Treatment Adherence Among Patients With Bipolar or Manic Disorder Taking Atypical and Typical Antipsychotics

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Objective: This retrospective claims-based study evaluated treatment adherence among patients with bipolar or manic disorder treated with atypical and typical antipsychotics.

Method: Claims data for 18,158 antipsychotic treatment episodes in 15,224 commercially insured patients with bipolar or manic disorder (ICD-9-CM criteria), from January 1999 through August 2003, were evaluated. Overall adherence was measured by adherence intensity (medication possession ratio) and treatment duration (length of treatment episodes). Treatment-related factors that may affect medication adherence were also investigated. Pairwise comparisons of the individual atypicals and a combined group of leading typical antipsychotics were undertaken using multiple regression analysis adjusting for differing patient characteristics.

Results: Adherence intensity with quetiapine was 3% greater than with the typicals combined ($p = .002$) and was greater than with risperidone or olanzapine by 4% ($p < .001$) and 2% ($p = .001$), respectively. Olanzapine (2%, $p < .001$) and ziprasidone (3%, $p = .001$) showed significantly greater adherence intensity than risperidone. Risperidone ($p = .002$), olanzapine ($p = .055$), and the typicals ($p = .021$) demonstrated negative associations between dose and adherence intensity, while quetiapine showed a nonsignificant trend for a positive association ($p = .074$). Quetiapine and risperidone had significantly longer treatment durations than the typicals combined (1.05 and 1.00 months, respectively, $p < .001$) and longer treatment durations than olanzapine (0.75 and 0.79 months, respectively, $p < .001$) or ziprasidone (0.78 months, $p = .002$ and 0.69 months, $p = .003$, respectively). Shorter treatment durations were associated with switching to other antipsychotics or remaining on or switching to other psychotropics (e.g., traditional mood stabilizers) only. All of the atypicals except ziprasidone were associated with a significantly lower likelihood of switching compared with the typicals ($p < .05$).

Conclusions: The claims-based findings of this study suggest that, for bipolar or manic disorder, quetiapine therapy may be associated with better treatment adherence than typical or some atypical antipsychotics. Estimated differences, however, were relatively small, particularly for adherence intensity.

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Poor adherence to prescribed treatment, characterized by treatment gaps and premature termination, is a common feature among patients with bipolar disorder.[1,2] Rates of nonadherence of up to 64% have been reported for patients with bipolar disorder hospitalized for acute mania,[2] and nonadherence is a particular problem during maintenance therapy for bipolar disorder, leaving patients at a higher risk of poorer treatment outcomes and increasing the use of emergency and inpatient services.[1] It has been reported that the median rate of nonadherence among patients with bipolar disorder is 40%,[3] which is substantially higher than the 25% nonadherence rate observed among patients with various medical disorders.[4]

A number of factors have been linked to nonadherence to treatment among patients with psychiatric disorders, including severity of psychopathology,[5–7] substance abuse,[8,9] and comorbid personality disorders.[1] In patients with bipolar disorder, the situation may be further confounded because patients experiencing hypomanic or manic episodes may discontinue or avoid seeking treatment due to the perceived pleasure, satisfaction, or benefit they associate with these mood states.[10] When reasons for discontinuing treatment are explored among patients with bipolar disorder, they frequently cite medication side effects,[11] especially those that cause them to feel stigmatized, such as extrapyramidal symptoms (EPS)[12] and weight gain. Studies in schizophrenia have also shown that EPS and weight

gain adversely affect treatment adherence.[13,14] Medication side effects are therefore likely to have a significant influence on adherence to treatment, and ultimately, its success or failure. It can therefore be reasoned that pharmacologic treatments with a good tolerability profile may lead to better treatment adherence and consequently improved clinical effectiveness.

While lithium and anticonvulsant compounds are recognized as key elements in the pharmacologic treatment of bipolar disorder, antipsychotic medications have assumed growing importance in clinical practice and have been identified as such in treatment guidelines for bipolar disorder.[15,16] Typical (conventional) and atypical antipsychotics are important pharmacotherapeutic options in the treatment of bipolar disorder, with the atypicals generally preferred over the typicals due to their more benign side effect profile.[17] A recent analysis of a Veterans Health Registry suggested that nearly 45% (N = 32,994) of patients with bipolar disorder are prescribed antipsychotic medication, and among those, 77.5% (N = 25,565) receive atypical medications.[18]

Few published reports have compared medication adherence for conventional and atypical antipsychotic medications among patients with serious mental illness,[19–24] and even fewer have examined adherence to these medications among patients with bipolar disorder. The limited number of published studies available suggests that, although nonadherence rates are significant among the atypicals, they may be superior to those of the typicals. Two studies of commercial health plan and Veterans Affairs (VA) data, respectively, found that patients (including those diagnosed with bipolar or manic disorder [*International Classification of Diseases*, 9th revision, Clinical Modification {ICD-9-CM} criteria] or mood disorder with psychotic features [DSM-IV criteria]) treated with atypicals had fewer gaps in medication use or more consistent prescription refills,[19,21] while another study based on Medicaid data found the atypicals to be associated with less switching or longer treatment duration than the typicals.[20] In contrast, an analysis based upon the VA Psychosis Registry suggested that treatment adherence with conventional agents was higher compared with atypical antipsychotics.[18]

Even fewer studies have compared adherence rates among atypical agents,[22,24,25] despite clinical data suggesting differences in tolerability among members of this class. A recent VA database study noted that adherence rates were fairly similar among atypical agents, with the exception of clozapine, which was associated with higher rates of adherence.[18] In a study of patients with schizophrenia, olanzapine was associated with greater treatment adherence than risperidone or haloperidol (85% vs. 74% and 70% at 6 months, respectively).[22]

To assess treatment adherence among patients receiving atypical and typical antipsychotics, the current retrospective study analyzed claims data from U.S. commercial health plans for patients with bipolar or manic disorder who had received monotherapy with any of the atypical agents (risperidone, olanzapine, quetiapine, and ziprasidone) or any of the typical agents (haloperidol, perphenazine, thioridazine, and thiothixine). Drug-related factors that could be associated with poorer treatment adherence were also investigated.

