

Original Article

Treatment adherence with antipsychotic medications in bipolar disorder

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Objectives: Atypical antipsychotic medications are a relatively new, increasingly prominent component of the treatment armamentarium for bipolar disorder. Information on adherence with antipsychotics among individuals with bipolar disorder in general, and atypical antipsychotics in particular, is currently quite limited. Using data from the VA National Psychosis Registry, we examined adherence with antipsychotic medications among patients with bipolar disorder (n = 73,964).

Methods: Antipsychotic medication adherence among veterans with bipolar disorder was evaluated using the medication possession ratio and categorizing patients into three groups: fully adherent, partially adherent and non-adherent. We compared characteristics of bipolar patients who received versus those who did not receive antipsychotic medication, and also identified predictors of poor adherence with antipsychotic medications.

Results: Approximately 45% (n = 32,993) of all individuals with bipolar disorder were prescribed antipsychotic medication. Individuals who were prescribed antipsychotic medications were younger and more often had comorbid substance abuse or post-traumatic stress disorder compared to individuals with bipolar disorder who were not prescribed antipsychotic medication. Just over half (51.9%) of individuals appear to be fully adherent with antipsychotic medications, while 48.1% of individuals are either partially adherent or non-adherent with antipsychotic medications. Factors associated with treatment non-adherence were younger age, minority ethnicity, comorbid substance abuse and homelessness.

Conclusions: Treatment non-adherence is a major issue for close to half of individuals with bipolar disorder prescribed antipsychotic medication. Additional studies are needed to better understand treatment adherence within the full range of pharmacologic therapies among individuals with bipolar disorder.

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Poor adherence with lithium and anticonvulsant medications has been found to be a common occurrence among individuals with bipolar disorder

der (estimates range between 20 and 55%) and is often associated with negative clinical outcomes (1–4). A variety of factors such as patient age, marital status, gender, educational level, symptoms, side effects of medications and comorbid substance abuse, as well as environmental factors such as psychosocial support and access to care are known to affect treatment adherence among individuals with bipolar disorder (1, 5–13). Post-traumatic stress disorder (PTSD), not infrequently

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seen among combat veterans, has been associated with treatment non-adherence (14), although whether PTSD is associated with non-adherence among individuals with bipolar disorder is not known. The past literature on medication adherence in bipolar disorder has predominantly focused on use of lithium and anticonvulsant compounds, as for many years these were the primary cornerstones of medication treatment (15–19).

Lithium remains a ‘gold standard’ for treatment (17); however, there are a variety of other compounds often prescribed for individuals with bipolar disorder. In the past, for individuals non-responsive to lithium, or where a faster response to pharmacologic treatment was needed, neuroleptics such as chlorpromazine and haloperidol were often utilized. However, adverse effects such as extrapyramidal symptoms, tardive dyskinesia and neuroleptic malignant syndrome limited the use of neuroleptics for the treatment of bipolar disorder.

In 2000, olanzapine was the first atypical antipsychotic to receive a U.S. Food and Drug Administration (FDA) bipolar mania indication. Subsequent FDA approvals for bipolar mania were received for risperidone in 2003 and three additional compounds in 2004 – quetiapine, ziprasidone and aripiprazole. Olanzapine and aripiprazole are also FDA approved for the maintenance treatment of bipolar disorder. Atypical antipsychotic medications are a relatively new, increasingly prominent component of the treatment armamentarium for bipolar disorder, a development that has expanded options for treatment (17, 20). However, information on adherence with antipsychotics among individuals with bipolar disorder in general, and atypical antipsychotics in particular, is currently quite limited (15).

Using the VA National Psychosis Registry, we examined adherence with antipsychotic medication among veterans with bipolar disorder within a 1-year period (October 1, 2002–September 30, 2003). We hypothesized that younger age, minority ethnicity and presence of substance use disorders and PTSD would all be associated with lower treatment adherence with antipsychotic medication. Further, we hypothesized that veterans with bipolar disorder would be more adherent with atypical antipsychotic medications compared to conventional antipsychotic compounds and those individuals prescribed a single antipsychotic medication would be more adherent compared to those prescribed multiple antipsychotic medications. Finally, we hypothesized that non-adherence with prescribed antipsychotic medication among individuals with bipolar disorder is associated with higher rates of hospitalization and longer hospital stays.

