Use Pattern and Off-Label Use of Atypical Antipsychotics in Bipolar Disorder, 1998-2002

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Background: Postmarketing surveillance that identifies patients at high risk for receiving off-label medications will help ensure that the benefits of such treatment outweigh the risks. Because many off-label uses have little scientific support, tracking the extent to which they occur as well as the particular circumstances under which they occur is important.

Objective: To describe the drug-use pattern for patients with bipolar disorder, and to identify demographic and clinical factors associated with off-label use of atypical antipsychotics before US Food and Drug Administration approval for this indication.

Methods: Using the PHARMetrics medical claims database, a total of 105,771 adult patients with a diagnosis of bipolar disorder were evaluated during the 5-year (1998-2002) study period. Study drugs included mood stabilizers, antipsychotics, and antidepressants. Off-label use of an atypical antipsychotic was defined as a patient taking olanzapine before March 2000 (when it received an indication for bipolar disorder) or any other atypical antipsychotic during the entire study period. Logistic regression analysis was used to determine the odds ratio of receiving a drug off-label.

Results: Utilization of and reimbursement for atypical antipsychotics increased during the 5-year period. Of the 10.5% of patients who took atypical antipsychotics, 7.1% took these drugs off-label. In addition, 11% of patients received lithium, 25% received other anticonvulsants, and 34% received antidepressants. Off-label use of atypical antipsychotics was associated with psychiatry specialist prescribers (odds ratio = 1.52; 95% CI, 1.44-1.59) and certain comorbidities, such as substance abuse (odds ratio = 1.51; 95% CI, 1.38-1.66), anxiety disorder (odds ratio = 1.20; 95% CI, 1.14-1.26), diabetes mellitus (odds ratio = 1.26; 95% CI, 1.16-1.37), cerebrovascular disease (odds ratio = 1.26; 95% CI, 1.10-1.45), and hypertension (odds ratio = 1.12; 95% CI, 1.05-1.20). Over time, there has been an increase in the number of drug therapies, including atypical antipsychotics, used to treat bipolar disorder.

Conclusion: Because of the significant association found between atypical antipsychotic use and several key comorbidities, it is important for physicians to recognize these associations and weigh the risks and benefits of atypical antipsychotics in their treatment strategies. [AHDB. 2009;2(4):184-191.]

Bipolar disorder (BPD) is a chronic, recurrent psychiatric illness characterized by episodes of both mania and depression. It is estimated that up to 2.6% of the US adult population is affected by this disorder, and that the lifetime prevalence rate for bipolar spectrum disorders ranges from 3.0% to 6.5%. Direct treatment costs are sizable, at $11,600 per patient-year. Medication is an essential part of successful treatment for BPD. Although mood stabilizers (eg, lithium, divalproex sodium, carbamazepine, lamotrigine) have traditionally been used for primary treatment of BPD, atypical antipsychotics (ie, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone) have also been found helpful for stabilizing mood and have been used with increasing frequency since the mid-1990s.

Atypical antipsychotics have been used for BPD even before they received a US Food and Drug Administration (FDA) indication (very recently) for this condition. Patients with BPD may need antidepres-
sant medication during periods of depression. Because of the risk of triggering mania, physicians often prescribe antidepressants (ie, tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors) with a mood stabilizer.

In March 2000, olanzapine was the first atypical antipsychotic to receive FDA indication for the treatment of mania. The off-label use of some atypical antipsychotics for BPD occurred before that. Subsequently, all the other atypical antipsychotics, with the exception of clozapine, received FDA approval for the treatment of BPD:
• Risperidone—in December 2003
• Quetiapine—in January 2004
• Aripiprazole—in September 2004
• Ziprasidone—in March 2006.

The use of medications for conditions other than those approved by the FDA is known as off-label use. Although medications are often used off-label in the pediatric patient population, off-label use has also been common in adult clinical practice for diseases such as cancer, cardiovascular disorders, psychiatric disorders, and dementia. Indeed, more than 60% of patients taking antipsychotics received these medications for at least 1 off-label use.

