Patterns of Atypical Antipsychotic Subtherapeutic Dosing Among Oregon Medicaid Patients

Daniel M. Hartung, Pharm.D., M.P.H.; Jennifer P. Wisdom, Ph.D., M.P.H.; David A. Pollack, M.D.; Ann M. Hamer, Pharm.D.; Dean G. Haxby, Pharm.D.; Luke Middleton, B.S.; and Bentson H. McFarland, M.D., Ph.D.

Objective: To examine a cohort of Medicaid patients with new prescriptions for atypical antipsychotic medication to determine the prevalence of subtherapeutic atypical antipsychotic medication use and to identify patient and prescribing provider characteristics associated with occurrence of subtherapeutic use.

Method: This observational cohort study examined Medicaid administrative claims data for patients aged 20 to 64 years with a new prescription for an atypical antipsychotic medication (clozapine, olanzapine, quetiapine, risperidone, ziprasidone) between January 1, 2004, and December 31, 2004. Patient diagnostic information was identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification* codes on submitted medical claims. Patient characteristics, prescribing provider characteristics, length of therapy, and dosing were examined. A logistic regression assessed the probability of subtherapeutic dosing.

Results: Among 830 individuals in our sample who began treatment with an atypical antipsychotic, only 15% had a documented diagnosis of schizophrenia, subtherapeutic dosing was common (up to 86% of patients taking quetiapine), and 40% continued less than 30 days with the index prescription. A logistic model indicated that a general practitioner as prescribing provider, length of therapy equal to or less than 30 days, and prescription of quetiapine were significantly associated with a subtherapeutic dose ($p < .001$, $p = .028$, and $p < .001$, respectively).

Conclusions: These results suggest that there is extensive use of expensive atypical antipsychotic medications for off-label purposes such as sedation or for other practice patterns that should be explored further. Approaches that minimize off-label atypical antipsychotic use could be of considerable value to Medicaid programs. In addition, these findings support the need for the introduction or increased use of utilization monitoring and the implementation of medication practice guidelines as appropriate decision support for prescribing providers.

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Corresponding author and reprints: Jennifer P. Wisdom, Ph.D., M.P.H., New York State Psychiatric Institute, Department of Mental Health Services and Policy Research, 1051 Riverside Dr., Unit/Box 100, New York, NY 10032 (e-mail: jwisdom@pi.cpmc.columbia.edu).

Atypical antipsychotic medications make up a large and growing portion of expenditures for Medicaid programs.[1,2] Banthin and Miller[1] reported that antipsychotic medications constituted 7.1% of Medicaid expenditures in 2001–2002. This percentage had increased 154% from 1996–1997, which is most likely due to increasing use of atypical antipsychotic medications. In Oregon, where psychiatric medications are a carved-out benefit, atypical antipsychotic medications represented nearly 30% of all outpatient drug expenditures in 2006.[3] State Medicaid and other public agencies fund much if not most of the atypical antipsychotic medication consumed in the United States.[4] In addition, states bear much of the costs of treating the serious adverse events that can be associated with atypical antipsychotic medication use, including weight gain and diabetes.[5]

State Medicaid agencies have attempted to reduce expenditures for medications by adopting policies such as prior authorization and utilization review.[6] Such policies are not uncommon in the Department of Veterans Affairs system for atypical antipsychotic medications; however, these types of policies have not been broadly applied to atypical antipsychotic medication.[7] A survey of state Medicaid agencies in 1998 by Sullivan et al.[7] showed that 6% had adopted policies such as prior authorization for atypical antipsychotic medications. Several states have also collaborated with pharmaceutical manufacturer Eli Lilly and Company and its contractor Comprehensive

Neuroscience, Inc., on projects intended to notify prescribing providers about inappropriate prescribing practices for atypical antipsychotic medications, such as doses outside the therapeutic ranges approved by the U.S. Food and Drug Administration.[8]

It has been suggested that policies such as prior authorization for atypical antipsychotic medications might reduce pharmaceutical expenditures but may have other unintended consequences, such as increased rates of hospitalization.[9] Several studies have indicated, however, that such claims may be unfounded. For example, Rothbard et al.[10] examined symptoms and expenditures for Medicaid clients with severe mental illness in several states and found no evidence that use of atypical antipsychotic medication was associated with reduced expenditures.[10] The randomized Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)[11] project found that participants with schizophrenia assigned to atypical antipsychotic arms of the protocol generated greater expenditures than did subjects taking conventional (first-generation or neuroleptic) antipsychotic medication, and the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS)[12] reached similar conclusions.