Method

Subjects

The database from which study results are derived was developed by the Serious Mental Illness Treatment Research and Evaluation Center (SMITREC) at the recommendation of the VA’s Committee on Care of Severely Chronically Mentally Ill Veterans in 1998. This database, the National Psychosis Registry, is an ongoing registry of all veterans diagnosed with psychosis (schizophrenia, schizoaffective disorder, bipolar disorder, and other non-organic psychosis) who have received VA services from 1988 to the present. Thus, the registry consists of records for all patients who received a diagnosis of psychosis during inpatient stays from Federal Fiscal Year 1988 (FY88) and later, and during outpatient visits from Federal Fiscal Year 1997 (FY97) and later. Pharmacy data are from the VA Pharmacy Benefits Management Strategic Healthcare Group.

Registry patients were identified using data obtained from the VA Patient Treatment File, census data files and Outpatient Care Files located at the Austin Automation Center in Texas, and were included provided that they had at least one qualifying psychosis diagnosis in the FY’s inpatient or outpatient data. A full report of the Psychosis Registry may be viewed over the SMITREC web site: <http://www.va.gov/annarbor-hsrdr>. Bipolar diagnoses were obtained from ICD9-CM codes used in the database. Bipolar diagnoses included ICD9 codes 296.0 (bipolar manic, single episode), 296.1 (bipolar manic, recurrent episode), 296.4 (bipolar manic/hypomanic), 296.5 (bipolar depressed), 296.6 (bipolar mixed), 296.7 (bipolar unspecified) and 296.8 (affective psychosis, manic-depressive, unspecified).

The results presented here focus on veterans with bipolar disorder active in the Registry in Federal Fiscal Year 2003 (FY03) ($n = 73,964$). For purposes of this analysis, veterans with bipolar disorder who were prescribed antipsychotics in FY03 were evaluated in three clinically relevant sub-groups: (i) individuals who were fully adherent with antipsychotic medication; (ii) individuals who were partially adherent with antipsychotic medication; and (iii) individuals who were non-adherent with antipsychotic medication.

Measurement of adherence

Medication adherence was evaluated using the medication possession ratio (MPR) for patients receiving any antipsychotic medication. An MPR was calculated for patients on any antipsychotic

medication. The MPR is the ratio of the 'number of days supply of medication that a patient has received' to the 'number of days supply that they should have received' had they been taking medication as prescribed. An MPR of 1 or 100% indicates that the patient has received all medication needed to take their antipsychotic medication as prescribed, whereas an MPR of 0.5% or 50% indicates that the patient has received medication sufficient to take only half of the prescribed dose. The MPR was calculated among patients with at least 90 outpatient days of observation during the fiscal year. The MPR was calculated for the time period of FY03 (October 2002–September 2003) following the date of the patient's first antipsychotic medication fill of the year. Days spent in institutional settings were subtracted from the numbers of days supply the patient 'should have received' to take their medication as prescribed. MPR calculations were limited to individuals who were taking no more than two antipsychotic medications during the fiscal year. In cases where an individual was on two antipsychotic medications, a weighted average of the two MPRs was calculated. The MPR or a similar method has been used to quantify treatment adherence in a number of earlier reports (21–24).

Antipsychotics prescribed in the VA during FY03 were conventional antipsychotic agents as well as novel or atypical antipsychotics. The atypical agents available in FY03 in the VA were clozapine, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole. Neither long-acting injectable medications nor medications prescribed for use in inpatient settings were included in this analysis.

Adherence intensity

Patients' degree of adherence was evaluated in three clinically relevant categories. Individuals who were fully adherent with antipsychotic medication had MPRs of 0.8 or higher. Individuals who were partially adherent with antipsychotic medication had MPRs of more than 0.5 and less than 0.8. Individuals who were considered to be non-adherent with medication (proportion of medication taken so minimal as to be unlikely to have desired therapeutic effect) had MPRs of less than or equal to 0.5. This method of categorizing ordinal level of adherence among patients with serious mental illness, including bipolar disorder, has been similarly used by other groups of investigators (21, 22).

