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Patterns of Atypical Antipsychotic Sub-Therapeutic Dosing Among Oregon Medicaid Patients

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Abstract

Objective—This study examined a cohort of Medicaid patients with new prescriptions for atypical antipsychotic medication to determine the prevalence of sub-therapeutic atypical antipsychotic medication use and to identify patient and prescribing provider characteristics associated with its occurrence.

Method—This observational cohort study examined Medicaid administrative claims data for patients age 20–64 with a new prescription for an atypical antipsychotic medication (clozapine, olanzapine, quetiapine, risperidone, ziprasidone) between 1/2004 and 12/2004. Patient characteristics, prescribing provider characteristics, length of therapy, and dosing were examined. A logistic regression assessed the probability of sub-therapeutic dosing.

Results—Among 830 individuals starting an atypical antipsychotic, only 15% had a documented diagnosis of schizophrenia, sub-therapeutic dosing was common (up to 86% of patients taking quetiapine), and 40% of the sample continued less than 30 days with the indexed prescription. A logistic model indicated that a general practitioner as prescribing provider, length of therapy less than 30 days, and prescription of quetiapine were significantly associated with a sub-therapeutic dose.

Conclusions—These results suggest there is extensive use of expensive atypical anti-psychotic 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, theses findings support the need for the

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introduction or increased use of utilization monitoring, and the implementation of medication practice guidelines as appropriate decision support for prescribing providers.

Keywords

antipsychotic medication; prescribing practices; practice parameters

Introduction

Atypical antipsychotic medications comprise a large and growing portion of expenditures for Medicaid programs.[1, 2] Banthin & Miller reported that antipsychotic medications constituted 7.1% of Medicaid expenditures in 2001–2002.[1] This percentage had increased 154% from 1996–1997 and is 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 on medications by adopting policies such as prior authorization and utilization review.[6] Such policies are not uncommon in the 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. showed that 6% had adopted policies such as prior authorization for atypical antipsychotic medications.[7] Several states have also collaborated with pharmaceutical manufacturer Eli Lilly and its contractor Comprehensive Neuroscience (CNS) 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 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] However, several studies have indicated that such claims may be unfounded. For example, Rothbard et al. 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 Community Antipsychotic Trials of Intervention Effectiveness (CATIE) 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) study reached similar conclusions.[11, 12]

These considerations have prompted investigations into use of atypical antipsychotic medications. Several projects have addressed concerns about polypharmacy with emphasis on concurrent use of two 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 dose 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 methodologically limited or no evidence supporting atypical antipsychotic use for many conditions including dementia-related agitation, depression, post-traumatic 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.

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

Methods

The goal of the analysis was to investigate the drug therapy patterns of non-institutionalized 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, ziprasidone) between January 1, 2004, and December 31, 2004, were identified. A new prescription (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 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 and 12 months following index fill). However, 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, ethnicity, urban or rural residence, dual Medicare eligibility, diagnostic information, and index prescribing provider type were summarized. Urban and rural classification was based on 2000 census information by the county listed as the patient's residence. Ethnic determination was based on enrollment data, which we consolidated into one of the following: White, African-American, Native American, Hispanic, Asian/Pacific Islander, 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 with any fee-for-service enrollment during the 12 month capture period.

Prescribing provider information was determined based on 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 which may also be entered, though 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 where a prescribing provider was identified, we classified the provider as a nurse practitioner (presumed to be a combination of psychiatric and primary care-based nurse practitioners), general practitioner (e.g., internal medicine, general practice, family practice specialty listed), or psychiatry (either a psychiatrist or a mental health clinic, whose prescribing providers could be psychiatrists or psychiatric nurse practitioners). These prescribing provider classifications may slightly underestimate the proportion of psychiatric

providers, but 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 International Classification of Disease – 9th Revision Clinical Modification (ICD9CM) codes on submitted medical claims. Depression was defined by the ICD9CM codes 3090x, 3091x, 311xx, 2969x, 2962x, and 2963x. Schizophrenia was defined by the ICD9CM code 295xx. Bipolar disorder was identified using the ICD9CM codes 2964x, 2965x, 2966x, 2967x, and 2968x. Anxiety disorder was defined by the ICD9CM code 300xx. Dementia was defined as ICD9CM code 290xx. Personality disorder was defined by ICD9CM codes 301xx. Codes 30981 and 308xx were used to identify PTSD. Insomnia was defined as ICD9CM codes 78050, 78051, and 78052. Finally, other psychiatric diagnoses were identified using the remaining ICD9CM codes in the mental disorders category (290xx–319xx) not already specified above. Diagnostic criteria were screened for 6 months before 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, 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 50% of the previous days supply dispensed is reasonable. To accommodate the small, but significant 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 day (50% of 30 day supply) and 45 days (50% of 90 day supply).[19] Each patient’s therapy was characterized by the length of atypical antipsychotic treatment, augmentation with other mental health medication, as well medication adherence. Augmentation was defined as concurrent use of either an antidepressant (selective serotonin reuptake inhibitors, venlafaxine, mirtazapine, nefazadone, duloxetine, and bupropion) or mood stabilizer (lithium, carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, pregabalin, tiagabine, topiramate, valproate/valproic acid/divalproex, and zonisamide) for at least 60 days at any point.

