks pathognomonic features, bipolar disorder is often incorrectly identified as MDD.\(^21\) Among patients who are eventually diagnosed with bipolar disorder, approximately 70% reportedly had an initial misdiagnosis and more than 33% remained misdiagnosed for 10 years or more.\(^22\) Delay in diagnosis is a particular problem in women with bipolar disorder type II, because the symptoms of hypomania may not be very apparent.\(^23\) Moreover, misdiagnosis during the postpartum period is common; in a study of 56 women referred for postpartum depression, 54% were later reclassified with bipolar disorder.\(^24\)

The delayed recognition of bipolar disorder has adverse clinical and healthcare cost consequences.\(^21,25,26\) From a clinical perspective, patients with bipolar disorder who are treated with antidepressants alone (the standard of care for MDD) are less likely to have an appropriate response and are at risk for manic switch or cycle acceleration (ie, increased frequency of mood episodes over time).\(^27,28\)

From a health economic perspective, care is likely to be more costly in patients with delayed diagnosis of bipolar disorder than in those diagnosed early. In an analysis from the California Medicaid program, 2 groups of patients with bipolar disorder were compared: those who were diagnosed with bipolar disorder at initial presentation and those who had a delayed diagnosis during a 6-year follow-up.\(^26\) Patients with a delayed diagnosis of bipolar disorder represented almost twice as many cases as those with initially recognized bipolar disorder (28.2% vs 14.5%, respectively), and the annualized total cost per patient in the delayed group was $2316 higher in the sixth year compared with the cost for patients whose disease was initially recognized as bipolar disorder (\(P < .001\)). Moreover, costs for patients with bipolar disorder and a delayed diagnosis increased by $10 monthly before the correct diagnosis (\(P < .001\)) and decreased by $1 afterward (\(P = .006\) for the change in slope).\(^26\) Thus, the consideration of the possibility of bipolar disorder in patients with depressive disorders is critical to improving outcomes and reducing the costs of care of patients with bipolar disorder.

Screening each patient for a history of mania and hypomania on their initial presentation of depressive symptoms is an early step toward the recognition of bipolar disorder.\(^29\) Validated instruments that can be used include the Mood Disorder Questionnaire,\(^30\) the Composite International Diagnostic Interview, version 3.0,\(^31\) and the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire.\(^32\) Clinical screening can be supplemented with electronic health record (EHR)-based case findings, in which information collected by self-report or a healthcare assistant is entered into the EHR and is screened for possible indicators of bipolar disorder.\(^33\)

These tools help to ensure that the clinician recognizes patients who are more likely to have bipolar disorder, help assist in directing the clinical interview, and can encourage active follow-up for any emerging symptoms of bipolar disorder. In a study modeling the clinical outcome and cost-effectiveness over 5 years of administering the Mood Disorder Questionnaire to all patients first presenting with symptoms of MDD, screening resulted in an increase in diagnostic accuracy for bipolar disorder, with an additional 38 cases identified per 1000 patients screened and a per-patient savings of $1937, for a total annual budgetary savings of more than $1.9 million.\(^34\)
Pharmacologic Treatment

Pharmacologic treatments for bipolar disorder include the conventional mood stabilizers (eg, lithium, valproate, lamotrigine, and carbamazepine) and most of the currently marketed atypical antipsychotics. A detailed review of randomized controlled trials (RCTs) and observational studies for every agent in the treatment of each of the phases of bipolar disorder is beyond the scope of this review; rather, a summary of the most important findings of the aggregated evidence is presented from systematic reviews and meta-analyses, as well as the results of recent studies that address previous gaps in the literature.

It is relevant to note that the level of trial evidence varies for the different pharmacotherapies that are approved for the treatment of bipolar disorder. Some of these agents have evidence of efficacy in acute mania, others in acute bipolar depression, and a limited number of therapies have efficacy at both poles of the disease spectrum. Some therapies demonstrate efficacy only in acute episodes, whereas others show efficacy as maintenance therapy.

Mood Stabilizers

Lithium has been the foundation of treatment of bipolar disorder for over 60 years, but its efficacy in the prevention and treatment of bipolar depression is limited, and it is not rapidly effective for acute mania. In a systematic review of RCTs with a lithium arm that were published between 1970 and 2006, lithium had a significant prophylactic effect for all relapses (random effects relative risk [RR], 0.65; 95% confidence interval [CI], 0.50-0.84) and manic relapses (RR, 0.62; 95% CI, 0.40-0.95) but not for depressive relapses (RR, 0.72; 95% CI, 0.49-1.07). Notably, lithium remains the only agent proved to reduce the risk for suicide in patients with bipolar disorder.