Statistical analysis

Descriptive statistics were used to characterize demographic and clinical characteristics of all

patients with bipolar disorder. Multivariate logistic regression was used to compare patients prescribed and not prescribed antipsychotic medications and multinomial logistic regression was used to compare demographic characteristics, hospitalization rates and length of hospital stay for patients with full, partial or non-adherence to antipsychotic medication. Sex, age, race, marital status, substance abuse, comorbid PTSD and homelessness were included as covariates in the models. Psychiatric hospitalization in the previous year was also evaluated separately and included in the models comparing hospitalization rates and length of stay. Wilcoxon tests were used to compare mean MPRs for patients receiving one versus two antipsychotics, mean MPRs for patients receiving atypical versus conventional antipsychotics and mean MPRs for patients receiving clozapine versus other atypical antipsychotics. The level for statistical significance was set at < 0.0001 .

Results

Use of antipsychotic medications

Antipsychotic medications were commonly used to treat individuals with bipolar disorder, usually on a long-term basis. Approximately 45% of individuals with bipolar disorder received treatment with antipsychotic medications. In FY03, olanzapine was the most commonly prescribed agent. The great majority of individuals prescribed antipsychotic agents received atypical compounds ($n = 25,559$, 94.7%), while less than 9% ($n = 2357$) of individuals with bipolar disorder received conventional compounds.

Table 1 demonstrates the characteristics of individuals with bipolar disorder who received any antipsychotic medication ($n = 32,993$, 44.6% of all individuals with bipolar disorder) compared to those who were not prescribed antipsychotic medication. Patients with bipolar disorder were more likely to receive antipsychotic medication if they were younger ($\chi^2 = 215.9$, $df = 1$, $p < 0.0001$) compared to individuals that were not prescribed antipsychotic medication. Individuals were also more likely to be prescribed antipsychotic medications if they had comorbid substance use ($\chi^2 = 181.6$, $df = 1$, $p < 0.0001$) or a PTSD diagnosis ($\chi^2 = 351.1$, $df = 1$, $p < 0.0001$). When comparing differences in age, gender, ethnicity, marital status, substance use and presence of PTSD or homelessness, individuals prescribed conventional antipsychotics were more likely to be older ($\chi^2 = 47.1$, $df = 1$, $p < 0.0001$), of minority race ($\chi^2 = 12.7$, $df = 1$, $p = 0.0004$) and

Table 1. Characteristics of veterans with bipolar disorder prescribed and not prescribed antipsychotic medications in FY03^a

Characteristics	All veterans with bipolar disorder, n (%)	Veterans prescribed antipsychotic medications, n (%)	Veterans not prescribed antipsychotic medications, n (%)	Test of significance between groups (controlling for other covariates)
Number of patients	73,964	32,993 (44.6)	40,971 (55.4)	
Mean age (SD)	52.3 (12.5)	51.2 (11.9)	53.1 (12.9)	Wald $\chi^2 = 215.9$, $p < 0.0001$, $df = 1$
Gender				
Male	65,212 (88.2)	28,987 (87.9)	36,225 (88.4)	ns
Female	8,752 (11.8)	4,006 (12.1)	4,746 (11.6)	
Ethnicity				
White	46,251 (62.5)	21,715 (65.8)	24,536 (59.9)	ns ^b
Black	7,694 (10.4)	3,909 (11.9)	3,785 (9.2)	
Hispanic	2,249 (3.0)	1,149 (3.5)	1,100 (2.7)	
American Indian	239 (0.3)	124 (0.4)	115 (0.3)	
Asian	172 (0.2)	70 (0.2)	102 (0.3)	
Unknown	17,359 (23.5)	6,026 (18.3)	11,333 (27.7)	
Marital status				
Never married	15,386 (21.0)	7,162 (21.9)	8,224 (20.3)	ns ^c
Married	27,651 (37.7)	11,642 (35.5)	16,009 (39.5)	
Divorced/separated	27,751 (37.9)	12,918 (39.4)	14,833 (36.6)	
Widowed	2,497 (3.4)	1,047 (3.2)	1,450 (3.6)	
Substance use disorder				
Yes	23,484 (31.8)	12,250 (37.1)	11,234 (27.4)	Wald $\chi^2 = 181.6$, $p < 0.0001$, $df = 1$
No	50,480 (68.3)	20,743 (62.9)	29,737 (72.6)	
PTSD diagnosis				
Yes	15,721 (21.3)	8,518 (25.8)	7,203 (17.6)	Wald $\chi^2 = 351.1$, $p < 0.0001$, $df = 1$
No	58,243 (78.8)	24,475 (74.2)	33,768 (82.4)	
Homelessness				
Yes	10,176 (13.8)	5,226 (15.8)	4,950 (12.1)	ns
No	63,788 (86.2)	27,767 (84.2)	36,021 (87.9)	