Off-label use of antipsychotics plays an important role in psychiatry because of the number of different indications for which there is no single, clearly preferred treatment. Currently, atypical antipsychotics have limited efficacy in, but are being used off-label for, dementia, non–BPD-related depression, obsessive compulsive disorder, and posttraumatic stress disorder.

Given drug safety considerations, postmarketing surveillance that can identify patients who are at high risk for receiving medications off-label will help ensure that the benefits of off-label treatment outweigh its risks. Because most off-label uses have little to no scientific support, it is important to keep track of the extent to which such uses occur, as well as the particular circumstances under which they occur.

We therefore proposed this study to determine the degree to which atypical antipsychotics were used off-label in patients with BPD and to identify patient characteristics most associated with off-label use. Although other drugs were prescribed off-label for patients with BPD, we focused specifically on atypical antipsychotics. This relatively new class of drugs has seen a tremendous rise in utilization and in spending, and has become a focus of attention for both private and public healthcare payers.

KEY POINTS

▷ Many off-label uses have little to no scientific support, so tracking the extent and circumstances under which they occur can enhance safety.

▷ This study focused on off-label use of atypical antipsychotics for patients with bipolar disorder, because this relatively new class has seen a tremendous rise in utilization and spending, thus becoming a focus for private and public payers.

▷ Results show a 5-year growing trend in the use of and spending on atypical antipsychotics and antidepressants for bipolar disorder. Reimbursement for atypical antipsychotics increased from $1050 per 100 patients to $4800, a more than 4-fold increase.

▷ During the study period, psychiatrists were more likely to prescribe off-label atypical antipsychotics than general physicians, which could be the result of earlier evidence showing benefits for these agents in bipolar disorder. The majority of these medications have since received an indication for this condition.

▷ Metabolic complications should be carefully considered when prescribing atypical antipsychotics for patients with bipolar disorder.

Methods, Materials

The primary data source was the PHARMetrics managed care medical claims database, a patient-level database consisting of claims for more than 45 million patients across 70 managed care plans nationwide. This database contains information on pharmacy claims, hospital institutional claims, outpatient medical claims, patient demographics (age and geographic distributions in the database are close to those for the entire United States), provider specialty, and other patient enrollment information. The study period was from January 1, 1998, through December 31, 2002.

We started with 709,865 patients who had at least 1 medical claim with a diagnosis of affective disorder (ICD-9 296.xx) or cyclothymia (ICD-9 301.13). We then excluded all Medicaid recipients (n = 44,095). Studies indicate that the Medicaid population is unique and may have different disease prevalence and drug-use patterns than the general population. Patients with schizophrenia (n = 15,199), who have been studied elsewhere in the literature, and patients (n = 633,050) with only a depression diagnosis code (ICD-9 311, 296.2x, and 296.3x) were also excluded. Because less than 0.1%
of the study group had cyclothymia, patients with that disorder were not categorized separately. Although some of these individuals with depression may be expected to be diagnosed with BPD eventually, no conclusive evidence of BPD was available during this study. A total of 17,521 patients younger than age 18 were also excluded.

After these exclusions, we were left with a study cohort of 105,771 adult patients (age ≥18) who met the criterion of having a BPD diagnosis, as indicated by ICD-9 codes 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, or 296.8.

Because some patients in the PHARMetrics database have limited (or nonexistent) drug coverage, we expected them to have a lower likelihood of atypical antipsychotic use. We conducted our analyses for a subcohort of 58,918 adult patients who received at least 2 prescriptions for BPD-related medications during the study period. By excluding patients who received ≤1 prescription, we could focus on BPD-diagnosed individuals with some nonzero probability of off-label drug use.