Sodium valproate is the most frequently used antiepileptic mood stabilizer for patients with bipolar disorder. In the BALANCE trial, a 2-year active controlled trial, 330 patients were receiving maintenance therapy with lithium or valproate, or the combination of both; the primary outcome was time to first mood episode. Although the combination performed best, lithium was more effective than valproate alone (hazard ratio [HR] for the primary outcome, 0.71; 95% CI, 0.51-1.00; \( P = .047 \)).

A nationwide observational study conducted in Denmark from 1995 to 2006 of 4268 patients who received lithium or valproate for the treatment of bipolar disorder found a higher rate of adding medications or switching to another drug among patients receiving valproate compared with lithium (HR, 1.86; 95% CI, 1.59-2.16) and a higher rate of hospitalization (HR, 1.33; 95% CI, 1.18-1.48).

Valproate is associated with hepatotoxicity, whereas lamotrigine is linked with rash and Stevens-Johnson–like syndrome. Valproate and lithium are both teratogenic.

Atypical Antipsychotics

A vast body of evidence supports the use of atypical antipsychotics in the treatment of bipolar disorder. The most established role for this class is in the treatment of acute mania. All approved atypical antipsychotics (with the exception of lurasidone) have been shown to be effective in the treatment of manic episodes of bipolar disorder. In contrast, only quetiapine (immediate-release and extended-release formulations) has the highest level (level 1) of evidence for efficacy as monotherapy for bipolar I or II depression. More recently, quetiapine was also shown to reduce the symptoms of depression in acute mixed episodes of bipolar II hypomania. One single trial of the combination agent of olanzapine and fluoxetine shows the efficacy of this agent in bipolar I depression; lurasidone was approved in 2013 by the US Food and Drug Administration (FDA) for the treatment of adults with bipolar I depression. Other atypical antipsychotics, including aripiprazole, have not shown efficacy in trials of patients with bipolar depression.

The safety and tolerability of atypical antipsychotics are well characterized in the literature. The adverse effects of atypical antipsychotics differ between individual agents. In a meta-analysis of 48 RCTs in which at least 2 atypical antipsychotics were compared and risperidone served as the index medication, weight gain was significantly increased with olanzapine (odds ratio [OR], 2.139; 95% CI, 1.764-2.626) and was decreased with ziprasidone (OR, 0.466; 95% CI, 0.317-0.657); extrapyramidal symptoms were decreased with quetiapine (OR, 0.441; 95% CI, 0.129-0.910).

Atypical antipsychotics as a class have a propensity to contribute to metabolic risk in patients with bipolar disorder, and monitoring strategies have been proposed to prevent, minimize, or detect symptoms early so that appropriate measures can be taken.
<table>
<thead>
<tr>
<th>Guideline</th>
<th>Acute Treatment</th>
<th>Mixed States</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAD/DoD  (2010)</td>
<td>Lithium, valproate, carbamazepine, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone</td>
<td>Valproate, carbamazepine, olanzapine, aripiprazole, risperidone, ziprasidone</td>
<td>Agent effective in acute phase; monotherapy advised</td>
</tr>
<tr>
<td>CANMAT  (2013)</td>
<td>Lithium, valproate, aripiprazole, olanzapine, quetiapine XR, risperidone, ziprasidone, asenapine, paliperidone XR, lithium/valproate + aripiprazole, lithium/valproate + olanzapine, lithium/valproate + quetiapine, lithium/valproate + risperidone, lithium/valproate + asenapine</td>
<td>Lithium, lamotrigine, quetiapine XR, lithium/valproate + SSRI, olanzapine + SSRI, lithium + valproate, lithium/valproate + bupropion</td>
<td>Bipolar I disorder</td>
</tr>
<tr>
<td>BAF  (2009)</td>
<td>Mild: lithium, carbamazepine</td>
<td>Quetiapine, lamotrigine, SSRI or other antidepressant (not TCA)</td>
<td>Mania</td>
</tr>
<tr>
<td>APA  (2002)</td>
<td>Severely ill: lithium/valproate + antipsychotic</td>
<td>Lithium, lamotrigine</td>
<td>Lithium, valproate, carbamazepine, oxcarbazepine</td>
</tr>
</tbody>
</table>

LAI indicates long-acting injection; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; XR, extended release.
**Antidepressants**

The use of antidepressants as pharmacotherapy for bipolar disorder is the area of greatest controversy related to this disease. In a random-effects meta-analysis of 10 studies that included 2226 patients with unipolar depression and 863 patients with bipolar disorder, antidepressant responses did not differ between the 2 groups (pooled RR, 1.05; 95% CI, 0.96-1.15; \( P = .34 \)). However, the risk rate for a switch to mania was 2.5% weekly in patients with bipolar depression compared with 0.28% in patients with unipolar depression.