METHOD

Study Population and Data Collection

A data extract for patients with bipolar or manic disorders from the PharMetrics (Watertown, Mass.) patient-centric database and covering the period January 1999 through August 2003 was used for this study. Patients with bipolar or manic disorder were identified by the corresponding ICD-9-CM codes reported on medical claims (296.4–296.8 for bipolar disorder and 296.0 and 296.1 for manic disorder). Patients diagnosed with manic disorder rather than bipolar disorder were included on the assumption that periods of depression, which may be very mild, always accompany mania.[26] Patients for whom other psychiatric disorders were reported on claims during time of antipsychotic treatment were classified as having bipolar or manic disorder only if this was the most recent diagnosis and there were multiple claims with this diagnosis.

To be eligible for inclusion, patients had to have received at least 2 monotherapy prescriptions (normally totaling 60 days' supply) for 1 of the atypical agents (risperidone, olanzapine, quetiapine, or ziprasidone) or 1 of the typical agents (haloperidol, perphenazine, thioridazine, or thiothixine). These typical agents were chosen because they represent the most widely used typicals within U.S. commercial health plans. Since the study utilized a treatment episode approach to estimate treatment adherence, a minimum of 2 prescription fills was necessary for calculating adherence intensity and for accurate measurement of treatment duration (see below). While the patients studied here were taking antipsychotic monotherapy, many were simultaneously treated with other psychotropic medications, including traditional mood stabilizers and antidepressants. The mean days supplied of any one of these medications, however, was far below that of the index antipsychotics.

Assessment of Treatment Adherence

Two measures of treatment adherence were investigated: adherence intensity and treatment duration (Figure 1). Adherence intensity was measured using the medication possession ratio (MPR),[18,27,28] which was calculated by dividing the total number of days for which the index antipsychotic was supplied (number of days' supply of medication that a patient actually received, as indicated on prescription claims) by the total number of days en-

Figure 1. Method for Evaluating the Medication Possession Ratio (MPR) and Treatment Duration Among Patients With Bipolar or Manic Disorder

$$\text{MPR} = \frac{\text{Total Number of Days for Which the Index Antipsychotic Was Supplied}}{\text{Total Number of Days Encompassed by the Treatment Episode}}$$

Treatment Duration = (length of the treatment episode) → Date of the First Episode ⋯⋯ Date of the Last Prescription Plus the Number of Days for Which it Was Supplied (unless preceded by patient disenrollment or data endpoint)

compassed by the treatment episode (number of days' supply that a patient should have received had he or she obtained the medication as prescribed). For example, if a typical or atypical agent was supplied to last for 285 days and the total days encompassed by the treatment episode was 325, then the MPR was 0.88. The higher the MPR, the greater (or higher) the adherence intensity. An MPR of 1 indicates that the patient has received all the medication required to take as prescribed, whereas an MPR of 0.5 indicates that the patient has received enough medication to take only half of the prescribed dose. Medication possession ratios greater than 1 were possible in cases in which prescriptions may not have been completely used due to interim changes in dosage. Unlike other studies (e.g., Al-Zakwani et al.[19]), a maximum ratio of 1 was not enforced, as this would bias comparisons against agents with a relatively high adherence intensity. While MPRs > 1 may also reflect over-prescribers,[29] this cannot be determined solely from claims data.

The second measure of treatment adherence–treatment duration was simply the length of the treatment episode: 325 days (or 10.8 months) in the example given above. Treatment episodes were measured from the date of the first prescription for a given medication to the final date of treatment, which was calculated from the date of the last prescription plus the number of days for which it was supplied (unless preceded by patient disenrollment from the health plan or the end of the data).

Because adherence intensity as gauged by the MPR is intended to reflect compliance behavior with prescription refills and potential gaps, a treatment episode with a study antipsychotic had to consist of at least 2 prescriptions. The 2-prescription minimum was also applied in the assessment of treatment duration to ensure consistency and greater accuracy. Treatment duration may be assessed inaccurately when measured with a single prescription because it would depend exclusively on the days' supply of that prescription (which, though normally 30 days, ranged from 5 to 90 days). In claims data, it is not possible to determine what portion of a stand-alone prescription was used or if it was used at all. The occurrence of a subsequent prescription gives reasonable assurance that the prior prescription was consumed.

Some patients had more than one treatment episode because they were treated on separate occasions, either with a different agent or the same agent. The first prescription in an episode was based on a prior gap in prescriptions of 90 days or more. Gaps of fewer than 90 days within treatment episodes were allowed. Larger gaps between prescription-fill dates for a given medication, which were rare, resulted in 2 qualifying treatment episodes if each episode had sufficient days' supply. This approach enabled us to distinguish between irregularity in prescription refills and discontinuation of an antipsychotic therapy altogether.

