Therapeutic Drug Monitoring of Mood Stabilizers in Medicaid Patients With Bipolar Disorder

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Objective: The authors’ goal was to determine the extent and pattern of blood serum monitoring of mood stabilizers in Medicaid patients with bipolar disorder. Method: Data were drawn from a Medicaid medical claims data set from Pittsburgh and the surrounding region. The authors identified bipolar patients using lithium, valproate, and carbamazepine (N=718) and then examined the patient demographic, diagnostic, and service use variables associated with therapeutic drug monitoring. Results: A substantial proportion of lithium users (36.5%), valproate users (42.4%), and carbamazepine users (42.2%) with bipolar disorder diagnoses did not receive therapeutic drug level testing during the 12-month study period. Carbamazepine users who were male or in the 30–49-year age range were significantly less likely to be tested for serum drug level. Lithium users who did not receive partial-hospitalization psychiatric services and valproate users who received mental health case management were also less likely to be tested for serum drug level. Over one-half of the lithium users (54.1%) did not receive thyroid function tests, and few (4.2%) received renal function tests. Patients who did receive tests for serum drug level were likely to receive the other recommended tests. Conclusions: Many Medicaid patients with bipolar disorder received no therapeutic drug monitoring. Patient sociodemographic characteristics contributed little to explaining this omission, although some types of service utilization were related to rates of serum drug level testing.

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High cost, extensive morbidity, and availability of effective treatment combine to make bipolar disorder a matter of clinical and public health importance. In the United States, the cost of bipolar disorder is estimated to exceed $45 billion per year (1).

Therapeutic drug monitoring is an established tool that gives clinicians greater control over medication dose and helps in determining patient compliance and detecting early signs of medication toxicity. Therapeutic drug monitoring has been widely cited as a method to evaluate the adequacy of lithium therapy and to titrate lithium doses (2).

Lithium has many characteristics that make it particularly well suited to therapeutic drug monitoring, including dose-dependent efficacy and individual variation in absorption, distribution, and excretion. Research (3, 4) has demonstrated that even small differences in lithium blood level substantially affect the risk of relapse. Lithium levels vary according to a wide range of factors, such as noncompliance with treatment, medication-related changes in lithium excretion (e.g., due to use of diuretics or nonsteroidal anti-inflammatory drugs), dietary changes, and intercurrent medical illness (5–7).

Regular lithium monitoring has been shown to decrease the risk of lithium toxicity when no clinical symptoms or side effects are present to indicate dangerously high lithium serum levels (8). It also can help increase detection of subtherapeutic drug levels and may help protect medical providers from liability claims.

Drug monitoring in bipolar disorder may increase early detection of subtherapeutic or elevated drug levels. It can also be used to help distinguish nonresponse from noncompliance. Some (9) have even argued that...
regular monitoring of serum blood levels improves treatment compliance by reinforcing the importance of taking medications as prescribed.

Although there is extensive experience in monitoring carbamazepine and valproate as antiepileptics, more recent efforts have focused on determining the serum levels of these agents required for mood stabilization. High levels of carbamazepine have been associated with higher rates of adverse events (10).

Professional consensus is reflected in two guidelines that endorse serum monitoring of lithium, carbamazepine, and valproate in the treatment of bipolar disorder (11, 12). Both guidelines state that blood should be drawn to monitor lithium serum level every 3–6 months, thyroid function every 6–12 months, and renal function every 6–12 months for patients on maintenance regimens of lithium. For valproate and carbamazepine users, the guidelines recommend drug level monitoring every 6–12 months and complete blood counts (CBCs) and liver function tests every year. Although clinical circumstances may require modifying these recommendations in individual cases, these testing schedules serve as a general standard of care.

We used a large Medicaid medical claims data set to investigate how often these recommendations are being followed in community practice and what patient and service use factors are related to medication monitoring.