These considerations have prompted investigations into use of atypical antipsychotic medications. Several projects have addressed concerns about polypharmacy, with emphasis on concurrent use of 2 or more atypical antipsychotic medications.[13–15] In a study focused chiefly on polypharmacy, Kogut et al.[14] noted substantial numbers of subjects who appeared to have been prescribed very low doses of atypical antipsychotic medication. This finding raised concerns about use of atypical antipsychotic medications for unapproved indications such as sedation.[16,17] A recent systematic review found either methodologically limited evidence or no evidence supporting atypical antipsychotic use for many conditions, including dementia-related agitation, depression, posttraumatic stress disorder (PTSD), and personality disorders.[18] Furthermore, adverse effects such as stroke and increased risk of death among subjects with dementia have negatively influenced the risk-benefit trade-off for these drugs.[19]

Accordingly, the present project was designed to examine atypical antipsychotic medication use in a noninstitutionalized, fee-for-service Medicaid population. The objectives of this study were to describe patterns of atypical antipsychotic use among incident users, to determine the prevalence of subtherapeutic atypical antipsychotic medication use, and to identify patient and prescribing provider characteristics associated with the occurrence of subtherapeutic use.

METHOD

The goal of the analysis was to investigate the drug therapy patterns of noninstitutionalized, adult (20–64 years of age) Oregon fee-for-service Medicaid enrollees prescribed atypical antipsychotic medications. Using an observational cohort constructed from administrative claims data, patients with a new prescription for an atypical antipsychotic medication (clozapine, olanzapine, quetiapine, risperidone, or ziprasidone) between January 1, 2004, and December 31, 2004, were identified. A new prescription (the index fill) was defined as a patient's first claim with no previous claim for any atypical antipsychotic medication for a minimum of 6 months (earliest historical date was July 1, 2003). To ensure complete ascertainment of claims and no loss of follow-up due to lost eligibility, patients were required to have continuous fee-for-service Medicaid enrollment for a total of 18 months (6 months prior to and 12 months following index fill). Patients were followed for up to 2 years following their index fill. If atypical antipsychotic therapy continued beyond 2 years, these data were omitted from analysis (i.e., patients were followed for a maximum of 2 years).

Demographic data including age, sex, race/ethnicity, urban or rural residence, Medicaid/Medicare dual eligibility, diagnostic information, and index prescribing provider type were summarized. Urban or rural classification was based on 2000 census information by the county listed as the patient's residence. Racial/ethnic determination was based on enrollment data, which we consolidated into the following categories: white, African American, Native American, Hispanic, Asian/Pacific Islander, or other/unknown. To evaluate the generalizability of our longitudinal cohort, we identified basic demographic and utilization data for a comparison group that included all patients between the ages of 20 and 64 years with any fee-for-service enrollment during the 12-month capture period.

Prescribing provider information was determined from the patient's index prescription. For each submitted claim, the dispensing pharmacy is required to submit information regarding the prescribing provider. If a prescribing provider is not an authorized Medicaid provider, however, a pharmacist may enter an emergency prescribing provider default code in order to facilitate timely claims processing. Unfortunately, this exemption is used beyond the initial intention, and roughly one third of processed claims have no prescribing provider information attached. Furthermore, institutions such as clinics and hospitals can have valid provider identifiers that may also be entered, although it may be difficult to identify an individual prescribing provider responsible for a specific claim. Data on physician specialty (e.g., psychiatry, internal medicine) are also kept in the Medicaid provider file. For index claims on which a prescribing provider was identified, we classified the provider type as nurse practitioner (presumed to be a combination of psychiatric and primary care–based nurse practitioners), general practitioner (e.g., internal medicine, general practice, or family

practice specialty listed), or psychiatry (either a psychiatrist or a mental health clinic, where prescribing providers could be psychiatrists or psychiatric nurse practitioners). These prescribing provider classifications may slightly underestimate the proportion of psychiatric providers, but they generally reflect the proportions of general practice versus psychiatric prescribing providers who are identified in the claims data.