Statistical Analysis

Pairwise comparisons of MPRs and treatment durations for olanzapine, risperidone, quetiapine, and ziprasidone alone and the combined group of typical antipsychotics (haloperidol, perphenazine, thioridazine, and thiothixene) were conducted using linear multiple regression. For each pairwise comparison, a single model was reestimated using all observations and alternating the excluded (or base) antipsychotic category. The model controlled for a number of patient characteristics that are likely to affect treatment adherence, which were prespecified based on the current literature (Table 1).

Assessment of treatment duration data indicated that the distribution of treatment duration was highly (right) skewed; therefore, log transformation of data was undertaken to normalize the distribution before regression estimation. Parameter estimates that were in log form were converted to actual amounts using the mean value of treatment duration as the base.

Database endpoints for the commercial plans and patient disenrollment from the plans prior to these endpoints resulted in a high proportion of treatment episodes (about 50%), with termination dates that were unknown (censored). Censoring would not affect comparisons of treatment duration if the probability of a treatment episode being censored were the same for all the agents included in the analysis. While this scenario is likely true for censoring due to patient disenrollment, it is unlikely for censoring due to database endpoints. Treatment episodes with newer atypicals, such as ziprasidone and quetiapine, are more concentrated in recent years because of their more recent introduction into the market. Consequently, they are more likely to have been censored by database endpoints. Differential probabilities of being censored were controlled for in the regression models for treatment duration by inclusion of a variable reflecting the start date for each treatment episode.

In addition to the pairwise comparisons of adherence intensity and treatment duration, secondary analyses were also performed to provide further information. To determine the effect of dose on adherence intensity, separate

Table 1. Control Variables in Regression Analysis With Justification From the Current Literature

Variable	Description	Justification
Age	Continuous measure	While patient age has been associated with antipsychotic treatment adherence, findings have been inconsistent[30,31]
Gender	Binary variable (male = 1)	Prior evidence suggests that males may be less treatment adherent[30]
Type of bipolar disorder	Binary variables	Different types of bipolar or manic disorder may differentially affect treatment adherence[5,6]
Prior mental health resource use	Total expenditure on mental health care 90 days prior to initiation of the antipsychotic treatment	A marker for illness severity; higher prior levels of mental health care (e.g., inpatient days) have been associated with poorer compliance[31]
Prior number of different psychotropic drugs used	Count reflecting use of atypicals/typicals, mood stabilizers, antidepressants, anxiolytics, etc, during the 90 days prior to entry into the study	A marker for illness severity and treatment resistance[31]
Switch from another atypical/typical agent	Binary variable indicating whether patient used another atypical or typical agent during the 90 days prior to treatment initiation	Reflects progression in finding an antipsychotic that is more effective and/or better tolerated; first-treatment cases may be less adherent[30]
Substance dependence/abuse	Binary variable	Studies suggest that these patients are less medication compliant[8,9,30]
Physician contact	Number of physician mental health encounters per month of psychotropic treatment	Studies suggest that patients with more frequent physician contact have better treatment adherence[31,32]
Use of depot atypical or typical agents	Binary variable indicating prior use	Prior use of depot antipsychotics suggests difficulty with treatment adherence
Use of other psychotropics	Total days supplied of other psychotropic medications per month of neuroleptic treatment	These medications may substitute for or complement neuroleptic treatment, possibly affecting adherence
Other morbidities	Health care expenditure per month of antipsychotic treatment unrelated to mental disorders or psychotropic side effects	Presence of serious other morbidities may interfere with antipsychotic treatment adherence
Type of insurance coverage	Binary variables indicating prior use	The level of care management may affect ease of access to treatment and thereby treatment adherence[33]
Time of treatment initiation (treatment duration models only)	Number of days from start of treatment episode to July 1, 2003	Controls for censorship of treatment episode due to end of data
Treatment duration (MPR models only)	Measured in months	Some side effects affecting adherence intensity may emerge later in treatment
Inpatient days (MPR models only)	Number of inpatient days during treatment episode	Adjusts for neuroleptics that may be obtained through an inpatient pharmacy and are therefore not reflected in prescription claims
Study medication dose (MPR models only)	The mean daily dose of the index medication	Drug tolerance and therefore adherence may decrease with higher doses[34]
Study medication side effects (MPR models only)	Binary variables indicating presence of extrapyramidal symptoms, diabetes, weight gain, sexual dysfunction, and hyperprolactinemia and related conditions	Side effects may adversely affect treatment adherence[13,35,36]
Disposition of patient at treatment termination (treatment duration models only)	Binary variables indicating whether patient switched to another antipsychotic, to other psychotropics only, or ceased all psychotropic use	Reason for termination may explain treatment duration

Abbreviation: MPR = medication possession ratio.

regression models were estimated for each of the atypicals and for the combined typicals. Uncensored treatment episodes were also compared to identify posttreatment information that might also explain differences in treatment duration.

Uncensored treatment episodes for each study medication were grouped according to 4 patient alternatives following treatment termination so that study medications could be compared with respect to reasons for treatment termination: (1) ceased use of all psychotropic medications, (2) returned to the same treatment (after a hiatus in excess of 90 days), (3) switched to another antipsychotic, and (4) remained on or switched to other psychotropic medications only. A 4-month interval following treatment termination was used to make these determinations. A 4-month window was chosen because this time frame exceeded by 1 month the maximum allowable gap within a treatment episode and because a larger window would have considerably reduced the sample of uncensored episodes. The expectation was that switching to another antipsychotic or to other psychotropics only would be associated with shorter treatment durations because these

switches were more indicative of treatment failure. The effect of switching on antipsychotic treatment duration was assessed with linear multiple regression, and likelihood of switching to an alternative antipsychotic or to other psychotropic medications only was estimated using a logistic regression model.

