Research report

Therapeutic drug and cardiovascular disease risk monitoring in patients with bipolar disorder

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Abstract

Objectives: We assessed whether patients with bipolar disorder received serum drug level and toxicity monitoring for mood stabilizers and assessment of cardiovascular disease (CVD)-related risk factors attributed to atypical antipsychotic medications.
Methods: A population-based study of individuals with bipolar disorder was conducted between July 2004 and July 2006. Based on American Psychiatric and American Diabetes Association guidelines, we assessed whether patients received recommended drug level and toxicity monitoring tests on or within 6 months for mood stabilizers, and lipid and glucose tests for atypical antipsychotics. Multivariable regression was used to determine the patient factors associated with receipt of lab tests.
Results: Of the 435 patients (mean age=49 years, 14.3% female, 22.8% nonwhite), 60.3% were currently prescribed mood stabilizers and 65.5% were prescribed atypical antipsychotics. Overall, 39.7% received a serum drug level for mood stabilizers, 38.8% received a thyroid function test for lithium, and the majority (71.4%–75.9%) received complete blood counts and hepatic function tests for valproate or carbamazepine. About half of patients prescribed atypical antipsychotics received cholesterol counts (49.6%), and 68.7% received serum glucose levels. After adjusting for patient factors, women prescribed atypical antipsychotics were less likely than men to receive cholesterol counts (OR=0.43; $p<0.05$).
Limitations: Single-site retrospective study and a relatively short observation period.
Conclusions: About half of patients received recommended lab tests for mood stabilizers and atypical antipsychotics. Additional research regarding whether the receipt of these lab tests is associated with improved outcomes will inform efforts to improve quality of care related to drug toxicities and CVD risk factors in patients with bipolar disorder.
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1. Background

Bipolar disorder is a chronic condition associated with substantial functional impairment, and is one of the most expensive mental health conditions in the U.S. (Bauer et al., 2002; Simon and Unutzer 1999). Up to 40% of costs associated with bipolar disorder are related to general medical care (Simon and Unutzer, 1999). Patients with bipolar disorder are prone to co-occurring medical conditions, with the most common conditions being hypertension (33%), hyperlipidemia (27%), and type 2 diabetes (15%) (Fenn et al., 2005; Kilbourne, 2005). These conditions are also leading risk factors for cardiovascular disease (CVD) (Folsom et al., 2006; Khot et al., 2003), which is the leading cause of morbidity and mortality among patients with bipolar disorder (Osby et al., 2001). Medications used to manage bipolar disorder can contribute to an increased risk of medical conditions including CVD. Specifically, adverse drug effects can include thyroid (Bocchetta et al., 1991; Bocchetta and Loviselli, 2006; Kleiner et al., 1999), kidney, (Nakajima et al., 2004) or hepatic dysfunction, (Patsalos 2005) as well as weight gain and its associated insulin resistance and risk of diabetes (Goldberg, 2000; Marcus et al., 1999; Newcomer, 2005).

Therefore, timely monitoring for drug toxicity is essential to preventing adverse effects of these medications in patients with bipolar disorder. Specifically, routine drug level monitoring of mood stabilizers (e.g., lithium, valproate) is recommended at least every 6 months by guidelines from the American Psychiatric Association and others, in order to assess adherence and monitor for potential drug toxicities (Bauer et al., 1999; Suppes et al., 2005). The guidelines also recommend thyroid function tests for lithium, and complete blood counts (CBCs) and hepatic function tests for valproate and carbamazepine.

Furthermore, the increasing use of atypical antipsychotic medications in bipolar disorder has also raised the concern of the subsequent risk of weight gain and diabetes associated with several of these medications (Newcomer, 2004). The American Diabetes Association recently recommended that patients prescribed atypical antipsychotic medications receive regular monitoring for diabetes and CVD-related risk factors, including fasting glucose and lipid panels every 3 months (Clark, 2004). Recent studies have assessed CVD-related risk factor monitoring in patients with schizophrenia (van Winkel et al., 2006; Weissman et al., 2006). However, whether patients with bipolar disorder are receiving adequate laboratory monitoring for these CVD-related risk factors has not been assessed. Therefore, the purpose of this study is to assess the prevalence of therapeutic drug and CVD-related risk factor monitoring among a large cohort of patients with bipolar disorder, and evaluate the patient factors associated with the receipt of drug monitoring.