Covariates include sex, age, race, marital status, substance abuse, post-traumatic stress disorder (PTSD) and homelessness.

^aFederal Fiscal Year 2003.

^bComparing race categories: white versus not white.

^cComparing marital status categories: married versus not married.

homeless ($\chi^2 = 34.2$, $df = 1$, $p < 0.0001$) and less likely to have comorbid substance abuse ($\chi^2 = 94.2$, $df = 1$, $p < 0.0001$) or PTSD ($\chi^2 = 46.2$, $df = 1$, $p < 0.0001$) compared to individuals prescribed atypical antipsychotics.

Intensity of adherence

Table 2 outlines the clinical characteristics among individuals who were fully, partially and non-adherent with antipsychotic medication. Among the patients with calculated MPR (n = 26,986) the majority of individuals were either fully (51.9%, n = 13,994) or partially adherent (21.2%, n = 5723) with antipsychotic medication while just over a quarter of the group (26.9%, n = 7269) was non-adherent with antipsychotic medication. Compared to fully or partially adherent groups, the group of non-adherent individuals (non-adherent versus others) was younger ($\chi^2 = 205.4$, $df = 2$, $p < 0.0001$) and had more minority individuals ($\chi^2 = 141.5$, $df = 2$, $p < 0.0001$). The poorly adherent group had more individuals with substance abuse ($\chi^2 = 79.3$, $df = 2$, $p < 0.0001$) and more individuals

who were homeless ($\chi^2 = 119.0$, $df = 2$, $p < 0.0001$). There were no gender differences with respect to degree of adherence with antipsychotic medications among this predominantly male sample with bipolar disorder.

Adherence with specific antipsychotic agents

Table 3 demonstrates adherence with specific antipsychotic agents in FY03. For all veterans with bipolar disorder who received any antipsychotic medication the mean MPR was 0.76 ± 0.36 . MPRs for individuals prescribed atypical antipsychotics except clozapine were fairly similar, ranging from 0.75 for risperidone to 0.79 for aripiprazole. The mean MPR for individuals on two antipsychotics was somewhat higher than MPRs for single antipsychotics (Wilcoxon $Z = 5.8$, $p < 0.0001$).

For individuals who were on only one antipsychotic medication (n = 21,917), the mean MPR for conventional agents (0.82 ± 0.33) was higher than the mean MPR for atypical antipsychotic agents (0.75 ± 0.37) ($Z = 7.0$, $p < 0.0001$). Although individuals who were prescribed clozapine had a

Table 2. Intensity of adherence with antipsychotic medications among individuals with bipolar disorder who were prescribed antipsychotics in Federal Fiscal Year 2003 (n = 26,986)