RESULTS

A total of 18,158 treatment episodes for bipolar or manic disorders met the criteria for inclusion in 15,224 patients: 17,346 episodes among patients treated with 1 of the 4 atypicals (risperidone, olanzapine, quetiapine, and ziprasidone) and 812 episodes among those treated with 1 of the 4 typicals (haloperidol, perphenazine, thioridazine, and thiothixine). More than 1 episode was recorded for 16% of patients because they were treated at separate times during the study period with the same or a different antipsychotic. Fifty-three percent of treatment episodes had insufficient data beyond the expected end of the treatment episode to confirm that treatment had terminated and were therefore classified as censored.

Baseline Characteristics of the Study Population

The baseline characteristics of patients are presented in Table 2. Patients treated with an atypical antipsychotic tended to be younger than those treated with a typical agent (mean ages of 33–38 years vs. 44–46 years) and also tended to be more seriously ill, as indicated by prior mental health care expenditure (mean U.S. amount of $3869–$4691 for atypicals vs. $2733–$3749 for typicals). Compared with the other agents, quetiapine and ziprasidone were more likely to have been initiated later and possibly as second-line therapies, as reflected in the higher percentages of patients receiving these drugs who had switched from an alternative medication (29.5% and 49.4%, respectively). These and the other patient characteristics described in Table 1 and quantified in Table 2 were specified as control variables in the regression models.

Treatment Adherence

Mean (± SD) and median MPRs and treatment durations are reported in Table 3 for each of the antipsychotics. With the exception of risperidone (0.91), the atypicals (range, 0.94–0.98) had higher mean MPRs than the typicals (range, 0.89–0.93), suggesting that greater adherence intensity was achieved with the majority of the atypicals. Among the atypicals, ziprasidone had the highest MPR (mean ± SD = 0.98 ± 0.27), followed by quetiapine (mean ± SD = 0.96 ± 0.31). A raw comparison of the mean and median values for treatment duration suggested that, as a group, the atypicals did not appear to have an advantage over the typicals in this regard. Comparisons that take into account differing patient characteristics through regression modeling allow for a more accurate representation of differences in adherence intensity and treatment duration among the groups analyzed.

Adjusted Comparisons of Adherence Intensity (MPRs)

Regression estimates of differences in MPR between each of the antipsychotic groups adjusted for differing patient characteristics are reported in Table 4. Comparisons between each of the atypicals and the typicals combined showed quetiapine alone to have a significantly higher MPR ($p = .002$), while differences for risperidone, olanzapine, and ziprasidone were not significant. Comparisons between pairs of atypicals showed that patients treated with quetiapine had significantly higher MPRs than risperidone- (4% greater; $p < .001$) and olanzapine-treated patients (2% greater; $p = .001$). Medication possession ratios for olanzapine and ziprasidone were also significantly higher than for risperidone (both 2% greater; $p < .001$ and $p = .001$, respectively). Differences between quetiapine and ziprasidone or olanzapine and ziprasidone were not significant.

Patient characteristics with a significant ($p < .05$) positive association with MPR included male gender, prior mental health expenditure, switch from another typical or atypical agent, more frequent physician contact, and greater use of other psychotropic drugs. Patient characteristics with a significant negative association with MPR included older age, bipolar-depressed versus other manifestations, higher number of prior different psychotropic drugs, substance dependence/abuse, more managed forms of health coverage, and longer treatment duration.

Adjusted Comparisons of Treatment Duration

Regression estimates of differences in treatment duration between each of the antipsychotic groups adjusted for differing patient characteristics are reported in Table 5. Quetiapine and risperidone had significantly longer treatment durations than the typical agents ($p < .001$). Olanzapine and ziprasidone showed no significant difference compared with the typicals. In pairwise comparisons of atypicals, quetiapine and risperidone had significantly longer treatment durations than olanzapine (month differences of 0.75 and 0.79, respectively; $p < .001$ in each case) and ziprasidone (0.78, $p = .002$ and 0.69, $p = .003$, respectively). The difference between quetiapine and risperidone was not statistically significant, nor was the difference between olanzapine and ziprasidone.

Patient characteristics with a significant ($p < .05$) positive association with treatment duration included older age, male gender, switch from another typical or atypical agent, substance dependence/abuse, more managed forms of coverage, and earlier start date for treatment episode. Patient characteristics with significant negative associations included bipolar-manic versus other manifestations and greater use of other psychotropic drugs.