METHOD

Data Source

Data were drawn from a Medicaid medical claims data set from Pittsburgh and the surrounding region. The data, collected on services provided between June 1994 and July 1995, were provided by the State of Pennsylvania Medical Assistance office. The data file included detailed service descriptions of approximately 8 million claims paid for 304,000 fee-for-service Medicaid enrollees in a seven-county region. Each line-item claim includes the patient’s primary and secondary diagnoses at the time of service along with the procedure code for the delivered service. Pharmacy claims include information on the brand and dose of medication for filled prescriptions. An associated data set enumerates the periods during which patients were eligible to receive Medicaid services. Patient demographic information, including age, sex, race, and zip code, was also available.

Case Selection

Patients were included in the analysis if they were adults aged 18–64 years who were enrolled in the Medicaid program for the entire 12-month study period and had two or more claims paid during the study year with a primary or secondary ICD-9 diagnosis of bipolar disorder (296.0, 296.4, 296.5, 296.6, 296.7, 296.8, 301.13). There were 1,336 subjects who met these criteria (274 persons were excluded from the analysis because they had only one claim for bipolar disorder during the study year). Since information about service use is not available during inpatient episodes, an additional 10 patients were excluded from the analysis because they were hospitalized for 30 or more days during the study period. In order for a patient to be considered a lithium user, a claim for a lithium prescription had to be paid in at least three of the four quarters during the study year. There were 518 lithium users. Similar criteria were used to define groups of valproate users (N=165) and carbamazepine users (N=147). These three groups were not mutually exclusive. All prescriptions were filled on an outpatient basis.

Procedure codes were used to identify each patient who had one or more paid claims during the year for testing of lithium, carbamazepine, or valproate serum level. Similarly, patients receiving CBCs or thyroid, renal, or liver function tests were identified. Since there is a range of recommended frequencies for these tests, we used a conservative approach and looked for only one or more of each type of test (serum drug level, CBC, thyroid function, renal function, and liver function) during the study year.

Analytic Strategy

We sought to determine the patient demographic, diagnostic, and service use variables associated with therapeutic drug monitoring for bipolar disorder. We did this in an attempt to measure the likelihood that these factors would increase or decrease compliance with the guideline recommendations.

Sociodemographic factors included age, sex, race, and urban residence. Patient residence in an urban or nonurban area was determined by using the U.S. Census Bureau Tape STF-3B (13), which summarizes the sample by zip code. A zip code was deemed to be nonurban if more than one-half of its residents lived in a nonurban region.

A co-occurring substance use disorder was defined as having one or more paid claims during the study year with a primary or secondary ICD-9 diagnosis of 291.xx, 292.xx, 303.xx, 304.xx, or 305.xx.

Categories of service providers and service types were used to identify patients who, during the study year, received at least one service for mental health case management, partial-hospitalization psychiatric services (day hospital treatment), or inpatient psychiatric services. These factors were considered in our analyses as markers of illness severity.

Statistical Methods

A chi-square statistic was used to evaluate the differences in the rates of serum level testing separately for each mood stabilizer within demographic and service use categories. Logistic regression models were used to estimate significant predictors of receiving a serum blood test. We ran separate models for each mood stabilizer group, using all demographic and service use variables as predictors. Phi coefficients were used to assess the association of receiving the recommended tests within each of the three medication groups. The analyses presented in this report are exploratory, and although we consider p<0.05 to indicate statistical significance, no corrections were made for multiple comparisons.

RESULTS

Use of Mood Stabilizers

Of the 718 bipolar patients who filled prescriptions for mood stabilizers, over one-half (57.8%) received lithium as the only mood-stabilizing medication. A substantially smaller fraction used valproate alone (15.2%) or carbamazepine alone (11.6%). Lithium and carbamazepine were used together by 7.7% of the bipolar patients, lithium and valproate by 6.5%, and carbamazepine and valproate by 1.1%. Only one of the bipolar patients (less than 0.1%) filled a prescription for all three mood stabilizers during the year. No differentiation was made between concurrent and sequential use.
TABLE 1. Characteristics of 718 Medicaid Patients With Bipolar Disorder and Mood Stabilizer Use Over 1 Year\textsuperscript{a}