	Fully adherent ^a , n (%)	Partially adherent ^b , n (%)	Non-adherent ^c , n (%)	Test of significance between groups (controlling for other covariates)
Number of patients	13,994 (51.9)	5,723 (21.2)	7,269 (26.9)	
Mean age (SD)	53.1 (11.7)	51.0 (11.6)	49.2 (11.8)	Wald $\chi^2 = 205.4$, p < 0.0001, df = 2
Gender				
Male	12,318 (88.0)	5,004 (87.4)	6,330 (87.1)	ns
Female	1,676 (12.0)	719 (12.6)	939 (12.9)	
Ethnicity				
White	9,982 (71.3)	3,745 (65.4)	4,421 (60.8)	Wald $\chi^2 = 141.5$, p < 0.0001, df = 2*
Black	1,168 (8.4)	771 (13.5)	1,115 (15.3)	
Hispanic	482 (3.4)	215 (3.8)	266 (3.7)	
American Indian	54 (0.4)	18 (0.3)	21 (0.3)	
Asian	30 (0.2)	10 (0.2)	18 (0.3)	
Unknown	2,278 (16.3)	964 (16.8)	1,428 (19.7)	
Marital status				
Never married	2,923 (21.0)	1,210 (21.3)	1,710 (23.7)	ns**
Married	5,408 (38.9)	2,046 (36.0)	2,384 (33.1)	
Divorced/separated	5,084 (36.6)	2,253 (39.6)	2,930 (40.7)	
Widowed	486 (3.5)	180 (3.2)	184 (2.6)	
Substance use disorder				
Yes	4,013 (28.7)	2,075 (36.3)	2,957 (40.7)	Wald $\chi^2 = 79.3$, p < 0.0001, df = 2
No	9,981 (71.3)	3,648 (63.7)	4,312 (59.3)	
PTSD diagnosis				
Yes	3,309 (23.7)	1,503 (26.3)	1,915 (26.3)	ns
No	10,685 (76.4)	4,220 (73.7)	5,354 (73.7)	
Homelessness				
Yes	1,327 (9.5)	838 (14.6)	1,361 (18.7)	Wald $\chi^2 = 119.0$, p < 0.0001, df = 2
No	12,667 (90.5)	4,885 (85.4)	5,908 (81.3)	

Covariates include sex, age, race, marital status, substance abuse, post-traumatic disorder (PTSD) and homelessness.

^aAdherent with 80% or more of medication.

^bAdherent with more than 50%, but less than 80% of medication.

^cAdherent with less than or equal to 50% of medication.

*Comparing race categories: white versus not white.

**Comparing marital status categories: married versus not married.

Table 3. Adherence with antipsychotic medication among individuals with bipolar disorder

	Number of individuals, n (%)	Medication possession ratio, mean (SD)
All veterans with bipolar disorder on any antipsychotic	26,986	0.76 (0.36)
Individuals on conventional antipsychotic	2,357 (8.7)	0.83 (0.33)
Individuals on atypical antipsychotics	25,559 (94.7)	0.75 (0.37)
Clozapine	38	0.84 (0.25)
Risperidone	8,343	0.75 (0.36)
Olanzapine	11,284	0.75 (0.36)
Quetiapine	8,810	0.77 (0.38)
Ziprasidone	1,069	0.77 (0.38)
Aripiprazole	136	0.79 (0.38)
Individuals on a single antipsychotic medication	21,917 (81.2)	0.75 (0.36)
Individuals on two antipsychotic medications	5,069 (18.8)	0.79 (0.36)
For individuals on only one antipsychotic		
Atypical	20,508 (93.6)	0.75 (0.37) ^a
Conventional	1,409 (6.4)	0.82 (0.33)
Clozapine	26 (0.13)	0.90 (0.14) ^b
Other atypicals	20,482 (99.9)	0.75 (0.37)

Single antipsychotic versus two antipsychotics: Wilcoxon test, Z = 5.8, p < 0.0001.

^aAtypical versus conventional antipsychotics, Wilcoxon test, Z = 7.0, p < 0.0001.

^bClozapine versus other atypicals, Wilcoxon test, Z = 2.0, p = 0.0498.