Table 2. Characteristics of Patients With Bipolar or Manic Disorder Treated With Atypical or Typical Antipsychotics

		Atypical Agents				Typical Agents			
Characteristic	All	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Haloperidol	Perphenazine	Thioridazine	Thiothixene
No. of observations (treatment episodes)	18,158[a]	5754	6894	3901	797	272	213	155	172
Age, mean (SD), y	36.0 (16.1)	32.8 (16.9)	38.2 (15.4)	35.1 (15.3)	35.5 (14.8)	45.1 (15.1)	46.1 (13.1)	43.7 (17.5)	45.5 (12.6)
Gender, % male	42.5	47.5	45.6	34.2	29.6	37.9	33.3	38.7	28.5
Type of bipolar or manic disorder, %									
Manic	5.4	6.1	5.3	5.2	4.5	11.8	9.4	6.5	2.3
Bipolar-manic episode	14.1	13.6	16.0	10.3	13.1	21.7	17.4	15.5	26.2
Bipolar-depressed episode	15.3	14.7	15.7	15.1	16.7	12.9	16.4	14.8	12.8
Bipolar-mixed episode	18.8	18.1	18.6	19.4	23.5	19.9	16.4	16.1	20.9
Bipolar-unspecified	46.5	47.6	44.4	50.1	42.3	33.8	40.4	47.1	37.8
Mean dose, mg/d	NA	1.8	8.5	171	71	6.7	10.3	100	9.0
Substance abuse/dependence, %	16.8	14.3	18.4	18.4	15.9	12.9	18.3	11.6	11.1
Mental health expenditure 90 days before treatment, mean (SD), U.S. $	4144 (11,934)	3869 (11,069)	4112 (11,246)	4691 (14,120)	4464 (12,756)	3749 (9001)	2812 (9553)	2744 (11,505)	2733 (12,591)
No. of different psychotropic drugs 90 days before treatment, mean (SD)	1.42 (1.19)	1.21 (1.11)	1.34 (1.16)	1.77 (1.24)	2.04 (1.21)	1.27 (1.21)	1.35 (1.19)	1.30 (1.19)	1.32 (1.24)
Switch from another atypical or typical agent, %	19.7	14.4	15.0	29.5	49.4	23.5	16.4	15.5	18.0
Other health expenditure per month during treatment, mean (SD)	530 (2039)	460 (1514)	565 (2745)	573 (1418)	524 (1040)	623 (2188)	473 (977)	405 (827)	344 (646)
Had prior use of depot antipsychotics, %	0.14	0.07	0.15	0.13	0.00	1.84	0.47	0.00	0.00
Days supplied per month of other psychotropic drugs during treatment, mean (SD)	39.9 (34.3)	37.7 (33.4)	38.0 (33.5)	44.3 (35.2)	49.6 (39.3)	37.3 (32.1)	44.6 (32.1)	42.6 (42.8)	44.2 (37.0)
Physician encounters per month during treatment, mean (SD)	0.70 (1.09)	0.70 (1.10)	0.73 (1.10)	0.71 (1.08)	0.68 (1.14)	0.50 (0.93)	0.57 (0.87)	0.50 (0.85)	0.46 (0.78)
Inpatient days per month during treatment, mean (SD)	1.40 (6.17)	1.40 (6.64)	1.28 (5.04)	1.69 (7.69)	1.00 (4.04)	1.56 (4.85)	1.60 (6.46)	0.80 (3.2)	1.02 (4.08)
Months between start of treatment episode and Aug 1, 2003, mean (SD)	24.7 (12.8)	26.3 (13.0)	25.0 (12.6)	22.2 (12.1)	16.6 (7.1)	28.7 (13.5)	30.2 (13.6)	37.5 (11.4)	31.5 (13.7)
Type of health coverage, %									
Health maintenance organization	50.1	54.7	50.0	45.7	45.4	52.6	47.0	45.2	34.9
Preferred provider	24.5	21.4	25.1	25.8	28.1	25.0	33.8	29.7	33.1
Point of service	15.1	14.1	15.1	17.5	14.6	9.9	11.7	12.3	16.3
Indemnity	2.7	2.5	2.7	2.7	2.9	2.9	2.8	3.9	4.1
Other	7.6	7.3	7.1	8.3	9.0	9.6	7.1	8.9	11.6

[a]Number of treatment episodes observed in 15,224 patients. Multiple treatment episodes were observed in 16% of patients.
Abbreviation: NA = not applicable.

Table 3. Medication Possession Ratios (MPRs) and Treatment Durations Among Patients With Bipolar or Manic Disorder Treated With Atypical or Typical Antipsychotics[a]

	Atypical Agents				Typical Agents			
Variable	Risperidone (5754 treatment episodes)	Olanzapine (6894 treatment episodes)	Quetiapine (3901 treatment episodes)	Ziprasidone (797 treatment episodes)	Haloperidol (272 treatment episodes)	Perphenazine (213 treatment episodes)	Thioridazine (155 treatment episodes)	Thiothixene (172 treatment episodes)
MPR[b]								
Mean (± SD)	0.91 (0.26)	0.94 (0.28)	0.96 (0.31)	0.98 (0.27)	0.93 (0.29)	0.89 (0.28)	0.93 (0.34)	0.91 (0.32)
Median	0.92	0.94	0.95	0.97	0.95	0.92	0.94	0.91
Treatment duration, mo								
Mean (± SD)	8.2 (7.3)	7.2 (6.6)	7.5 (6.5)	6.1 (4.6)	7.9 (8.2)	8.8 (8.1)	8.2 (8.5)	7.7 (6.9)
Median	5.7	4.8	5.3	4.5	4.7	6.0	4.9	5.6

[a]Treatment durations reflect censored as well as uncensored treatment episodes.
[b]Medication possession ratios greater than 1 are possible because many prescriptions may not be completely used due to interim changes in dosage. Unlike other studies,[19] we chose not to force a maximum ratio of 1, since this would bias comparisons against antipsychotics with relatively high adherence intensity.