Adherence was assessed using the medication possession ratio (MPR).[20–22] The MPR is a commonly employed method for measuring medication adherence and is calculated by dividing the length of therapy on medication by the total day supply dispensed during the period.[19] 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 only analyzed for subjects with more than 30 days of therapy to minimize the impact of those subjects with only one 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.[23, 24]

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 as well as CATIE protocol specifications.[25–30] The daily adult dose for clozapine was defined as 300–900 mg, 10–30 mg for olanzapine, 300–800 mg for quetiapine, 2–6 mg for risperidone, and 80–160 mg for ziprasidone. Patients were considered on a sub-therapeutic dose if their modal dose fell below the recommend range. Demographic and drug therapy characteristics were compared between those receiving sub-therapeutic doses versus those prescribed therapeutic and supra-therapeutic doses. Statistical comparisons were made using the Chi-Square test of proportions, or Fisher's exact test, for categorical data. Continuous data were compared using Student's t-test. Finally, a multivariate logistic regression was used to model the association between sub-therapeutic 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 0.05. 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 version 9.1.

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, 7,141 unique, non-institutionalized individuals between 20 and 64 years of age with any fee-for-service enrollment had at least one prescription for an atypical antipsychotic. Of these, 830 (11.6%) unique patients 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 average 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 codes 6 months prior and following 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%), PTSD (15% vs. 8%), and less likely to have schizophrenia diagnoses (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 comprised general practitioners (26%), followed by psychiatry (21%), and nurse practitioners (11%). More than a third of cohort members had an unidentified prescribing provider of their index prescription, which is consistent with previous administrative evaluations of drug use. Close to 35% of study subjects also had dual Medicare enrollment.

Quetiapine was the most frequently prescribed atypical antipsychotic with 335 (40%) patients 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=0.054). Approximately 40% of subjects received less than 31 days of therapy. Between 14–18% of subjects (excluding those prescribed clozapine) remained on therapy for greater than 360 days. While the cohort contained only three subjects on clozapine, all three remained on therapy for greater than 360 days. Between 8–11% of subjects augmented with a mood stabilizer with no significant differences among antipsychotic drugs. Addition of an antidepressant occurred more frequently, being observed in 17–24% of subjects. The mean modal dose of clozapine was 433 mg, 10.2 mg for olanzapine, 140 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 sub-therapeutic dose of their atypical antipsychotic medication was observed (p<0.0001). Nearly 86% of subjects on quetiapine received a sub-therapeutic dose compared to between 48–59% of the other non-clozapine atypical antipsychotic medications. No significant differences in MPR classification were observed among drug types. Excluding clozapine, adherence ranged from 83% with ziprasidone to 90% with risperidone.

A total of 548 subjects (66%) were observed to receive a sub-therapeutic dose. Table 3 summarizes patient and therapy characteristic differences between those receiving a therapeutic versus sub-therapeutic dose. The average age was significantly higher among those receiving sub-therapeutic doses (43.9 years) compared to those on therapeutic doses (42.2 years). There were significantly more females in the sub-therapeutic dose group (p=0.014). Subjects receiving a sub-therapeutic dose were more likely to have a diagnosis of depression (54% versus 47%) and less likely to have a diagnosis of schizophrenia (11% versus 22%) and bipolar disorder (25% versus 31%). There were no differences in the prevalence of the other studied diagnoses. For those receiving a sub-therapeutic dose, the initiating prescribing provider was more likely to be a general practitioner and less likely to be a psychiatrist (p=0.007). Augmentation with a mood stabilizer occurred in 15% of subjects receiving a therapeutic dose compared to 6% of subjects on a sub-therapeutic dose (<0.001). The overall length of therapy also differed significantly (p=0.003) between those subjects receiving a sub-therapeutic dose and those on a therapeutic dose. The proportion of patients who received less than 31 days of treatment was higher among patients taking a sub-therapeutic dose (43%) compared to those receiving a full dose (34%).

Table 4 shows the results of the multivariate logistic model and 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 and bipolar disorder were 57% (adjusted OR 0.43; 95% CI 0.28–0.67; p<0.0001) and 3l% (adjusted OR 0.69 95% CI 0.48–0.99; p<0.044) less likely to be receiving a sub-therapeutic dose respectively. Subjects receiving quetiapine were 4.8 times more likely (adjusted OR 4.76; 95% CI 3.08–7.35; p<0.0001) to receive a sub-therapeutic dose compared to those who received risperidone. General practitioners were 2.7 times more likely (adjusted OR 2.74; 95% CI 1.67 – 4.51; p<0.0001) than psychiatrists to be associated with sub-therapeutic dosing. Finally, subjects with a length of therapy less than 31 days were 74% more likely (adjusted OR 1.74; 95% CI 1.06 – 2.84; p = 0.028) to be prescribed a sub-therapeutic dose compared to those who were treated for >360 days.