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lithium Users (N=518)</th>
<th>Valproate Users (N=165)</th>
<th>Carbamazepine Users (N=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>N %</td>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>18–29</td>
<td>76 14.7</td>
<td>24 14.5</td>
<td>29 19.7</td>
</tr>
<tr>
<td>30–39</td>
<td>175 33.8</td>
<td>55 33.3</td>
<td>43 29.3</td>
</tr>
<tr>
<td>40–49</td>
<td>129 24.9</td>
<td>52 31.5</td>
<td>37 25.2</td>
</tr>
<tr>
<td>50–64</td>
<td>138 26.6</td>
<td>34 20.6</td>
<td>38 25.9</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>453 87.5</td>
<td>153 92.7</td>
<td>126 85.7</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>65 12.5</td>
<td>12 7.3</td>
<td>21 14.3</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>302 58.3</td>
<td>113 68.5</td>
<td>93 63.3</td>
</tr>
<tr>
<td>Male</td>
<td>216 41.7</td>
<td>52 31.5</td>
<td>54 36.7</td>
</tr>
<tr>
<td>Residence\textsuperscript{b}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>418 82.9</td>
<td>136 85.0</td>
<td>116 81.1</td>
</tr>
<tr>
<td>Nonurban</td>
<td>86 17.1</td>
<td>24 15.0</td>
<td>27 18.9</td>
</tr>
<tr>
<td>Service use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental health case management</td>
<td>138 26.6</td>
<td>75 45.5</td>
<td>41 27.9</td>
</tr>
<tr>
<td>Partial-hospitalization psychiatric services</td>
<td>122 23.6</td>
<td>56 33.9</td>
<td>33 22.4</td>
</tr>
<tr>
<td>Inpatient psychiatric services</td>
<td>179 34.6</td>
<td>87 52.7</td>
<td>48 32.7</td>
</tr>
<tr>
<td>Co-occurring diagnosis of substance or alcohol abuse</td>
<td>Laboratory testing</td>
<td>93 18.0</td>
<td>30 18.2</td>
</tr>
<tr>
<td>Serum drug level</td>
<td>329 63.5</td>
<td>95 57.6</td>
<td>85 57.8</td>
</tr>
<tr>
<td>Thyroid function test</td>
<td>238 45.9</td>
<td>95 57.6</td>
<td>85 57.8</td>
</tr>
<tr>
<td>Renal function test</td>
<td>22 4.2</td>
<td>93 56.4</td>
<td>92</td>
</tr>
<tr>
<td>CBC</td>
<td>--</td>
<td>77 46.7</td>
<td>66 44.9</td>
</tr>
<tr>
<td>Liver function test</td>
<td>--</td>
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</tr>
</tbody>
</table>

\textsuperscript{a} Drug groups are not mutually exclusive (see text for details).
\textsuperscript{b} Numbers do not add to total owing to missing data.
\textsuperscript{c} Not appropriate as specified by the guidelines for this medication.

Demographic and Service Use Characteristics

The bipolar patients in this Medicaid sample were primarily white (85.2%), urban (82.8%), and female (61.3%). Overall, the three drug groups were demographically similar (table 1). Approximately one-quarter of the lithium and carbamazepine users received care from case managers as part of their treatment, while about one-half of the valproate users did so. A similar distribution was found for partial hospitalization; approximately one-quarter of the lithium and carbamazepine users received such services, compared to one-third of the valproate users. Approximately one-third of the lithium and carbamazepine users received inpatient psychiatric services, while about one-half of the valproate users did so.

Therapeutic Drug Monitoring

Approximately two-thirds of the lithium users received a blood test to determine the lithium blood level during the 12-month study period (table 1). Slightly smaller percentages of the valproate and carbamazepine users received serum drug level testing during this period. The patients who received prescriptions during four calendar quarters did not have significantly higher rates of drug monitoring than those with three quarters of use.