2. Methods

This is a retrospective study of therapeutic drug and CVD-related risk factor monitoring among patients diagnosed with bipolar disorder in a routine care setting. Data for this study were obtained from the Continuous Improvement for Veterans in Care-Mood Disorders (CIVIC-MD), a population-based cohort study examining factors associated with quality and outcomes of care for bipolar disorder. Patients were enrolled if they received a diagnosis from their clinicians of bipolar disorder (bipolar I, II, NOS) or schizoaffective disorder-bipolar subtype, and were receiving care at a large VA Medical Center between July 2004 and July 2006. Patient exclusion criteria were designed to be minimal in order to assess quality of care in a naturalistic setting, and included the inability to complete a survey or provide informed consent. As veterans, these patients were eligible for care if they served in the U.S. military, and as a requirement, understood English. All patients provided informed consent and this study was approved by local institutional review boards.

2.1. Data collection and measures

Enrolled patients completed a baseline survey on demographic, behavioral, and treatment factors. Medication use and lab tests were obtained from the VA electronic administrative data.

2.2. Pharmacologic treatment

Medication use was ascertained from the local VA data system, which contains information on all psychotropic medication use, including drug name, drug class codes, dose, fill and refill dates, days supply, and quantity. The vast majority of enrolled VA patients receive medications through the VA health care system because of the nominal costs of the drugs compared to other sources (e.g., $7–$8 per 30-day prescription). VA drug class codes were used to extract prescription data for each patient and for each medication. We identified the patients' prescription or refill that occurred closest to the enrollment date (referred to as the "index" prescription date). We focused on prescriptions that were filled for at least 6 months, because we wanted to

examine receipt of lab tests for maintenance purposes among patients who were routinely prescribed these medications.

We focused on the three most common first-line mood stabilizers used to treat bipolar disorder that were prescribed in our study cohort: lithium, valproate (or valproic acid or divalproex), and carbamazepine. We also ascertained atypical antipsychotic prescriptions in order to examine CVD risk assessment for patients using these medications. We included the following atypical antipsychotic medications that were most commonly used for bipolar disorder at this VA Medical Center during the study: olanzapine, clozapine, quetiapine, and risperidone. These medications are associated with an increased risk of weight gain and diabetes according to the American Diabetes Association consensus panel on antipsychotic drugs (Clark, 2004).

2.3. Therapeutic monitoring: criteria and measures

Our primary outcomes included receipt of drug level and toxicity monitoring for mood stabilizers (lithium and anticonvulsants), as well as receipt of blood tests to monitor CVD-related risk factors (lipids, glucose) among patients prescribed atypical antipsychotics. For all tests, we chose to measure receipt of a lab test on or within 6 months after the index prescription date to reflect the minimum necessary standards of care for maintenance pharmacotherapy, and the vast majority of patients were in continued treatment for bipolar disorder at the time of study enrollment.

We developed indicators for receipt of drug level and toxicity monitoring based on the American Psychiatric Association's (APA's) practice guidelines for bipolar disorder (Unutzer et al., 2000). The same guidelines for mood stabilizer drug level and toxicity monitoring are also present in the VA Bipolar Disorder Practice Guidelines (Bauer et al., 1999) and recently published recommendations from the Texas Medication Algorithm Project (Suppes et al., 2005). The guidelines recommend routine monitoring of drug levels every 6 months for lithium and valproate (including valproic acid and divalproex) to achieve therapeutic range (Table 1). For carbamezapine, drug level monitoring every 6 months is primarily recommended for seizure control. Routine monitoring of drug levels is required to gauge adequate dosing and to detect potential toxic levels that can lead to side effects and comorbidity. The guidelines also recommend routine thyroid function and renal function (BUN: blood urea nitrogen/creatinine) tests every 6 months for lithium, as this drug increases the risk of thyroid and kidney abnormalities. Complete blood counts and hepatic function tests every 6 months for valproate and carbamazepine are also recommended because of the increased risk of thrombocytopenia (low platelet counts) and effects on liver function.

We also ascertained receipt of lab tests recommended by the American Diabetes Association's consensus panel for diabetes and CVD risk monitoring among patients taking atypical antipsychotic medications (Clark, 2004). The panel recommended routine monitoring of lipids and fasting glucose to ascertain risk of diabetes and cardiovascular disease. We determined whether patients received lipid tests (i.e., total cholesterol, triglycerides) and serum glucose level on or within 6 months after the index prescription date. The optimal frequency of lab tests for CVD risk factors has not been officially established, although the American Diabetes Association recommends every 3 months for lipids and fasting glucose. We chose to use 6 months as a criterion because of the concern that obtaining these tests every 3 months is unrealistic for many patients, and because of the lack of evidence linking quarterly testing to improved health outcomes.