Patient diagnostic information was abstracted from the Medicaid medical encounter claims dataset. Depression, anxiety disorders, bipolar disorder, schizophrenia, dementia, personality disorder, PTSD, and insomnia were identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes on submitted medical claims. Depression was defined by codes 309.0x, 309.1x, 311.xx, 296.9x, 296.2x, and 296.3x. Schizophrenia was defined by code 295.xx. Bipolar disorder was identified using codes 296.4x, 296.5x, 296.6x, 296.7x, and 296.8x. Anxiety disorder was defined by code 300.xx. Dementia was defined by code 290.xx. Personality disorder was defined by code 301.xx. Codes 309.81 and 308.xx were used to identify PTSD. Insomnia was defined by codes 780.50, 780.51, and 780.52. Finally, other psychiatric diagnoses were identified using the remaining ICD-9-CM codes in the mental disorders category (290.xx–319.xx) not already specified above. Diagnostic criteria were screened for 6 months before the index fill and during the entire patient follow-up.

Patients were followed from index fill for up to 2 years depending on continuation of therapy. For patients with more than 2 years of treatment, we included only the first 2 years of data. For each claim, an interval of treatment was quantified by using the dispensing date and days' supply (i.e., begin date = dispensing date, and end date = dispensing date + days' supply). Follow-up of patients was stopped if they switched to another atypical antipsychotic medication, had no further atypical antipsychotic claims, had a gap in therapy of longer than 31 days, or had continuous therapy beyond 2 years. Although there is not current consensus regarding medication persistence and what would be considered an allowable "gap" in therapy, many have suggested that 50% of the previous days' supply dispensed is reasonable. To accommodate the small proportion of patients who receive their prescriptions through the state's mail-order pharmacy, which allows a maximum of 90 days' supply to be dispensed, an absolute gap of 31 days was selected as the midpoint between 15 days (50% of a 30-day supply) and 45 days (50% of a 90-day supply).[20] Each patient's therapy was characterized by the length of atypical antipsychotic treatment, augmentation with other mental health medication, and medication adherence. Augmentation was defined as concurrent use of either an antidepressant (selective serotonin reuptake inhibitor, venlafaxine, mirtazapine, nefazodone, duloxetine, or bupropion) or a mood stabilizer (lithium, carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, pregabalin, tiagabine, topiramate, valproate/valproic acid/divalproex, or zonisamide) for at least 60 days at any point.

Adherence was assessed using the medication possession ratio (MPR).[21–23] The MPR is a commonly employed method for measuring medication adherence and is calculated by dividing the length of therapy with a medication by the total days' supply dispensed during the period.[20] An MPR of 1 indicates sufficient supply for a dose every day during the treatment period. Subjects with an MPR of less than 0.8 were classified as having poor adherence because they did not have sufficient medication for the treatment period. If the MPR was greater than or equal to 0.8, subjects were considered fully or overly adherent. The MPR was analyzed only for subjects with more than 30 days of therapy to minimize the impact of those subjects with only 1 fill. This categorization is similar to that used in other studies in which antipsychotic medication adherence measured with medication claims has been associated with an increased risk of admission as well as increased costs of care.[24,25]