The guidelines recommend that lithium users receive, at a minimum, yearly thyroid and renal function tests. Slightly fewer than one-half were tested for thyroid function, and few were tested for renal function during that time (table 1). Somewhat more than one-half of the valproate and carbamazepine users received CBCs, and slightly fewer than one-half received liver function tests. Among the lithium users, those who received partial-hospitalization psychiatric services had a higher rate of serum drug level testing (73.8% versus 60.4%) ($\chi^2=7.2$, df=1, $p=0.001$). Mental health case management for valproate users was associated with a lower rate of serum drug level testing (49.3% versus 64.4%) ($\chi^2=3.8$, df=1, $p=0.05$). Age, race, sex, urban/nonurban residence, co-occurring diagnosis, and other service use were not significantly associated with receiving serum drug level testing for any of the three mood stabilizers (data not shown).

Lithium users were more likely to receive the recommended serum level test if they also received partial hospitalization. Somewhat surprisingly, valproate users who received mental health case management services were less likely to receive serum level testing than those who did not receive case management. There were no statistically significant factors for carbamazepine testing.

After the demographic and service use variables were controlled for, logistic models revealed that lithium users who received partial hospitalization were approximately twice as likely as receiving a serum level test as were other lithium users (odds ratio=1.9, Wald $\chi^2=7.0$, df=1, $p=0.008$). Women were 1.3 times more likely (Wald $\chi^2=4.6$, df=1, $p=0.03$). Carbamazepine users who were 30 to 39 years old were 7.4 times less likely (Wald $\chi^2=9.8$, df=1, $p=0.002$) to receive a serum level test than the 18–29-year-old group. Those 40 to 49 years old were 0.6 times less likely to receive such tests (Wald $\chi^2=8.3$, df=1, $p=0.004$). Women were 3.3 times more likely (Wald $\chi^2=7.9$, df=1, $p=0.005$) to receive the test than men. Valproate users who were 30 to 39 years old were 3.3 times less likely (Wald $\chi^2=4.0$, df=1, $p=0.04$) to receive a serum level test than the 18–29-year-old group. Those 40–49 years old were 3.4 times more likely to receive such tests (Wald $\chi^2=4.1$, df=1, $p=0.04$). In addition, valproate users were 2.6 times less likely to be tested if they used mental health case management (Wald $\chi^2=6.4$, df=1, $p=0.01$) and 2.4 times more likely if they were users of partial hospitalization (Wald $\chi^2=5.1$, df=1, $p=0.02$).

Correlations between the recommended laboratory tests were generally high. A lithium user who received a serum level test was also likely to receive a thyroid function test ($\phi=0.62$, $\chi^2=198.0$, df=1, $p=0.001$) but not necessarily a renal function test ($\phi=0.14$, $\chi^2=10.1$, df=1, $p=0.001$). Valproate users who were tested for serum drug level were likely to receive a CBC ($\phi=0.65$, $\chi^2=46.8$, df=1, $p=0.001$) and a liver function test ($\phi=$...
We found that a substantial proportion of patients with bipolar disorder received no therapeutic drug monitoring during the course of 1 year. Approximately one-third of the patients treated with lithium and approximately 40% of patients treated with either valproate or carbamazepine did not receive serum drug level testing. Possible explanations for this degree of departure from guidelines include inaccessibility of laboratory testing, patient noncompliance with testing recommendations, individual clinical experience that fails to support the utility of therapeutic drug monitoring, and lack of physician familiarity with literature supporting monitoring.

A gender effect was observed in lithium and carbamazepine testing; women were more likely to receive the test. In addition, a strong age effect was observed in carbamazepine and valproate testing. Younger adults receiving carbamazepine and valproate were significantly more likely than their older counterparts to receive serum drug level testing. Prescribing physicians may exercise greater caution in the prescription of these medications to younger patients because of greater concern with erratic medication consumption in this age group.

Some types of service utilization were related to rates of serum drug level testing. Bipolar patients who received partial-hospitalization psychiatric services tended to be more likely to receive drug level testing. For lithium users, partial hospitalization was significantly associated with serum drug level testing. Partial hospitalization may offer a sustained, controlled treatment environment that facilitates lithium level testing.