Table 4. Duration of treatment with antipsychotic medications

	Median, range	≤90 days, n (%)	91–180 days, n (%)	181–270 days, n (%)	>270 days*, n (%)
Any antipsychotic	240 (1,885)	5,563 (20.6)	5,291 (19.6)	5,012 (18.6)	11,120 (41.2)
Any conventional antipsychotic	270 (1,780)	570 (24.2)	339 (14.4)	412 (17.5)	1,036 (44.0)
Any atypical antipsychotic	240 (1,885)	5,578 (21.8)	5,140 (20.1)	4,734 (18.5)	10,107 (39.5)
Two antipsychotics	268 (5,820)	577 (11.4)	1,043 (20.6)	1,102 (21.7)	2,347 (46.3)
Aripiprazole	81.5 (2,330)	82 (60.3)	37 (27.2)	13 (9.6)	4 (2.9)
Clozapine	322 (7,378)	5 (13.2)	1 (2.6)	7 (18.4)	25 (65.8)
Olanzapine	210 (1,840)	3,154 (28.0)	2,269 (20.1)	1,928 (17.1)	3,933 (34.9)
Quetiapine	180 (1,885)	2,795 (31.7)	1,894 (21.5)	1,431 (16.2)	2,690 (30.5)
Risperidone	180 (1,780)	2,491 (29.9)	1,737 (20.8)	1,466 (17.6)	2,649 (31.8)
Ziprasidone	150 (5,690)	409 (38.3)	224 (21.0)	151 (14.1)	285 (26.7)

*Approximately 12% with >365 days supply.

numerically higher mean MPR compared to individuals prescribed other atypical agents (clozapine: 0.90 ± 0.14 , others: 0.75 ± 0.37 ; Wilcoxon $Z = 2.0$, $p = 0.0498$), this did not reach significance at a <0.0001 level.

Duration of treatment for specific antipsychotic agents is shown in Table 4. Overall, the median length of antipsychotic medication use following the first prescription of the year was 240 days. For all antipsychotics except aripiprazole, the majority of individuals with bipolar disorder received more than 90 days of medication treatment. In situations where two antipsychotic medications were prescribed concurrently, 11.4% of individuals ($n = 577$) received therapy for 90 days or less.

There were fewer total and psychiatric hospitalizations during FY03 among individuals with bipolar disorder who were adherent with antipsychotic medication (23.7% and 14.9% respectively), compared to individuals who were partially adherent with medication (24.8% and 16.9% respectively), or non-adherent with antipsychotic medication (25.2% and 16.9% respectively). After controlling for covariates, adherent patients were more likely to be hospitalized ($\chi^2 = 17.5$, $df = 2$, $p = 0.0002$ for all hospitalizations and $\chi^2 = 15.9$, $df = 2$, $p = 0.0003$ for psychiatric hospitalizations), although this did not reach significance at the 0.0001 level. Once hospitalized, length of stay was longer for individuals who were adherent with medication ($\chi^2 = 10.4$, $df = 2$, $p = 0.0056$ for all hospitalizations and $\chi^2 = 18.1$, $df = 2$, $p = 0.0001$ for psychiatric hospitalizations) although this did not reach significance at the 0.0001 level.

Discussion

Current guidelines for the treatment of patients with bipolar disorder (17, 20) suggest that special clinical features may influence medication prescrib-

ing. For example, individuals with psychotic mania may benefit from the addition of antipsychotic medications (17, 20), while traditional mood stabilizers or antipsychotics with less potential risk to worsen metabolic problems may be preferred for individuals with bipolar disorder and comorbid diabetes.

A recent Expert Consensus Panel (20) has noted growing support for the use of antipsychotics either alone or in combination with traditional mood stabilizers such as lithium, valproate and carbamazepine for the treatment of both acute phases and maintenance treatment of bipolar disorder. In this study, we found widespread use of antipsychotic medications among individuals with bipolar disorder, with 45% of individuals receiving these medications during the year and most of these individuals continuing on these medications long term.

There were important differences between individuals prescribed antipsychotic medications compared to those not prescribed antipsychotic medications. Individuals with bipolar disorder who were prescribed antipsychotic medication were younger and more often had comorbid substance abuse or PTSD compared to individuals with bipolar disorder who were not prescribed antipsychotic medication.

Similar to previous studies examining adherence with lithium or anticonvulsants, adherence with antipsychotic medication varied widely. Just over half (51.9%) of individuals appear to be fully adherent with antipsychotic medications, while 48.1% of individuals are either partially adherent or non-adherent with antipsychotic medications. Non-adherence with antipsychotic medication among individuals with bipolar disorder in this study was substantially greater than the 25% rate noted in a recent, large-scale review of adherence to treatment among patients with medical disorders by DiMatteo (25), but is consistent with

estimates of poor adherence with treatment among patients with medical disorders reported by Cramer (26).