Finally, atypical antipsychotic medication dosing was evaluated. A daily dose was calculated from the unit strength, dispensed quantity, and days' supply fields from each claim. For each individual, the most frequently prescribed daily dose (modal dose) was established and averaged (mean modal dose). For each drug, the mean modal dose was compared to the recommended therapeutic dose according to the labeled indication[26–30] as well as CATIE protocol specifications.[31] The daily adult dose was defined as 300–900 mg for clozapine, 10–30 mg for olanzapine, 300–800 mg for quetiapine, 2–6 mg for risperidone, and 80–160 mg for ziprasidone. Patients were considered to be receiving a subtherapeutic dose if their modal dose fell below the recommended range. Demographic and drug therapy characteristics were compared between those receiving subtherapeutic doses and those prescribed therapeutic or supratherapeutic doses. Statistical comparisons were made using the χ^2 test of proportions or the Fisher exact test for categorical data. Continuous data were compared using the Student t test. Finally, a multivariate logistic regression was used to model the association between subtherapeutic dosing (yes/no) and demographic and drug therapy characteristic variables previously described. Variables were entered into the model using a backwards stepwise procedure with the selection criteria set at a p value of .05. Multicollinearity between predictor variables was assessed using correlation matrices and the variance inflation factor and was deemed not to be significant. All statistical analyses were conducted using SAS software, version 9.1 (SAS Institute Inc., Cary, N.C.).

The research protocol was approved by the Institutional Review Board for the Protection of Human Subjects at Oregon Health & Science University.

RESULTS

Between January 1, 2004, and December 31, 2004, 7141 unique, noninstitutionalized individuals between 20 and 64 years of age with any fee-for-service enrollment had at least 1 prescription for an atypical antipsychotic. Of these, 830 unique patients (11.6%) met the required inclusion criteria for the study cohort. Table 1 provides a summary of demographic and clinical characteristics for both groups. Both groups were relatively similar in general characteristics. The mean age of study subjects was 43. The cohort was predominately female (64%) and white (87%). About three quarters (74%) of subjects resided in an urban county.

Diagnoses were quantified by evaluating medical encounter claims for specific ICD-9-CM codes for 6 months prior to and during the subject's follow-up period. The diagnostic code date was not necessarily associated with the index prescription date, allowing for the broadest inclusion of diagnoses. Patients in the study sample were more likely than those in the comparison population to have a diagnosis of depression (52% vs. 29%), anxiety (34% vs. 20%), or PTSD (15% vs. 8%) and less likely to have a schizophrenia diagnosis (15% vs. 31%). In the study sample of individuals who had been prescribed an atypical antipsychotic medication, 52% of subjects were found to have a diagnosis of depression but only 15% had a documented diagnosis of schizophrenia. A diagnosis involving anxiety or bipolar disorder was observed in 34% and 27% of subjects, respectively. Nearly 15% of those treated had a diagnosis of PTSD. Of those prescribing providers who could be identified, the largest group of prescribing providers was general practitioners (26%), followed by psychiatric practitioners (21%) and nurse practitioners (11%). More than one third of cohort members had an unidentified prescribing provider of their index prescription, which is consistent with previous administrative evaluations of drug use. Approximately 35% of study subjects also had dual Medicare enrollment.

Quetiapine was the most frequently prescribed atypical antipsychotic, with 335 patients (40%) having an index fill for this drug. The next most frequently used atypical antipsychotic was olanzapine (29%), followed by risperidone (25%), ziprasidone (6%), and clozapine (< 1%).

Table 2 summarizes the therapy characteristics of subjects by drug. The proportion of subjects who had less than 31 days of therapy was quantitatively similar between all drug types, although marginal statistical significance was reached (p = .054). Approximately 40% of subjects received less than 31 days of therapy. Between 13% and 18% of subjects (excluding those prescribed clozapine) remained on therapy for more than 360 days. While the cohort included only 3 subjects receiving clozapine, all 3 remained on therapy for more than 360 days. Between 6% and 10% of subjects received augmentation with a mood stabilizer, with no significant differences among antipsychotic drugs. Augmentation with an antidepressant occurred more frequently, being observed in 50% to 54% of subjects. The mean modal dose for each atypical antipsychotic was 433.3 mg for clozapine, 10.2 mg for olanzapine, 140.2 mg for quetiapine, 1.7 mg for risperidone, and 78.3 mg for ziprasidone, with quetiapine, risperidone, and ziprasidone all having mean modal doses below the recommended dosing range. A statistically significant difference in the proportion of subjects on a subtherapeutic dose of their atypical antipsychotic medication was observed (p < .001). Nearly 86% of subjects receiving quetiapine received a subtherapeutic dose compared to between 48% and 59% of those receiving the other nonclozapine atypical antipsychotic medications. No significant differences in MPR classification were observed among drug types. Excluding clozapine, adherence ranged from 83% with quetiapine to 90% with risperidone.