Antidepressants are not FDA-approved for the treatment of bipolar disorder, with the exception of fluoxetine in combination with olanzapine, although antidepressants are frequently prescribed in clinical practice for the depressive symptoms of bipolar disorder.

The current guidelines are generally consistent in making the recommendations listed in the Table regarding antidepressant use in bipolar depression, indicating that selective serotonin reuptake inhibitors (other than paroxetine) and bupropion may be used as first-line treatments in patients with bipolar disorder with no history of rapid cycling and without concomitant manic symptoms, but always in conjunction with a mood stabilizer or an atypical antipsychotic. Antidepressants should be tapered and discontinued after full remission of depression; the role of antidepressants in maintenance treatment is unclear.

**Treatment Guidelines**

Treatment guidelines are a critical source for the rational pharmacotherapy of bipolar disorder. The American Psychiatric Association guidelines for bipolar disorder have not been updated since 2002, and therefore do not include data that became available more recently. In a systematic overview of the current international guidelines for bipolar disorder conducted in 2011, the recommendations with the greatest degree of consensus and best evidence for first-line treatment were the use of (1) lithium, divalproex, or an atypical antipsychotic (other than paroxetine) and bupropion may be used as first-line treatments in patients with bipolar disorder with no history of rapid cycling and without concomitant manic symptoms, but always in conjunction with a mood stabilizer or an atypical antipsychotic. Antidepressants should be tapered and discontinued after full remission of depression; the role of antidepressants in maintenance treatment is unclear.

**Figure 2A** Canadian Network for Mood and Anxiety Treatments Mania Algorithm

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Review general principles and assess medication status</th>
</tr>
</thead>
<tbody>
<tr>
<td>No response</td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td>Initiate/optimize, check compliance</td>
</tr>
<tr>
<td>No response</td>
<td></td>
</tr>
<tr>
<td>Step 3</td>
<td>Add-on or switch therapy</td>
</tr>
<tr>
<td>No response</td>
<td></td>
</tr>
<tr>
<td>Step 4</td>
<td>Add-on or switch therapy</td>
</tr>
<tr>
<td>No response</td>
<td></td>
</tr>
<tr>
<td>Step 5</td>
<td>Add-on novel or experimental agents</td>
</tr>
</tbody>
</table>

AAP indicates atypical antipsychotic; D/C, discontinue; DVP, divalproex.

antipsychotic, for acute mania; (2) divalproex or an atypical antipsychotic, for mixed episodes (ie, manic and depressed symptoms together); (3) quetiapine, olanzapine/fluoxetine combination, or lamotrigine, for bipolar depression; and (4) group or individual psychological education should be offered to all patients with bipolar disorder. 53

The Table provides a summary of first-line pharmacotherapy recommendations from a selected set of comprehensive guidelines.21,38,52,54-57 However, implementation of the guidance in any treatment algorithm for bipolar disorder is challenging, because of the multiple factors involved in drug selection, drug interactions, adverse side effects, and patient adherence (Figure 2A and Figure 2B).38

### Major Challenges in the Treatment of Bipolar Disorder

In addition to the importance of implementing an expeditious diagnosis, evidence-based prescribing, and cost-effective therapies, other challenges must be recognized and addressed in the treatment of patients with bipolar disorder to improve treatment outcome.