Prescribed Drugs

The study focused on 4 types of BPD medications: (1) lithium and other anticonvulsants, including divalproex sodium, carbamazepine, lamotrigine, gabapentin, topiramate, and oxcarbazepine; (2) atypical antipsychotics, including olanzapine, risperidone, ziprasidone, aripiprazole, and quetiapine; (3) typical antipsychotics, including haloperidol, chlorpromazine, and perphenazine; and (4) antidepressants, including nefazodone, trazodone, mirtazapine, venlafaxine, and bupropion. For each quarter during the 5-year study period, the number of prescriptions per 100 patients was calculated using the total number of prescriptions divided by the total number of patients (in 100s) in that quarter. Similarly, the quarterly reimbursement per 100 patients was calculated by dividing the total drug reimbursements by the number of patients (in 100s) in the quarter.

Off-Label Use Definition

The off-label use of an atypical antipsychotic was defined as a patient’s receipt of olanzapine before March 2000 or any other atypical antipsychotic during the entire study period. Hence, the dependent variable is a dichotomous variable (off-label use = 1, non–off-label use = 0). Patients may have been taking other medications for BPD.

Covariates

There are 2 known major types of clinical comorbidities among patients with BPD: psychiatric disorders and general medical comorbidities.20-22 Psychiatric disorders include alcohol and substance abuse disorders, anxiety disorder, impulse-control disorder, personality disorder, and eating disorders. General medical comorbidities include diabetes mellitus, cancer, hypertension, chronic obstructive pulmonary disease, cerebrovascular disease,
ischemic heart disease, arthritis, and obesity. All comorbidities were identified by their ICD-9 codes in either institutional or medical claims files after the date of first diagnosis of BPD. All comorbidities were represented by dichotomous variables in the statistical analyses.

The age of BPD onset for each patient was calculated as the year of bipolar diagnosis minus the patient’s birth year. Sex was a dichotomous variable (male = 1, female = 0). A final dichotomous variable distinguished between whether a patient visited a psychiatric specialist (yes = 1, no = 0). Because the PHARMetrics database does not provide a patient’s race or ethnicity, neither could be included in the data analysis.

Data Analysis

For the patient cohort and subcohort, descriptive statistics were computed for off-label use of atypical antipsychotics, use of other BPD medications, such as mood stabilizers, as well as for the demographic and comorbidity covariates mentioned above. And a logistic regression analysis was performed to assess the association between off-label use of atypical antipsychotics and the covariates. The data were analyzed using SAS version 8.2 (SAS Institute, Cary, NC).

Results

Figures 1 and 2 depict the drug-use and drug-reimbursement patterns, respectively, for patients with BPD in the database from 1998 to 2002. Quarterly lithium prescriptions remained steady, at approximately 10 prescriptions per 100 patients, but use of other medications—including anticonvulsants, antipsychotics, and antidepressants—increased during the study period. Consequently, the overall drug reimbursement trend was increasing; atypical antipsychotic reimbursements alone increased from $1050 to $4800 per 100 patients, a more than 4-fold increase.

Descriptive statistics are presented in Table 1. Of the entire cohort consisting of 105,771 patients, 7499 (7.1%) received off-label prescriptions of atypical antipsychotics for the treatment of BPD. Of the subcohort of patients who received pharmaceutical prescriptions for BPD, the off-label use was 12.4%.

During the study period, 54.0% of patients in the cohort (54.4% of patients in the subcohort) visited at least 1 psychiatric specialist. Among the cohort group, 11,513 (10.9%) patients received at least 1 prescription for lithium, 26,149 (24.7%) received prescriptions for anticonvulsants, 35,472 (33.5%) received prescriptions for antidepressants, 19,138 (18.1%) received prescriptions for typical antipsychotics, and 11,065 (10.5%) received prescriptions for atypical antipsychotics.