Table 1. Population and Study Sample Characteristics[a]

Variable	All Atypical Antipsychotic Users (N = 7141)	Study Sample (N = 830)
Age, mean (SD)	42.0 (11.2)	43.3 (11.5)
Female	3796 (53.2)	527 (63.5)
Race/ethnicity		
White	6341 (88.8)	725 (87.3)
Native American	220 (3.1)	34 (4.1)
African American	263 (3.7)	27 (3.3)
Hispanic	164 (2.3)	23 (2.8)
Asian	104 (1.5)	15 (1.8)
Other/unknown	49 (0.7)	6 (0.7)
Medicaid/Medicare dual eligibility	2792 (39.1)	290 (34.9)
Urban residence	5379 (75.3)	614 (74.0)
Diagnosis		
Depression	2075 (29.1)	430 (51.8)
Anxiety	1394 (19.5)	281 (33.9)
Bipolar disorder	1558 (21.8)	222 (26.7)
Schizophrenia	2236 (31.3)	121 (14.6)
Dementia	80 (1.1)	8 (1.0)
Personality disorder	121 (1.7)	17 (2.0)
Posttraumatic stress disorder	567 (7.9)	122 (14.7)
Insomnia	240 (3.4)	64 (7.7)
Other psychiatric diagnoses	607 (8.5)	59 (7.1)
Any of above diagnoses	6106 (85.5)	736 (88.7)
Initiating prescriber type		
Psychiatry	…	176 (21.2)
General practice	…	214 (25.8)
Nurse practitioner	…	94 (11.3)
Other	…	45 (5.4)
Unidentified	…	301 (36.3)
Drug[b]		
Quetiapine	2715 (38.0)	335 (40.4)
Olanzapine	2483 (34.8)	238 (28.7)
Risperidone	2317 (32.4)	208 (25.1)
Ziprasidone	592 (8.3)	46 (5.5)
Clozapine	352 (4.9)	3 (0.4)
Subtherapeutic dosing	3689 (51.7)	548 (66.0)

[a]Data are given as N (%) except where indicated otherwise.
[b]Because patients could have used more than 1 agent, the sum does not equal the total N for the group of all atypical antipsychotic users.
Symbol: … = not applicable.

Table 2. Therapy Characteristics of Atypical Antipsychotic Medication Use[a]

Characteristic	Clozapine (N = 3)	Olanzapine (N = 238)	Quetiapine (N = 335)	Risperidone (N = 208)	Ziprasidone (N = 46)	p Value
Length of therapy, d						.054
≤ 30	0 (0.0)	98 (41.2)	135 (40.3)	84 (40.4)	18 (39.1)	
> 30 and ≤ 180	0 (0.0)	86 (36.1)	107 (31.9)	70 (33.7)	14 (30.4)	
> 180 and ≤ 360	0 (0.0)	20 (8.4)	34 (10.1)	19 (9.1)	8 (17.4)	
> 360	3 (100)	34 (14.3)	59 (17.6)	35 (16.8)	6 (13.0)	
Augmentation therapy						
Mood stabilizer	0 (0.0)	15 (6.3)	34 (10.1)	12 (5.8)	4 (8.7)	.722
Antidepressant	3 (100)	125 (52.5)	166 (49.6)	112 (53.8)	24 (52.2)	.062
Mean modal dose, mg	433.33	10.15	140.21	1.68	78.25	
Established therapeutic range, mg	300–900	10–30	300–800	2–6	80–160	
Subtherapeutic dosing	0 (0.0)	115 (48.3)	287 (85.7)	122 (58.7)	24 (52.2)	< .001
Medication possession ratio[b,c]	N = 3	N = 140	N = 200	N = 124	N = 28	.275
< 0.8	0 (0.0)	15 (10.7)	34 (17.0)	12 (9.7)	4 (14.3)	
≥ 0.8	3 (100)	125 (89.3)	166 (83.0)	112 (90.3)	24 (85.7)	

[a]Data are given as N (%) except where indicated otherwise.
[b]Includes subjects with > 30 days of therapy.
[c]A medication possession ratio < 0.8 indicates poor adherence; a medication possession ratio ≥ 0.8 indicates full adherence or overadherence.