#### Treatment Nonadherence

Nonadherence to treatment is perhaps the most significant contributing factor to poor outcome in patients with bipolar disorder.50,59 Medication possession ratio (MPR) has been used to assess treatment adherence. MPR is the ratio of the number of days that an antipsychotic medication, for example, was filled...
determined by the total number of days during the follow-up period. An MPR of 1 indicates that for a medication prescribed for a patient over a given time, prescriptions were filled 100% of that period. A priori MPR percentage thresholds of 70% to 80% have been set to define adherence versus nonadherence; a threshold of 75% or 80% represents a level of adherence that is associated with better outcomes in patients with bipolar disorder.58-61

In one study with 1973 commercially insured patients, the mean MPR was only 0.46 (SD, ±0.32); patients whose MPR was ≥0.75 had a lower risk for all-cause rehospitalization (OR, 0.73; 95% CI, 0.58-0.92) and mental health–related rehospitalization (OR, 0.76; 95% CI, 0.60-0.96).58 Similarly, among 1399 commercially insured patients, reduced adherence (<80%) to traditional mood-stabilizing therapy was associated with a greater risk for emergency department visits (OR, 1.98; 95% CI, 1.38-2.84) and inpatient hospitalizations (OR, 1.71; 95% CI, 1.27-2.32).59

In one of the largest studies of its type, using claims data from the 2000-2006 PharMetrics database (a large US database of commercial health plans), 78.7% of the 7769 patients with bipolar disorder had an MPR <0.75. An MPR ≥0.80 was associated with a reduction in risk for mental health–related hospitalization (OR, 0.82; 95% CI, 0.70-0.95), and an MPR ≥0.90 was also associated with a reduction in the risk for a mental health–related emergency department visit (OR, 0.71; 95% CI, 0.54-0.91).60 Similar findings have been reported in Medicaid-insured populations.61

Because adherence tends to worsen with the addition of each medication to a pharmacotherapeutic regimen, monotherapy may be considered a practical option in patients with poor adherence.62,63

**Psychiatric Comorbidities**

Patients with bipolar disorder are predisposed to other comorbid psychiatric disorders at higher rates than patients with other psychiatric disorders.64,65 Anxiety disorders and alcohol or drug dependence are particularly common comorbidities, with major consequences for treatment outcome and increased cost.64,66 Comorbidity is the rule rather than the exception in bipolar disorder,64,65 with approximately 66% of patients having 1 comorbid mental health diagnosis and approximately 66% having 2 other conditions.66

These comorbid psychiatric conditions are associated with longer episodes of bipolar illness64,66; shorter time in remission (ie, euthymia)64,66; polypharmacy, with the potential for drug interactions65; and an increase in related problems, such as poor treatment compliance and suicidality.65

**General Medical Comorbidities**

Patients with bipolar disorder also have a high rate of other medical comorbidities, including diabetes, cardiovascular disease, obesity, and hepatitis C virus (HCV) infection.66,68 In a Veterans Administration (VA) study, patients with bipolar disorder had a higher prevalence of diabetes than patients in a national VA cohort (17.2% vs 15.6%, respectively; P = .0035) and of HCV (5.9% vs 1.1%, respectively; P < .001).68 Several reasons can potentially account for this increased burden of medical illness, including shared biologic predisposition (eg, migraine), comorbid substance misuse (HCV), as well as adverse effects of treatment (obesity and diabetes).69 Not surprisingly, medical comorbidities are associated with a significant increase in the total cost of care.70,71

**Suicide**

Suicide is more frequent among patients with bipolar disorder than among patients with any other psychiatric or general medical disorder.72,73 Suicide among patients with bipolar disorder is estimated to occur at an annual rate of 0.4% (1 for every 250 individuals with bipolar disorder), which is more than 20 times than in the general US population.73 In the Epidemiologic Catchment Area database, which is still one of the best US databases regarding the epidemiology of psychiatric disorders, the lifetime rate of suicide attempts for persons with bipolar disorder was 29.2%—almost twice the rates of MDD (15.9%) and other Diagnostic and Statistical Manual of Mental Disorders, Third Edition–defined Axis I disorder (4.2%).72

Suicide attempts are very costly.74 In a study using data from the PharMetrics Integrated Outcomes Database (1995-2005), the total costs for 352 patients with bipolar disorder who attempted suicide were compared between the years after and before the first suicide attempt. The mean healthcare cost for the 1 year after the suicide attempt was $25,012 versus $11,476 for the 1 year before (P <.001). During the month after the suicide attempt, a large increase was reported in inpatient and emergency services, followed by enduring long-term increases in medication and outpatient costs.74

**Women of Childbearing Age**

Women of childbearing age comprise a special population requiring vigilance by caregivers and healthcare providers.75 In a prospective observational study of 89 pregnant women with bipolar disorder who were euthymic at the time of conception, 71% had at least 1 recurrence of a bipolar episode during pregnancy; depression was the most common type of recurrence (38%), followed by mixed states (29%), hypomania (17%), and
mania (7%). Those who discontinued pharmacotherapies were at twice the risk for a recurrence as those who continued therapy, had a recurrence earlier, and their illness was almost 5 times as long; abrupt treatment withdrawal posed the greatest risk.75

Given the demonstrated teratogenic risk associated with antiepileptic drugs and with lithium, atypical antipsychotics are an essential treatment option in this vulnerable population.76 Close coordination between obstetric, psychiatric, and primary medical care providers during pregnancy is critical.