The most common psychiatric and medical comorbidities (seen in more than 5% of the BPD-diagnosed patients) for the cohort and the subcohort included alcohol abuse and substance abuse, anxiety disorder, hyper-
A proportion of patients with BPD received the traditional mood stabilizer lithiunm for the treatment of BPD between 1998 and 2002. But there was an increasing trend in the use of other anticonvulsants, as well as the use of atypical antipsychotics and antidepressants. Overall, drug utilization among BPD patients increased during the study period, and the trend was especially pronounced for atypical antipsychotic medications.

This finding is consistent with other studies. For example, Jing and colleagues reported that the Medicaid expenditure for antipsychotics increased sharply from $166 million in 1991 to $5.5 billion in 2005 as a result of rising drug utilization and entry of new high-priced atypical antipsychotics. In the Medicaid program, the total number of antipsychotic prescriptions increased from 7.2 million in 1991 to 24.1 million in 2005. Although conventional antipsychotics were also used for the treatment of acute mania, long-term use was limited due to intolerable adverse events, including akathisia, extrapyramidal symptoms, and tardive dyskinesia. Atypical antipsychotics are generally regarded as having lower risk for causing extrapyramidal symptoms. However, with increasing evidence linking diabetes mellitus and other metabolic complications with some of the atypical antipsychotics,
many clinicians have become cautious about prescribing specific atypical antipsychotics.23-28

Between 1998 and 2002, off-label use of atypical antipsychotics was established as a treatment for BPD. Results show that 7.1% of patients with BPD (and 12.4% of the subcohort of patients being treated with medication) received atypical antipsychotics off-label. Moreover, atypical antipsychotics represented 10.5% of the total prescriptions (18.3% for the subcohort) used for BPD management. Because BPD is a complex disorder that can be characterized by a wide range of symptoms that vary in type and severity, treatment is likewise complicated, and it is not surprising that physicians turn to off-label therapies. According to a recommendation from the American Psychiatric Association, treatment for patients with severe BPD could involve lithium or divalproex in combination with an antipsychotic.25,29

Male patients had 22% lower odds than female patients of receiving atypical antipsychotics off-label, and patients who visited a psychiatric specialist had 52% higher odds than those seeing general physicians for receiving prescriptions for off-label atypical antipsychotics. These findings are consistent with findings from a recent study based on the Georgia Medicaid population.14 Of note, results from several clinical trials had demonstrated the efficacy of some atypical antipsychotics for BPD; the studies had been published before the FDA approved these medications for BPD.26-27 It is therefore possible that trained psychiatrists were familiar with these studies, and that could have influenced their prescribing behaviors.

Our study also shows that patients with some psychiatric comorbidities had increased odds of receiving atypical antipsychotics off-label: 51% increased risk with substance abuse, 47% with personality disorder, and 20% with anxiety disorder. These increases in risk could be related to the progression of BPD and the inability to manage symptoms effectively using conventional therapy. Moreover, these results are consistent with studies about off-label use of central nervous system pharmacotherapies.12-14

Another finding in this study is that increased odds (26.8%) of receiving atypical antipsychotic prescriptions for off-label use are associated with patients with cerebrovascular disease. Although it is not clear why this should be the case, some studies suggest that cerebrovascular events may occur in patients taking risperidone,39 olanzapine,39 or other antipsychotics.39,42 That is, there is some evidence of reverse causation. Further exploration of the link between cerebrovascular disease and atypical antipsychotics is certainly warranted. Clinicians should be aware of this potential when prescribing atypical antipsychotics for patients with BPD.

Similarly, the present study reveals that diabetes mellitus, obesity, and hypertension were significantly associated with the use of atypical antipsychotics. Again, why this association is more prevalent in patients with these comorbidities is unclear, but studies have linked the use of atypical antipsychotics to the development of metabolic complications.23,24,33 Therefore, metabolic complications should be carefully considered when prescribing atypical antipsychotics for patients with BPD.