A total of 548 subjects (66%) were observed to receive a subtherapeutic dose. Table 3 summarizes patient and therapy characteristic differences between those receiving a therapeutic dose and those receiving a subtherapeutic dose. The mean age was significantly higher (p = .043) among those receiving subtherapeutic doses (43.9 years) compared to those receiving therapeutic doses (42.2 years). There were significantly more female patients in the subtherapeutic dose group (p = .015). Subjects receiving a subtherapeutic dose were more likely to have a diagnosis of depression (54% vs. 47% for the therapeutic dose group) and less likely to have a diagnosis of schizophrenia (11% vs. 22%) or bipolar disorder (25% vs. 31%). There were no differences in the prevalences of the other studied diagnoses. For those receiving a subtherapeutic dose, the initiating prescribing provider was more likely to be a general practitioner and less likely to be a psychiatrist (p = .008). Augmentation with a mood stabilizer occurred in 15% of subjects receiving a therapeutic dose compared to 6% of subjects receiving a subtherapeutic dose (p < .001). The overall length of therapy also differed significantly (p = .003) between those subjects receiving a subtherapeutic dose and those receiving a therapeutic dose. The proportion of patients who received less than 31 days of treatment was higher among patients taking a subtherapeutic dose (43%) compared to those receiving a full dose (34%).

Table 4 shows the results of the multivariate logistic model, and they are generally consistent with univariate comparisons in Table 3. Age and gender were not significant in the final logistic model. Individuals with a diagnosis of schizophrenia or bipolar disorder were 57% (adjusted OR = 0.43, 95% CI = 0.28 to 0.67; p < .001) and 31% (adjusted OR = 0.69, 95% CI = 0.48 to 0.99; p = .044) less likely to be receiving a subtherapeutic dose, respectively. Subjects receiving quetiapine were 4.8 times more likely (adjusted OR = 4.76, 95% CI = 3.08 to 7.35; p < .001) to receive a subtherapeutic dose compared to those who received risperidone. General practitioners were 2.7 times more likely (adjusted OR = 2.74, 95% CI = 1.67 to 4.51; p < .001) than psychiatrists to be associated with subtherapeutic dosing. Finally, subjects with a length of therapy less than 31 days were 74% more likely (adjusted OR = 1.74, 95% CI = 1.06 to 2.84; p = .028) to be prescribed a subtherapeutic dose compared to those who were treated for more than 360 days.

DISCUSSION

This study sought to determine the prevalence of subtherapeutic atypical antipsychotic medication use among incident users and to identify patient and prescribing provider characteristics associated with the occurrence of subtherapeutic use. Several of the observations noted in this analysis raise questions about the prescribing of atypical antipsychotic medication.

Prescribing practices that are outside the range of recommended dosing raise the most concerns. Although many patient presentations could call for dosing below the recommended range, these findings raise questions regarding the likelihood of off-label dosing and the administration of these medications for off-label symptoms, especially insomnia and nonpsychotic agitation. It is likely that atypical antipsychotic medications (especially quetiapine) were often prescribed for sedation rather than for treatment of psychosis. These practices can also be expensive: during 2006, the Oregon Medicaid program spent approximately $2.5 million (excluding rebate) for chronic (> 90 days), subtherapeutically dosed quetiapine among adult patients aged 20 to 65 years. For antipsychotic medications that are used off-label, more effective and/or less expensive alternatives may be more

Table 3. Characteristics of Subjects Receiving Subtherapeutic or Therapeutic Doses of Atypical Antipsychotic Medication[a]