Case management services tended to be associated with less likelihood of therapeutic drug monitoring. Among valproate users, use of case management significantly decreased the likelihood of receiving drug level testing. It is possible that patients who are assigned case managers are less likely to follow through with recommended drug monitoring. In addition, case managers may be more oriented toward psychosocial rehabilitative than medical dimensions of patient care.

An important finding to emerge from our analysis is that various components of mood stabilizer monitoring cluster together. Patients who receive serum level testing are also likely to receive the other recommended laboratory tests. This clustering of monitoring tests suggests that medication-nonspecific factors—such as patient compliance, practice style, routine, and custom—may figure prominently in decisions concerning monitoring of mood stabilizers. Only the very low rate of renal testing of lithium users (4.2%) is an exception to this general finding. The low rate of renal function testing may delay the recognition of loss of urinary concentrating capacity that has been associated with long-term lithium treatment (14, 15).

Physicians may selectively monitor mood stabilizers for patients they view as at high risk of treatment noncompliance, toxicity, or relapse due to inappropriate medication levels. However, if clinical considerations drive monitoring practices, one would have expected significantly higher rates of serum level testing in high-risk groups, such as those with co-occurring substance use disorders or psychiatric hospitalizations. The general absence of these associations suggests that other factors may be operating, including problems with patient access to or acceptance of this sometimes intrusive procedure. In addition, some clinicians may believe that a clinical mental status examination is an equally effective and less intrusive method of detecting early effects of toxicity and inappropriately low levels of mood stabilizers.

There are several significant limitations of the study data. The findings are based on bipolar patients in the Medicaid program in the Pittsburgh region and so do not generalize to bipolar patients in other regions or to uninsured, privately insured, or other publicly insured patients. It is possible that higher rates of therapeutic drug monitoring would have been found in a more stable sample of patients with bipolar disorder. Furthermore, the diagnoses obtained from administrative data sets are less reliable than those based on clinician report. This uncertainty may be relevant for pharmacological management and therapeutic drug monitoring, as in the case of a patient with claims for schizophrenia, as well as bipolar disorder, who receives a mood stabilizer as an adjunctive medication. Although previous research with Medicaid data (16) revealed acceptable concordance between clinical and claims data diagnoses of severely mentally ill patients, we did not cross-reference or audit the case reports in the present study. In addition, we did not attempt to model the variation in drug testing that may occur in different phases of treatment. A 1-year period of observation may not be sufficient for assessing serum drug level testing because of in-hospital monitoring and episode truncation. These types of errors are likely to result in underrepresentation of the true rate of annual testing. Another limitation is that some patients may receive medications or laboratory testing outside the Medicaid plan. These transactions would not be recorded in our data set. Furthermore, there are undoubtedly unmeasured clinical factors that may affect the decision to monitor mood stabilizer levels (e.g., patients who are known to have stopped taking medication but have filled a prescription). We also have no means of determining the effects of variation in drug monitoring on clinical outcomes. It should also be noted that the APA guidelines (11) were published during the study period and the consensus guidelines (12) appeared well after that time. However, both sets of guidelines make recommendations based on literature that was readily available at the time of the study.
monitors of mood stabilizers.

Research demonstrates the benefits of therapeutic drug monitoring in general clinical practice. In one study (7), patients who received drug monitoring were almost three times less likely to experience adverse drug reactions than were nonmonitored patients. Another study (17) indicated that the cost of monitoring antidepressant treatment was more than offset by a reduction in the costs of outpatient treatment. This was confirmed in a study in which therapeutic drug monitoring was associated with reduced overall treatment costs (18).

Substantial numbers of bipolar patients taking mood-stabilizing medications do not appear to receive drug monitoring. Further clinical research is necessary to better understand the role of illness severity in determining patterns of drug monitoring. While the clinical consequences of this variation in practice remain unknown, the clinical literature supports therapeutic monitoring of patients taking these medications. Outcomes research is needed to evaluate the effects of monitoring of mood stabilizers on the symptom course, impairment level, and cost of treatment for bipolar disorder under different financial arrangements and treatment settings. There is a special need to study therapeutic drug monitoring as a quality improvement strategy in the rapidly growing managed Medicaid sector.

REFERENCES