The non-adherence rate findings in the study reported here are similar to non-adherence rates with lithium and anticonvulsants that have been reported by previous investigators (15, 27). Lingham and Scott (27) noted a 41% median rate of treatment non-adherence among individuals with bipolar disorder, while Perlick et al. (15) found an overall median rate of non-adherence of 42%. In the study reported here, 21.2% of individuals with bipolar disorder were partially adherent with antipsychotic medications, while 26.9% were essentially non-adherent with antipsychotic medication. Thus, although antipsychotic medications do not require regular serum level monitoring, and may be considered relatively simple to take, poor adherence remains a problem.

Predictors of poor adherence among individuals with bipolar disorder in this study included younger age, minority race, substance abuse and homelessness. Similarly, most (5, 10, 28–30) studies that have examined adherence in relation to age among individuals with bipolar disorders have found that younger age is a risk factor for non-adherence. In this report, gender did not appear to be associated with adherence status, although this could be potentially explained by the fact that only 11–12% of the individuals with bipolar disorder in this VA sample were women. Similar to our findings, Keck (31) has reported that non-Caucasian ethnicity may be a risk factor for non-adherence among individuals with bipolar disorder.

Perlick et al. (15) have reported that the most consistent sociodemographic variable associated with adherence among individuals with bipolar disorder is marital status/living situation. Numerous studies from the pre-atypical antipsychotic era suggest that being non-married or living alone is a significant risk factor for non-adherence among individuals with bipolar disorder (5, 30, 32, 33). In the study reported here, among non-adherent individuals with bipolar disorder, 33.1% (n = 2384) were married, compared to adherent individuals where 38.9% (n = 5408) were married. However, after adjustment for covariates, marital status was no longer a predictor for adherence.

Differences in rates of homelessness were substantial between non-adherent and adherent individuals, with 18.7% (n = 1361) of non-adherent individuals being homeless compared to 9.5% (n = 1327) of adherent individuals being homeless. In addition to its negative psychological impact, it is likely that homelessness may be associated with difficulties in access to medication and treatment.

Substance abuse appears to be associated with non-adherence in this study, a finding that has been reported by numerous other investigators (10, 31, 34). Weiss (12) has noted that some patients with bipolar disorder report ‘wanting to take drugs’ as a reason for non-adherence. The database upon which this study is based did not permit an evaluation of reasons for non-adherence; however, previous work by this group of investigators suggests that treatment non-adherence is not simply a ‘patient problem’, but appears to be an important component of the provider–patient relationship (35). In addition to the life problems that result with substance abuse, it is possible that individuals with substance abuse disorders are not as fully engaged in treatment or may not have as good a relationship with treatment providers as those individuals without substance abuse.

Atypical antipsychotics have a more benign side effect profile compared to older, conventional antipsychotics, and atypicals are preferred over conventional antipsychotics in bipolar disorder treatment guidelines (17, 20). Given this, one might expect that treatment adherence would be better in agents that are better tolerated and less frequently associated with problematic side effects. However, in contrast to our hypothesis, the results of this study did not suggest that adherence with atypical antipsychotics is better than with conventional antipsychotic medications. While side effects from medications have been noted to be a consideration for patients with bipolar disorder with respect to adherence (7, 36), a number of studies have failed to find an association between side effects and treatment adherence in bipolar disorder treatment (30, 32, 34). One potential reason why the results of this naturalistic study might have found higher adherence for conventional antipsychotics may be that the relatively small proportion of individuals who were treated with conventional antipsychotics (<10%) may represent a sub-group of patients who have been maintained on traditional neuroleptics long term with particularly good response and have particularly high rates of adherence. Providers may be reluctant to switch this group of individuals to atypical agents. Additionally, the widespread use of atypical antipsychotics for symptomatic improvements such as sleep or anxiety may lead to common prescribing for a heterogeneous group of patients, thus having higher rates of non-adherence in the atypical prescribed group.

In this study, treatment with two antipsychotic medications was not associated with less treatment adherence compared to treatment with a single agent – in fact the reverse was true – patients

receiving treatment with two agents had a higher mean MPR than those treated with any single antipsychotic agent with the exception of clozapine. In contrast, Keck et al. (37) reported that treatment with more than one mood stabilizer was associated with reduced adherence. An analysis from a prospective trial involving VA patients with bipolar disorder noted that therapy with multiple medications may be a reflection of intensity of treatment, and that polytherapy is associated with greater treatment adherence (38).