Characteristic	Subtherapeutic Dose (N = 548)	Therapeutic Dose (N = 282)	p Value
Age, mean (SD)	43.9 (11.5)	42.2 (11.4)	.043
Female	364 (66.4)	163 (57.8)	.015
Race/ethnicity			.450
White	485 (88.5)	240 (85.1)	
Native American	22 (4.0)	12 (4.3)	
African American	15 (2.7)	12 (4.3)	
Hispanic	14 (2.6)	9 (3.2)	
Asian	10 (1.8)	5 (1.8)	
Other/unknown	2 (0.4)	4 (1.4)	
Medicaid/Medicare dual enrollment	189 (34.5)	101 (35.8)	.704
Rural residence	147 (26.8)	69 (24.5)	.464
Diagnosis			
Depression	298 (54.4)	132 (46.8)	.039
Anxiety	194 (35.4)	87 (30.9)	.190
Bipolar disorder	134 (24.5)	88 (31.2)	.037
Schizophrenia	58 (10.6)	63 (22.3)	< .001
Dementia	5 (0.9)	3 (1.1)	.833
Personality disorder	11 (2.0)	6 (2.1)	.908
Posttraumatic stress disorder	86 (15.7)	36 (12.8)	.259
Insomnia	47 (8.6)	17 (6.0)	.192
Other psychiatric diagnoses	44 (8.0)	15 (5.3)	.150
Any of above diagnoses	483 (88.1)	253 (89.7)	.497
Initiating prescriber type			.008
Psychiatry	107 (19.5)	69 (24.5)	
General practice	158 (28.8)	56 (19.9)	
Nurse practitioner	68 (12.4)	26 (9.2)	
Other	24 (4.4)	21 (7.4)	
Unidentified	191 (34.9)	110 (39.0)	
Augmentation therapy			
Antidepressant	106 (19.3)	65 (23.0)	.211
Mood stabilizer	35 (6.4)	41 (14.5)	< .001
Medication possession ratio[b]			.050
< 0.8	60 (10.9)	19 (6.7)	
≥ 0.8	488 (89.1)	263 (93.3)	
Length of therapy, d			.003
≤ 30	238 (43.4)	97 (34.4)	
> 30 and ≤ 180	187 (34.1)	90 (31.9)	
> 180 and ≤ 360	43 (7.8)	38 (13.5)	
> 360	80 (14.6)	57 (20.2)	

[a]Data are given as N (%) except where indicated otherwise.
[b]A medication possession ratio < 0.8 indicates poor adherence; a medication possession ratio ≥ 0.8 indicates full adherence or overadherence.

Table 4. Multivariate Logistic Regression Model of Subtherapeutic Dosing

Variable	OR	95% CI	p Value
Diagnosis of schizophrenia	0.43	0.28 to 0.67	< .001
Diagnosis of bipolar disorder	0.69	0.48 to 0.99	.044
Drug (vs risperidone)			
Clozapine	< 0.001	< 0.001 to > 999.999	.986
Olanzapine	0.53	0.35 to 0.79	.002
Quetiapine	4.76	3.08 to 7.35	< .001
Ziprasidone	0.87	0.44 to 1.72	.684
Mood stabilizer augmentation	0.39	0.22 to 0.68	< .001
Prescriber type (vs psychiatry)			
General practice	2.74	1.67 to 4.51	< .001
Nurse practitioner	1.73	0.93 to 3.23	.083
Other	0.71	0.33 to 1.53	.385
Unidentified	1.19	0.77 to 1.85	.430
Length of therapy (vs > 360), d			
≤ 30	1.737	1.063 to 2.839	.028
> 30 and ≤ 180	0.783	0.416 to 1.474	.449
> 180 and ≤ 360	1.531	0.938 to 2.500	.089

appropriate. Given the likelihood of concomitant antidepressant or mood stabilizer use, and given the differences in subtherapeutic dosing by the prescribing providers, these findings suggest that a statewide initiative to provide guidance regarding the administration of antipsychotic medication could be beneficial. Processes that support evidence-based use of this medication could potentially save substantial amounts of money that could support other mental health benefits and programs. Additionally, atypical antipsychotics have many important adverse effects that could be minimized if these drugs were used only for conditions in which the evidence of benefit is strong.

In addition, only 15% of the patients in this study had a diagnosis of schizophrenia and only 27% had a bipolar disorder diagnosis on record for the treatment period in which they were taking antipsychotic medication. This lack of a diagnosis that reflects psychotic symptoms raises concerns about what symptoms were being treated by antipsychotic medication. Most studies of antipsychotic medication effectiveness include only individuals diagnosed with schizophrenia, so there may be a gap of information regarding the effectiveness of these medications for individuals who do not meet criteria for a diagnosis of schizophrenia. Other states should assess their Medicaid programs to determine the frequency of antipsychotic medication administration to individuals without schizophrenia diagnoses.