Table 4. Differences Between Atypical and Typical Antipsychotic Medication Possession Ratios (MPRs) Adjusted for Differing Characteristics Among Patients With Bipolar or Manic Disorder

	Estimated MPR Difference Versus				
Medication	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Typicals
Risperidone (5754 treatment episodes)	…	–0.02 (p < .001)	–0.04 (p < .001)	–0.03 (p = .001)	–0.01 (p = .424)
Olanzapine (6894 treatment episodes)	0.02 (p < .001)	…	–0.02 (p = .001)	–0.01 (p = .348)	0.02 (p = .129)
Quetiapine (3901 treatment episodes)	0.04 (p < .001)	0.02 (p = .001)	…	0.01 (p = .419)	0.03 (p = .002)
Ziprasidone (797 treatment episodes)	0.03 (p = .001)	0.01 (p = .348)	–0.01 (p = .419)	…	0.03 (p = .074)
Typicals (812 treatment episodes)	0.01 (p = .424)	–0.02 (p = .129)	–0.03 (p = .002)	–0.03 (p = .074)	…

Table 5. Differences Between Atypical and Typical Antipsychotic Treatment Durations Adjusted for Differing Characteristics Among Patients With Bipolar or Manic Disorder[a]

	Estimated Difference in Treatment Duration (mo) Versus				
Medication	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Typicals
Risperidone (5754 treatment episodes)	…	0.79 (p < .001)	0.00 (p = .772)	0.69 (p = .003)	1.00 (p < .001)
Olanzapine (6894 treatment episodes)	–0.79 (p < .001)	…	–0.75 (p < .001)	–0.09 (p = .688)	0.18 (p = .418)
Quetiapine (3901 treatment episodes)	0.00 (p = .772)	0.75 (p < .001)	…	0.78 (p = .002)	1.05 (p < .001)
Ziprasidone (797 treatment episodes)	–0.69 (p = .003)	0.09 (p = .688)	–0.78 (p = .002)	…	0.28 (p = .342)
Typicals (812 treatment episodes)	–1.00 (p < .001)	–0.18 (p = .418)	–1.05 (p < .001)	–0.28 (p = .342)	…

[a]Based on log transformation to adjust for skewed distribution of treatment durations.

Table 6. Association Between Adherence Intensity (MPR) and Daily Dose Among Patients With Bipolar or Manic Disorder

Drug Category	Effect on MPR per 100-Chlorpromazine Equivalent, mg/d	p
Typical antipsychotics	–0.0087	.021
Atypical antipsychotics		
Risperidone	–0.0196	.002
Olanzapine	–0.0064	.055
Quetiapine	+0.0045	.074
Ziprasidone	–0.0023	.937

Abbreviation: MPR = medication possession ratio.

Dose Effects on Adherence Intensity (MPR)

Associations between MPR and prescribed daily dose are reported in Table 6. Estimated dose effects on MPR are measured per 100-chlorpromazine equivalent mg/day because of vastly different milligram scales among the study antipsychotics. A negative correlation between MPR and dose was observed for all agents studied except quetiapine. This correlation was significant for the combined typicals (p = .021) and for risperidone (p = .002).

Patient Disposition Following Treatment Discontinuation

To explore possible reasons for the length of time a patient stayed with a particular treatment, patient disposition after termination was examined. Uncensored treatment episodes for each study agent, grouped according to 4 patient alternatives, are shown in Table 7.

The atypicals had lower proportions of patients switching to other antipsychotics when compared with the typicals (0.14–0.22 vs. 0.27–0.38), while proportions of patients remaining on or switching to other psychotropics only were more similar between the 2 medication classes.

The association between treatment duration and treatment failure was further investigated with multiple regression controlling for differing patient characteristics. Switching to another antipsychotic and switching to other

Table 7. Disposition of Patients With Bipolar or Manic Disorder at Treatment Termination

		Atypical Agents				Typical Agents			
Variable	All	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Haloperidol	Perphenazine	Thioridazine	Thiothixene
No. of uncensored treatment episodes	8491	2828	3412	1484	293	151	109	109	94
Take no psychotropic medications, %	35	39	35	34	24	24	31	23	31
Return to same antipsychotic, %	3	3	3	3	2	0	0	0	0
Switch to other antipsychotic, %	15	14	14	14	22	30	28	27	38
Remain on or switch to other psychotropics only, %	47	44	48	49	52	44	41	50	31

Table 8. Adjusted Odds Ratios at Treatment Termination of Switching to Another Antipsychotic or Remaining on or Switching to Other Psychotropics Only Among Patients With Bipolar or Manic Disorder[a]

	Odds Ratio (95% CI) Versus				
Medication	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Typicals
Risperidone (2828 uncensored episodes)	…	0.93 (0.84 to 1.04)	1.13 (0.98 to 1.30)	0.79 (0.59 to 1.10)	0.61 (0.48 to 0.77)[b]
Olanzapine (3412 uncensored episodes)	1.07 (0.96 to 1.20)	…	1.21 (1.05 to 1.39)	0.85 (0.63 to 1.14)	0.65 (0.52 to 0.82)[b]
Quetiapine (1484 uncensored episodes)	0.89 (0.77 to 1.03)	0.83 (0.72 to 0.95)	…	0.70 (0.52 to 0.95)[b]	0.54 (0.42 to 0.70)[b]
Ziprasidone (293 uncensored episodes)	1.26 (0.94 to 1.69)	1.18 (0.88 to 1.58)	1.42 (1.05 to 1.92)[b]	…	0.77 (0.54 to 1.10)
Typicals (463 uncensored episodes)	1.64 (1.30 to 2.07)[b]	1.53 (1.22 to 1.93)[b]	1.85 (1.44 to 2.36)[b]	1.30 (0.91 to 1.86)	…

[a]Odds ratios estimated with logistic regression to adjust for differing patient characteristics.
[b]Significant at $p < .05$.
Abbreviation: CI = confidence interval.

psychotropics only were specified as binary variables. Switching to another antipsychotic shortened treatment duration by 0.34 months (5% shorter; $p = .002$) and remaining on or switching to other psychotropics shortened it by 0.50 months (7% shorter; $p < .001$).