Finally, our hypothesis that treatment non-adherence would be associated with higher rates of hospitalization was not confirmed. Other investigators have demonstrated that non-adherence is associated with higher rates of re-hospitalization among individuals with bipolar disorder. Svarstad et al. (22) reported that among individuals with bipolar disorder, hospitalization rates for individuals who regularly use medication are 31% compared to 73% for individuals who irregularly use medication. This same report by Svarstad (22) demonstrated that hospital costs also vary significantly between individuals with bipolar disorder who are adherent (regular medication users) and those who are non-adherent (irregular medication users) with annual hospital costs of \$1,657 for adherent individuals compared to annual costs of \$9,701 for non-adherent individuals.

Veterans in this study had relatively high rates of hospitalization overall, potentially reflecting easier access to inpatient care within the Veterans Health Association (VHA) compared to other care systems. Relatively high rates of hospitalization among adherent veterans may reflect greater help-seeking behaviors on the part of these patients. Additionally, clinical features seen in some veterans such as high rates of comorbid substance abuse may also make relapse and rehospitalization more likely.

Limitations

The study is limited by its retrospective nature, the relative gender homogeneity of the study sample and inability to validate some features of the data (for example, the medical record diagnoses were utilized as opposed to use of a standardized diagnostic interview). An additional limitation is the fact that treatment adherence was determined based upon rates of prescription refills and it was not possible to guarantee that low MPR was due to non-adherence. Patients may have stopped filling antipsychotic medications because their physician discontinued the medication rather than from poor adherence. Some physicians may have written for

short-term use of antipsychotic medications rather than advising patients to continue on these medications long term. However, we note the prevalence of poor adherence seen in this study (48%) was similar to previous reports of poor adherence with lithium and anticonvulsants using other methods for assessing adherence (15). Most patients received long-term antipsychotic prescriptions, suggesting that long-term use is becoming the norm in clinical practices and the overall MPR for these patients was only slightly lower than that seen among patients with schizophrenia, a group of patients for which the standard of care is long-term antipsychotics (24).

This report focuses on atypical antipsychotic treatment adherence, an area that has been little studied in the bipolar literature rather than addressing the comprehensive nature of medication and psychosocial treatments for bipolar disorder. Many of the individuals with bipolar disorder in the VA system receive treatment with a variety of other psychotropic and non-psychotropic compounds for both psychiatric and medical illness or may receive psychosocial interventions for bipolar illness, and thus findings from this report limit interpretation of adherence patterns across the full spectrum of bipolar disorder treatments. Strengths of the study include large sample size and the fact that adherence was examined under naturalistic conditions.

Clinical implications and conclusions

Antipsychotic medications are commonly used to treat individuals with bipolar disorders, often on a long-term basis. Younger individuals, and those with comorbid substance abuse or PTSD appear particularly likely to receive treatment with antipsychotic medications. Although antipsychotic medications do not require the frequent blood draws that are characteristic of treatment with lithium or anticonvulsants, treatment adherence remains a problem with these medications. Close to half of individuals with bipolar disorder prescribed antipsychotic medication are poorly adherent. Clinical implications of poor adherence include worsening symptoms, relapse, psychosocial deterioration, increased costs and in the worst-case scenario – suicide. Even in clinical trials with carefully selected patient participants, treatment non-adherence can be relatively common (39). Identification of risk factors for non-adherence, such as substance abuse and homelessness, with focused treatment for substance abuse and interventions to obtain stable

housing may improve outcomes for individuals most vulnerable to non-adherence related relapse. Psychosocial interventions have been demonstrated to potentially enhance treatment adherence (1, 16) and systems interventions such as calls, letters or reminders and outreach to individuals known to be at high risk for non-adherence may enhance adherence within healthcare networks. While a growing literature points out the pervasive issue of treatment non-adherence, additional studies are needed to better understand treatment adherence within the full range of pharmacologic therapies among individuals with bipolar disorder.

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