Table 1
Receipt of recommended drug level and toxicity monitoring tests for mood stabilizers and cardiovascular risk factors

Medication	Recommended routine tests (every 6 months)	N (%) receiving test
Mood stabilizers (N=232) [a]		
	Drug serum level concentration	92 (39.7%)
Lithium (N=121)		
	Drug serum level concentration	23 (19.0%)
	Toxicity monitoring	
	Thyroid function test	47 (38.8%)
	Renal function (creatinine/BUN)	100 (82.6%)
Valproate (N=141)		
	Drug serum level concentration	79 (56.0%)
	Toxicity monitoring	
	Complete blood count (CBC)	102 (72.3%)
	Hepatic function (ALT/AST)	107 (75.9%)
Carbamazepine (N=28)		
	Drug serum level concentration	12 (42.9%)
	Toxicity monitoring	
	Complete blood count (CBC)	20 (71.4%)
	Hepatic function (ALT/AST)	21 (75.0%)
Atypical antipsychotics (N=252) [b]		
	Lipids	
	Total cholesterol	125 (49.6%)
	Triglycerides	124 (49.2%)
	Serum fasting glucose level	173 (68.7%)

[a] American Psychiatric Association Guidelines for Bipolar Disorder Treatment.
[b] American Diabetes Association guidelines for CVD risk assessment for patients receiving atypical antipsychotic medications.

2.4. Patient factors

Patient factors thought to be associated with receipt of lab tests were chosen based on prior research on factors influencing receipt of care and outcomes in bipolar disorder (Kilbourne et al., 2005b,a). We considered patient demographics, including age, race/ethnicity, gender, and education. We also included enabling factors that potentially impede access to care for mental disorders, including current illicit drug use (marijuana, cocaine, hallucinogens, or stimulants), use of care outside the VA, access to transportation, and distance to the mental health facility (Kilbourne et al., 2005b,a; McCarthy and Blow, 2004). We also included clinical factors including bipolar diagnosis and whether the patient was hospitalized at the time of enrollment (Kilbourne et al., 2005b).

2.5. Analyses

Descriptive statistics were used to determine the frequency of patients prescribed lithium, valproate, carbamazepine, and atypical antipsychotic medications as well as the frequencies of the pertinent lab tests within a 6-month period (Table 1). Multivariable logistic regression analysis was used to determine the patient factors that were independently associated with receipt of drug level and toxicity monitoring tests, and receipt of lipid or glucose monitoring. Patient factors were entered into each model if bivariate analyses demonstrated significance at the level of $p < 0.10$. All analyses were performed using SAS version 9.0 (SAS Institute, Cary, NC).

3. Results

Of the 435 patients enrolled in CIVIC-MD, the mean age was 49 years (SD=11, range: 21–78), 14.3% ($n = 62$) were female, 13.3% ($n = 58$) were African-American, and 9.4% ($n = 41$) other race/ethnicity. The majority (74%) were diagnosed with bipolar I disorder, 2% bipolar II, 7% bipolar not otherwise specified, and 17% schizoaffective disorder-bipolar subtype. In addition, 17.5% ($n = 76$) completed college, 28.3% ($n = 123$) reported any illicit drug use, 29.4% ($n = 128$) relied on public transportation to get to appointments, and 16.3% ($n = 71$) lived >50 miles from the VA mental health facility. Almost a quarter (22.5%, $n = 98$) were enrolled during an inpatient stay.

Complete pharmacy data were available on 385 CIVIC-MD enrollees (88.5%). Demographic characteristics did not differ between those with or without pharmacy data. Overall, 60.3% ($n = 232$) were prescribed any of the three mood stabilizers, and 31.4% ($n = 121$) were prescribed lithium, 36.6% ($n = 141$) valproate, and 7.3% ($n = 28$) carbamazepine. A total of 252 (65.5%) were prescribed an atypical antipsychotic medication.

3.1. Mood stabilizer monitoring

Of those prescribed any one of three mood stabilizers (lithium, valproate, carbamazepine), 39.7% ($n = 92$) received a serum drug level on or within 6 months from the index prescription date (Table 1). Receipt of serum drug level by specific drug ranged from 19.0% (lithium) to 56.0% (valproate). Among those prescribed lithium, 38.8% ($n = 47$) received a thyroid function test while 82.6% ($n = 100$) received a renal function test.