The results of this retrospective analysis can be applied to off-label drug use for other therapeutic classes.
The use of drugs off-label is expected to continue to play an important role in clinical psychiatry and in other complicated diseases, such as cancer and cardiovascular disorders. Although off-label use is often based on scientifically sound results from clinical trials or other relevant studies, risk/benefit management should be part of any off-label drug therapy.

Limitations
This study population was limited to individuals in US managed care organizations. Thus, findings should not be generalized to Medicaid or other populations. Because we were unable to assess each patient’s drug therapy and diagnosis prior to the study period, patients who were in remission from BPD were not included in the study. Moreover, because healthcare coverage varies among health plans, the healthcare utilization and drug-use patterns may reflect the characteristics of the particular managed care plans in this database.

Because of the limited information from retrospective claims, we are unable to assess treatment for patients who received a bipolar diagnosis but had no follow-up drug therapy. To minimize potential bias, we conducted analyses based on both a cohort and subcohort of patients who were treated with medication.

Conclusion
BPD is a complex psychiatric condition that has proved difficult to treat. The disease severity and response to previous treatment are used to guide drug therapy. As this study has shown, off-label drug use for patients with BPD is common in clinical practice. Because the odds of using atypical antipsychotics were greater for patients who had some key comorbidities, such as substance abuse, diabetes, or hypertension, it is important to recognize these associations and consider the risks and benefits of atypical antipsychotic use in the treatment strategies.

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References
STAKEHOLDER PERSPECTIVE

Health Plans’ Approaches to Managing Appropriate Use of Antipsychotic Drugs

Outpatient prescription drug formularies were originally developed in the early 1990s, when only the first “atypical” antipsychotic—Clozaril—had entered the market. At that time, first-generation antipsychotics, such as Haldol, Mellaril, Prolixin, and Thorazine, were often prescribed. These agents, however, were associated with extrapyramidal, anticholinergic, and alpha-adrenergic side effects, leading physicians to carefully assess the risks and benefits before prescribing any of them. With limited utilization, this drug class did not hit the “radar screen” of managed care.

When the newer atypical antipsychotics—such as Risperdal, Zyprexa, and Seroquel—hit the market, they were touted as having an improved side-effect profile and reduced extrapyramidal effects. The drug companies heavily marketed these new agents as superior to their first-generation counterparts, and premium priced their products, anticipating that clinicians would quickly adopt them as their preferred drugs.

The utilization and cost of these antipsychotics quickly escalated. Pharmacy & Therapeutics Committees at health plans and pharmacy benefit management (PBM) companies across the country thoroughly reviewed the clinical attributes and limitations of the typical and atypical antipsychotic medications. Along with safety and efficacy, cost was also taken into consideration.

Some plans and PBM companies decided it was prudent to restrict the use of the newer agents to specialists and use the prior authorization mechanism to review requests from primary care physicians. Others decided to review all requests for the atypical antipsychotics to ensure that they were being prescribed in accordance with (1) US Food and Drug Administration–approved indications; (2) indications recognized in well-respected drug compendia; or (3) positive outcomes substantiated in well-designed and well-conducted studies published in peer-reviewed journals.

This approach to a new class of drugs was common when closed formularies—with a flat copay or a brand/generic copay structure—were prevalent. As the industry moved to a 3-tier drug benefit design, the use of prior authorization structure was reduced to an extent, although it is still practiced in some instances.

Any health plan or PBM company that has a drug or a drug class under prior authorization will periodically review the pattern associated with the requests it is receiving, and how the standard of care has changed over time. As a result, some plans and PBM companies will (1) remove the prior authorization requirement on that class entirely; (2) require reviews from nonspecialists only; or (3) use the tier structure as the only means of differentiating medications as preferred or nonpreferred.

This process occurs with many new agents and drug classes as they are used over the course of time in many different patient types. This pattern is not exclusive to atypical antipsychotics being prescribed for bipolar disorder.

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