Kogut et al.[14] reported low-dose prescribing to be associated with female gender and older ages. The present study also found such relationships in bivariate analyses. Multivariate logistic regression, however, suggested that age and gender were not associated with subtherapeutic dosing. Therefore, it appears that subtherapeutic dosing cannot be explained by patient factors (such as age and gender) that would be expected to influence drug metabolism. Conversely, provider factors (such as provider specialty) do appear to account for at least some low-dose prescribing. In particular, primary care providers were much more likely than mental health specialists to prescribe atypical antipsychotics in low doses.

A valid prescriber was not identified for over 36% of subjects in this study because of pharmacies' using a default provider number. If, however, analyses are restricted to only those subjects with identifiable prescribers, general practitioners are the most frequently identified specific prescriber type (214 of 529 [40.5%]).

Finally, this research raises questions regarding the length of therapy; only one third of this sample stayed on therapy with their initial antipsychotic medication for more than 30 days, and many discontinued with no further medications or had a gap in therapy of more than 30 days. Leslie and Rosenheck[32] found that among patients with schizophrenia who had stable antipsychotic use for 3 months, about 25% of them switched medication within the following year. Although patients who are initiating antipsychotic treatment can be expected to have more variability in their length of therapy while the correct regimen is identified, effective interventions can also increase patients' adherence to antipsychotic treatment. For example, Dolder et al.[33] found that combinations of educational, behavioral, and affective strategies were effective in increasing length of therapy and that these interventions also had secondary gains of reduced relapse, decreased hospitalization, and improved social function.

This study has several limitations. It used pharmacy and medical claims data to make inferences about patterns of medical care. While the validity of pharmacy claims data is believed to be high, the accuracy of medical claims may be questionable. Diagnostic inaccuracy may partially explain the low prevalence of psychiatric conditions among our study subjects. Inaccurate claims data could also affect the accuracy of calculated prescribed doses and identification of prescribers. The assumption that subtherapeutic dosing automatically indicates off-label use may also be incorrect. For example, it is possible that subjects prescribed low doses never attained a targeted therapeutic dose because of adverse effects. Such prescribing could benefit from evidence-based guidance. Our choice to select a sample of incident users versus prevalent users of atypical antipsychotics may have reduced representation of individuals with certain disorders (e.g., schizophrenia) and could potentially have skewed the representation of those who are receiving services in the Medicaid fee-for-service system. Indeed, the cross-section of all atypical antipsychotic users in the population suggests that new initiators were more likely to have diagnoses of off-label conditions such as depression, anxiety, and PTSD. Notwithstanding, the sample characteristics do not alter the primary findings about prescribing practices of subtherapeutic dosing and the substantial number of individuals with mood disorders who are receiving atypical antipsychotic medication. Moreover, the proportion of subjects from the source population using low-dose atypical antipsychotics was only marginally lower at 52%. Additionally, these data may not be applicable to other non-Medicaid populations. Finally, because we performed multiple statistical tests in this study, the possibility of type I errors may be increased.

States wishing to reduce costs and improve the quality of use for atypical antipsychotic medications should examine prescribing patterns to ensure that these drugs are prescribed within acceptable practice limits and are not used for off-label uses when other approaches may be more appropriate and less expensive.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Equetro, and others), clozapine (FazaClo, Clozaril, and others), divalproex (Depakote), duloxetine (Cymbalta), gabapentin (Neurontin and others), lamotrigine (Lamictal and others), levetiracetam (Keppra), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal and others), phenytoin (Dilantin, Phenytek, and others), pregabalin (Lyrica), quetiapine (Seroquel), risperidone (Risperdal), tiagabine (Gabitril), topiramate (Topamax), valproate sodium (Depacon and others), valproic acid (Depakene and others), venlafaxine (Effexor and others), ziprasidone (Geodon), zonisamide (Zonegran and others).

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