Among those prescribed valproate, the majority received complete blood counts (72.3%, $n = 102$) and hepatic function tests (75.9%, $n = 107$) within 6 months. Similar frequencies were evident for patients prescribed carbamazepine: the majority received complete blood counts (71.4%, $n = 20$) and hepatic function tests (75.0%, $n = 21$).

3.2. CVD risk monitoring — atypical antipsychotics

Approximately one-half of patients prescribed atypical antipsychotic medications received recommended CVD risk factor lab tests <=6 months, including total cholesterol (49.6%, $n = 125$) and triglycerides (49.2%, $n = 124$). About two-thirds (68.7%, $n = 173$) had a glucose level measured.

3.3. Multivariable analyses

After adjusting for age, gender, bipolar disorder diagnosis, college education, and inpatient enrollment, women prescribed valproate were less likely to receive a drug level monitoring test (adjusted OR=0.31; 95% CI: 0.10, 0.97; $p < 0.04$). Women prescribed atypical antipsychotic medications were also less likely to receive a total cholesterol test (adjusted OR=0.43; 95% CI: 0.19, 1.00; $p < 0.05$) or triglyceride test (adjusted OR=0.44; 95% CI: 0.19, 1.00; $p < 0.05$). No other patient factors were significantly associated with receipt of recommended labs for mood stabilizers or atypical antipsychotic medications (data not shown).

4. Discussion

We conducted one of the first comprehensive studies assessing receipt of laboratory monitoring for patients taking medications for bipolar disorder, and one of the

first to assess receipt of CVD risk factor monitoring among patients prescribed atypical antipsychotic medications. Drug level and toxicity monitoring of mood stabilizers are crucial for maintaining adequate care and overall health for patients with bipolar disorder. The increased use of atypical antipsychotics in bipolar disorder (Bauer and Mitchner 2004) has increased the call for the monitoring of CVD risk factors among these patients as well. Our findings regarding the receipt of serum drug level and toxicity monitoring were mixed. Less than 40% of patients prescribed mood stabilizers received monitoring of drug levels, and a similar percentage of patients prescribed lithium received the recommended thyroid function test. At the same time, the majority of patients prescribed valproate or carbamazepine received recommended toxicity monitoring tests. Still, only half of patients prescribed atypical antipsychotic medications received recommended lipid tests, and two-thirds received glucose testing, falling short of current recommendations for routine CVD risk monitoring.

Our results are similar to drug level and toxicity monitoring rates reported elsewhere. Notably, a study of Medicaid patients from the same region as our cohort found that about half (58%–64%) received adequate mood stabilizer level monitoring and even fewer (4%–56%) received drug toxicity monitoring such as thyroid function or complete blood counts (Marcus et al., 1999). A more recent analysis of data from a privately insured cohort of 769 bipolar patients from Medicaid and private sector health plans revealed similar trends for mood stabilizer toxicity monitoring. Among patients prescribed lithium, 65.8% received a thyroid function test; and among those prescribed valproate, only 51.9% received a complete blood count (Kilbourne and Pincus, 2004). However, only 29.8% of these patients from this private sector health plan who were prescribed an atypical antipsychotic medication received a cholesterol test, and 15.5% received a fasting glucose. The discordance in CVD risk assessment between our results and the results from this private sector health plan may be due to the VA's efforts to educate providers to monitor diabetes risk among patients taking atypical antipsychotic medications.

The majority of patients in our cohort received adequate drug toxicity monitoring. Nonetheless, the apparent gap in serum drug level monitoring is problematic in part because even small differences in these levels can lead to relapse, and drug level monitoring is an important indicator of medication adherence (Suppes et al., 2005). Still, we were surprised at the low rates of serum drug level and CVD risk factor

monitoring in this VA, which is considered once of the most integrated health care systems in the United States, and despite the fact that patients are not charged for blood work. The reasons for inadequate monitoring may include system-level barriers at this study site, notably the inaccessibility to laboratory testing (the laboratory at this facility often closes at 2 pm). In addition, the mental health facility is located several miles away from the main general medical clinic of this VA, and hence, suboptimal testing rates may be due to a lack of coordinated care (e.g., VA schedulers not coordinating blood work on mental health appointment days). Providers might also believe that frequent routine drug level monitoring is too burdensome on patients. Still, our 6-month time frame as a minimum necessary standard still demonstrated substantial gaps in guideline-concordant monitoring for patients with bipolar disorder.