Study agents were also compared with respect to the likelihood of switching to other treatments. Relative odds of switching either to another antipsychotic or to other psychotropics only were estimated with logistic regression controlling for differing patient characteristics. Each of the atypical antipsychotics was first compared with the typicals as a group and then with one another (Table 8). All of the atypicals except ziprasidone had significantly lower odds of switching than the typicals as a group ($p < .05$). In pairwise comparisons of the atypicals, quetiapine had a significantly lower likelihood of switching than ziprasidone ($p < .05$); other comparisons were not significant.

DISCUSSION

In this retrospective, claims-based study, 4 atypical agents were compared with a group of 4 widely used typical agents and with each other to assess differences in treatment adherence. The atypicals included risperidone, olanzapine, quetiapine, and ziprasidone, while the typicals included haloperidol, perphenazine, thioridazine, and thiothixine.

Overall treatment adherence can be measured by adherence intensity (how well a patient follows physician instructions during the course of treatment with an antipsychotic) and persistence with therapy (how long a patient stays on treatment). In this study, treatment adherence was measured using 2 parameters, MPR and treatment duration, in order to gauge adherence intensity and persistence with therapy. A number of other claims-based studies have also measured gaps or irregularities in prescription refills to gauge adherence.[18,19,21,28,31,37]

Of all the atypicals included in the analysis, adherence intensity with quetiapine exceeded that with the typical agents (combined into 1 category) by the largest margin, which was the only adjusted difference that was statistically significant ($p = .002$). In addition, we also compared the atypicals with each other in terms of adherence intensity. Quetiapine showed a significant advantage over risperidone ($p < .001$) and olanzapine ($p = .001$), and both olanzapine ($p < .001$) and ziprasidone ($p = .001$) showed a significant advantage over risperidone. Quetiapine and olanzapine did not differ significantly from ziprasidone.

Comparisons of treatment duration showed that risperidone and quetiapine had significantly longer treatment durations than the typicals. Among atypicals, quetiapine and risperidone had significantly longer treatment durations than olanzapine ($p < .001$ in each case) and ziprasidone ($p = .002$ and $p = .003$, respectively). It should be noted, however, that relatively short treatment durations are not necessarily indicative of treatment failure; in cases in which the symptoms of bipolar disorder may be relatively mild, continuous maintenance therapy may not always be required. Treatment guidelines for bipolar disorder suggest that, in circumstances in which mood stabilizers and atypical antipsychotics are used concurrently, it may be reasonable to taper and discontinue the antipsychotic for long-term maintenance therapy.[15,16,38]

Patients with single stand-alone prescriptions for the study antipsychotics were excluded to ensure consistent and accurate assessments of adherence intensity (MPR) and treatment duration. However, we realize that a biased comparison of treatment durations could have resulted from the exclusion of these observations. To assess this potential, we compared among the antipsychotics percentages of patients with single prescriptions. (To avoid the effect of the database endpoint on accurate identification of single stand-alone prescriptions, only prescriptions with fill dates from 1999–2002 were used.) The percentages are as follows: risperidone 20.3%, olanzapine 23.4%, quetiapine 18.5%, ziprasidone 21.7%, and typicals 25.7%. Quetiapine and risperidone had lower percentages of patients with single stand-alone prescriptions than the typicals and olanzapine, which is consistent with our finding that they also had significantly longer treatment durations. The exclusion of patients with single stand-alone prescriptions does not appear to have an impact on the results and the inferences that may be drawn from the study.

Assessment of patient disposition in the 4-month period following treatment termination identified lower proportions of patients receiving atypicals switching to other antipsychotics when compared with those receiving typicals. Treatment failure, as represented by shorter treatment durations, is likely the case when patients switch to other therapies, but it cannot be inferred when patients cease treatment altogether. Among patients who discontinued treatment in this study, those patients who switched to another antipsychotic or remained on or switched to other psychotropics only had significantly shorter treatment durations than those who discontinued treatment altogether (5% and 7% shorter, respectively), indicating that treatment failure was a likely reason for the short treatment duration. Comparison with typical agents showed that all of the atypicals except ziprasidone were associated with a significantly lower likelihood of switching. Comparisons between atypicals showed quetiapine to have a significantly lower likelihood of switching than ziprasidone ($p < .05$), with other comparisons being nonsignificant.