Conclusion
The lifetime management of patients with bipolar disorder is challenging, because of the dynamic, chronic, and fluctuating nature of this disease. The healthcare costs for patients and their caregivers are enormous from psychosocial and economic perspectives. It is incumbent on healthcare professionals to reduce the burden of bipolar disorder. Pharmacologic treatment is the mainstay of treatment for patients with bipolar disorder. Although mood stabilizers have been the cornerstone of therapy, the availability of atypical antipsychotics has significantly modified the approach to care. Individual atypical antipsychotic medications have been shown to be effective for acute mania/hypomania, for acute depression, and for maintenance treatment (of mania and depression), and have been incorporated into many treatment guidelines. The diligent selection of a specific agent that takes into account its efficacy in the various phases of bipolar disorder, along with its safety profile, can help to ameliorate the impact of this devastating condition. ■

Acknowledgment
Editorial support for the preparation of the manuscript was provided by Bill Wolvey of PAREXEL.

Funding Source
Funding for writing this review article was provided by AstraZeneca.

Author Disclosure Statement
Dr Jann is on the Speaker’s Bureau for Janssen Pharmaceuticals.

References
Bipolar Disorders: Balancing Formulary Management and Clinical Outcomes for a Vulnerable Patient Population

By Gary M. Owens, MD
President, Gary Owens Associates

PATIENTS: Bipolar disorders are a major health concern, with significant lifelong social and occupational impairment to patients, and poor prognosis. It is estimated that the lifetime prevalence of clinical bipolar spectrum disorders is approximately 3% to 7% of the US population, and the average age of onset is 15 to 30 years. Astoundingly, the prevalence of bipolar disorders may be just slightly less than the prevalence of asthma (8%) in adult patients.3

In addition to the debilitating clinical burden on patients, there is also significant cost associated to patients and to the healthcare system with this disorder, in large part secondary to its substantially elevated morbidity and mortality rates, which are largely due to associated cardiovascular disease, metabolic syndrome, substance abuse or misuse, and potential for physical self-harm from reckless or impulsive behaviors or suicide.

MEDICAL/PHARMACY DIRECTORS: As noted in the review article by Dr Jann in this issue of American Health & Drug Benefits,4 payers recognize that this disorder brings both clinical and economic challenges. The management of bipolar disorder has evolved over the past decade, as new treatments and new evidence for the use of atypical antipsychotics and other agents emerge. Payers are certainly aware of the changing treatment environment, and they are challenged to keep up with these changes as they expand beyond even the most recent treatment guidelines.

As Dr Jann notes, “Although mood stabilizers have been the cornerstone of therapy, the availability of atypical antipsychotics has significantly modified the approach to care.” This makes it a challenge for payers, who must optimize current formularies to take advantage of the availability of low-cost generic drugs yet maintain access to essential treatments for this important patient population.

Management of the treatments for bipolar disorder includes generics-first programs, preferred brand drugs step therapy, and prior authorization of the atypical antipsychotics. Although these programs are essential to sound formulary management, recent studies have cast some doubt on the overall effectiveness of these efforts.5,6 For example, Zhang and colleagues provide evidence for a small decrease in pharmacy expenditures associated with formulary restrictions for patients with bipolar disorder, but this was associated with an increase in treatment discontinuation.6 More recently, a 2014 study by Seabury and colleagues concluded that formulary restrictions resulted in medical cost increases that eliminated much, if not all, of the possible savings among atypical antipsychotic users with schizophrenia or with bipolar disorder.6

Because of this growing evidence, it is important for payers to continuously assess their clinical management programs for this disease category to ensure that they are optimizing cost management and not creating negative clinical impact on this vulnerable patient population.

Payers can also make substantial contributions to the multidisciplinary team who are caring for patients with bipolar disorder. Specific pharmacy programs can serve as medication information resources such as providing medication counseling, counseling on lifestyle modifications to ensure optimal clinical response to therapies, and monitoring of patients on issues of medication compliance and the consequences of nonadherence. By taking these steps, payers will ensure that they are providing the optimum balance of clinical and economic outcomes for this population.