Few patient factors were associated with receipt of lab tests, with the exception of gender. In contrast to our observed findings that VA women were less likely to receive drug level monitoring for valproate, women were more likely than men in the Medicaid cohort to receive drug level monitoring tests (Marcus et al., 1999). In our study, women prescribed atypical antipsychotic medications were also less likely to receive recommended lipid tests, perhaps because of the assumption that men are at increased risk of CVD. Reliance on public transportation, substance use, and clinic distance had no significant association with receipt of lab tests. Perhaps patients with limited transportation options or who live far away have adapted by scheduling visits and lab tests back-to-back, and hence, are just as likely to receive these services as those who live closer to the VA facility (McCarthy et al., 2006). The VA facility where patients were enrolled represents the sole provider of VA specialty mental health services for veterans living in the region, and represents the only VA site in which lab tests can be completed. Nonetheless, the lack of association of other patient factors with receipt of lab tests serves as a reminder that access to important laboratory monitoring is suboptimal for many patients irrespective of individual characteristics.

4.1. Limitations

There are limitations to this study that warrant consideration. The study was limited to a single site and region. In general, however, VA patients with bipolar disorder represent a vulnerable patient population (i.e., older, lower income) similar to that seen by other publicly funded mental health provider settings (e.g., Medicaid) to which our findings may be generalizable.

In addition, the aforementioned system-level barriers in our study setting (e.g., physically separate mental and general medical facilities) may reflect barriers typically seen outside the VA. Second, VA administrative data do not differentiate fasting versus non-fasting lipid labs, nor do they differentiate labs ordered by the provider versus those not followed through by the patient. Hence, we are unable to reliably report the actual results of specific lab tests in a manner that would provide clinically meaningful information. Finally, as a retrospective study, we were unable to assess monitoring rates of other CVD-related risk factors, notably weight, BMI, and waist circumference. At the time of this study, these data were not routinely available from the VA administrative data files, and is available, were often missing. To increase the generalizability of our findings, we focused on indicators of guideline-concordant care for patients with bipolar disorder based on available administrative (claims) data. In contrast, data on weight, BMI, and other clinical indicators are only available from chart reviews. Still, a more extensive chart review involving primary data collection of these data was beyond the scope of this current retrospective study.

Nonetheless, our findings indicate significant gaps in the receipt of laboratory monitoring related to mood stabilizers and atypical antipsychotics. Monitoring rates should be at a minimum 80% at a population level and optimally, at 95%. Mood stabilizer drug level and toxicity monitoring labs are crucial tools that providers can use to manage the risk of adverse outcomes, and help inform patients of the potential risks and benefits of these medications. (Masand et al., 2002) Given the increased use of atypical antipsychotics for the management of bipolar disorder, ongoing monitoring of CVD risk factors is essential to prevent adverse outcomes among these patients.

At the same time, there is a lack of consensus regarding the optimal frequency of CVD risk factor monitoring in patients taking atypical antipsychotics. Currently, in the VA and elsewhere, there is also a lack of clarity regarding which provider is responsible for CVD risk factor monitoring among patients prescribed atypical antipsychotic medications. Once deemed solely a "general medical issue", many mental health providers are opting to assess diabetes risk and run lipid panels on their patients. Recently, the National Committee on Quality Assurance adopted measures that assess lithium and valproate toxicity monitoring across health plans in order to monitor the quality of care for these patients. However, no measures have been officially adopted for CVD risk factor monitoring among patients taking atypical antipsychotic medications.

In addition, while laboratory monitoring is clinically reasonable and many of these tests are routine in general medical care, these recommendations have not been validated with regard to an associated reduction in adverse patient outcomes. For example, frequent lipid panels and glucose levels may be less appropriate for patients with no family history of CVD and unrealistic for publicly funded providers with limited resources. For these recommendations to enjoy widespread adoption by providers, they need to be validated and operationalized as indicators of quality of care in order to benchmark whether gaps in necessary care exist.

5. Conclusions

Further research is necessary to determine whether routine laboratory monitoring correlates with patient outcomes, especially in regards to the optimal time period for re-measurement. In the future, validated and feasible quality indicators for laboratory monitoring can be used as performance measures to benchmark quality of care and identify potential gaps in the receipt of these services. Validated performance measures for laboratory testing can also be used in evaluating interventions designed to improve the quality of care for patients with mental disorders. Ultimately, the refinement of guidelines and indicators for therapeutic drug monitoring will inform efforts to improve management of drug toxicities and CVD risk factors in patients with bipolar disorder.

Acknowledgements

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