A negative correlation with respect to prescribed daily dose and adherence intensity was observed for all the agents except quetiapine. This correlation was significant for the typicals as a group and for risperidone. In contrast, the correlation between daily dose and adherence intensity for quetiapine was positive but was nonsignificant ($p = .074$). One possible explanation could be that higher doses of quetiapine encourage better adherence because they are more effective than lower doses of quetiapine.[39]

Findings of this study with respect to adherence intensity are corroborated by another study.[21] The study assessed pharmacy refill records to measure treatment compliance (or adherence intensity) among outpatient veterans (including those with a diagnosis of mood disorder with psychotic features [DSM-IV]) receiving typical and atypical antipsychotics and reported that compliance rates were numerically highest with quetiapine but could not conclude further due to the small number of patients receiving the agent. Another report based upon a large VA case registry[18] suggested that adherence intensity was greater for patients taking typical antipsychotic agents compared with atypicals. However, the generally declining proportion of patients treated with typical antipsychotics (8.7% of the total number of patients in that study) may have resulted in a subpopulation of "robust neuroleptic responders." While the commercial data in the present study also reflect the declining proportion of patients treated with typicals (about 5% of the total) and the possibility of more treatment-respondent patients within this group, we did not find greater treatment adherence with the typicals. It is possible that this is a reflection of differences in the types of patients remaining on typical antipsychotic therapy in public versus commercially insured populations.

A potentially important difference between the analysis presented here and in other reports[18,21] is the fact that this was a population of individuals with commercial health insurance. Medication possession ratios were fairly high for all treatments, suggesting that adherence intensity was relatively good, while prevalence of substance abuse was relatively low. It might be expected that individuals with bipolar disorder who have private health insurance are more likely to be employed and perhaps less severely ill than individuals who receive care for bipolar disorder in publicly funded settings. In a veteran population with bipolar disorder, MPRs for atypical antipsychotic medications have been reported to range from 0.76 (for risperidone) to 0.84 (for clozapine), and substance abuse has been reported in 34.8% of all patients who were prescribed antipsychotic medications.[18]

Some patients had multiple treatment episodes, raising the possibility of interdependence of sampling units. This possibility was assessed and noted to be a nondeterminant

issue. Treatment episodes for the same patient were usually separated by long intervals during which patient circumstances, including health state, may have changed considerably. Also, interdependence of sampling units can arise from other factors, such as 2 patients being treated by the same physician or having the same specific type of health coverage. In light of these considerations and the moderate percentage of patients with multiple episodes (about 16%), we made the decision not to exclude data or make any adjustments.

An important caveat to this study's findings is that estimated differences among the antipsychotics, though statistically significant, are relatively small. This is particularly true of adherence intensity. Differences in MPR of 2% to 4% by themselves do not appear to be clinically meaningful. However, they may indicate underlying problems of treatment compliance that are not directly measurable with claims data (e.g., failure to fully use acquired prescriptions). Differences in treatment duration were in the 1-month range, which appears to be more clinically relevant given a mean antipsychotic treatment duration of 7.5 months for bipolar or manic disorder.

While this study attempted to address a number of limitations inherent in a retrospective, claims-based analysis, other limitations remain and must be acknowledged. A main drawback of this study was the use of prescription refills to gauge adherence intensity. Low adherence intensity associated with prescriptions that are filled but not used is not measured, which could create bias if the degree to which prescriptions are unused differs among the typicals and atypicals included in this study. In addition, unused prescriptions not only reflect low adherence intensity, but may also result from changes in medication strength before prior prescriptions are fully depleted.

Another limitation relates to the assumption that only treatment terminations associated with switches to other antipsychotics or other psychotropics reflect failure of treatment. Situations in which patients ceased using all psychotropic medications, which were more prevalent among the atypicals, were interpreted as no further treatment being required. While the observed tendency for switches to be associated with shorter treatment durations supports this interpretation, it cannot be ruled out that some treatment terminations associated with no subsequent use of psychotropics may also have been treatment failures. Moreover, 2 atypical antipsychotics in use for the treatment of bipolar and manic disorders were not included in this study. Clozapine was excluded because it has a relatively high adherence intensity, which may be attributed to close physician monitoring during its administration due to the risk of agranulocytosis. Therefore, its inclusion could have biased the study findings. Aripiprazole, the most recent of all the atypicals to be approved for the treatment of bipolar mania, was excluded because the sample size would have been too small to draw any firm conclusions. Treatment adherence may differ between commercially insured and public sector patients (e.g., Medicaid and VA), with the former tending to be less seriously ill and higher functioning. Therefore, findings from this study are not strictly comparable with those of the more numerous public sector studies, but may provide necessary insight into treatment behaviors among a large but less explored patient population.

CONCLUSION

Pharmacotherapies with proven treatment adherence provide physicians with options that may reduce treatment failure in patients with bipolar or manic disorders. Within the context of inherent limitations associated with health insurance claims databases, this study suggests that, among the atypicals studied, quetiapine may have significantly higher adherence intensity than the typicals. Moreover, in comparison with other atypicals, quetiapine had the highest adherence intensity, which was significantly greater than that associated with risperidone or olanzapine. Estimated differences, however, were relatively small.

Comparisons of treatment durations also suggested that the atypicals are superior to the typicals and that quetiapine and risperidone may be better than olanzapine and ziprasidone in this respect. Moreover, in this analysis, all the atypicals, except ziprasidone, appeared to have a lower likelihood of switching in comparison to the typicals. Between atypicals, quetiapine seemed to have a significantly lower likelihood of switching than ziprasidone, with other comparisons being nonsignificant. Quetiapine was the only treatment that demonstrated a positive association between daily dose and adherence intensity. Although this association was not significant, it may indicate a relationship between higher doses of quetiapine and improved adherence.

The findings of this study highlight the need for further research into the clinical predictors of poor treatment adherence among patients with bipolar disorder, so that the clinical management of these patients may be enhanced and outcomes optimized. In addition, the advantage of treatment adherence with quetiapine over some atypicals, as suggested by the current study, warrants confirmation, and its clinical significance needs to be explored.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane and others), ziprasidone (Geodon).

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