Discussion

This study sought to determine the prevalence of sub-therapeutic atypical antipsychotic medication use among incident users and to identify patient and prescribing provider

characteristics associated with its occurrence. Several of the observations noted in this analysis raise questions about the prescribing of atypical anti-psychotic 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 non-psychotic agitation. It is likely that atypical antipsychotic medications (especially quetiapine) were often prescribed for sedation rather than 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 ages 20–65. For anti-psychotics that are used off-label, more effective and/or less expensive alternatives may be more appropriate. Given the likelihood of concomitant antidepressant or mood stabilizer use, and differences in sub-therapeutic dosing by the prescribing provider, these findings suggest that a state-wide initiative to provide guidance regarding the administration of anti-psychotic medication could be beneficial. Processes which support evidence-based use of this medication could potentially save significant amounts of money which could support other mental health benefits and programs. Additionally, atypical antipsychotics have many important adverse effects that could be minimized if only used for conditions where 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 anti-psychotic medication. This lack of a diagnosis that reflects psychotic symptoms raises concerns about what symptoms were being treated by anti-psychotic 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.

Kugot et al. reported low-dose prescribing to be associated with female gender and older ages.[14] The present study also found such relationships in bivariate analyses. However, multivariate logistic regression suggested that age and gender were not associated with sub-therapeutic dosing. Therefore, it appears that sub-therapeutic 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 in over 40% of subjects identified in this study due to pharmacies using a default provider number. However, if data on identified prescribers is extrapolated to those not identified, we would expect almost half (214/484 = 44%) of all subjects using an atypical antipsychotic to be prescribed by a general practitioner.

Finally, this research raises questions regarding the length of therapy; only a third of this sample stayed on their initial anti-psychotic 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 found that among patients with schizophrenia who had stable anti-psychotic use for 3 months, about 25% of them switched medication within the following year.[31] Although patients who are initiating anti-psychotic use can be expected to have more variability in their length of therapy as the correct regimen is identified, effective

interventions can also increase patients' adherence to anti-psychotic treatment. For example, Dolder et al. 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.[32]

This study has several limitations. First, 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 subjects prescribed low doses never attained a targeted therapeutic dose due to adverse effects. Such prescribing could benefit from evidence-based guidance. Our choice to select a sample of incident users of atypical antipsychotics compared to prevalent users 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 sub-therapeutic dosing and the substantial number of individuals with mood disorders receiving atypical antipsychotic medication. Moreover, the proportion of subjects using low dose atypical antipsychotics from the source population was only marginally lower at 51.7%. Also, 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 may want to examine prescribing patterns to ensure 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.

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References

1. Banthin JS, Miller GE. Trends in prescription drug expenditures by Medicaid enrollees. Med Care. 2006; 44:I27–35. [PubMed: 16625061]
2. Goode, E. New York Times. New York: 2003. Leading drugs for psychosis come under new scrutiny.
3. Polinski JM, Wang PS, Fischer MA. Medicaid's prior authorization program and access to atypical antipsychotic medications. Health Aff (Millwood). 2007; 26:750–60. [PubMed: 17485754]
4. Peterson, M. New York Times. New York: 2004. Making Drugs, Shaping the Rules.
5. McDonagh, M. Drug Class Review on Atypical Antipsychotic Drugs. Portland, Oregon: Oregon Evidence-based Practice Center; 2006.
6. Koyanagi C, Forquer S, Alfano E. Medicaid policies to contain psychiatric drug costs. Health Aff (Millwood). 2005; 24:536–44. [PubMed: 15757941]

7. Sullivan G, Perry DM, Grimes W, Wetherbee H. Benefit coverage of novel antipsychotics in Medicaid programs and the Veterans Health Administration. Am J Med Qual. 2004; 19:37–40. [PubMed: 14977024]
8. Saul, S. New York Times. New York: 2007. In Some States, Maker Oversees Use of Its Drug.
9. Surles RC. Atypical antipsychotics: considerations for Medicaid coverage. Am J Manag Care. 2005; 11:S248–53. [PubMed: 16180963]
10. Rothbard A, Murrin MR, Jordan N, et al. Effects of antipsychotic medication on psychiatric service utilization and cost. J Ment Health Policy Econ. 2005; 8:83–93. [PubMed: 15998980]
11. Jones PB, Barnes TR, Davies L, et al. Randomized controlled trial of the effect on Quality of Life of second- vs. first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry. 2006; 63:1079–87. [PubMed: 17015810]
12. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005; 353:1209–23. [PubMed: 16172203]
13. Ganguly R, Kotzan JA, Miller LS, Kennedy K, Martin BC. Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients, 1998–2000. J Clin Psychiatry. 2004; 65:1377–88. [PubMed: 15491242]
14. Kogut SJ, Yam F, Dufresne R. Prescribing of antipsychotic medication in a medicaid population: use of polytherapy and off-label dosages. J Manag Care Pharm. 2005; 11:17–24. [PubMed: 15667230]
15. Morrato EH, Dodd S, Oderda G, Haxby DG, Allen R, Valuck RJ. Prevalence, utilization patterns, and predictors of antipsychotic polypharmacy: experience in a multistate Medicaid Population, 1998–2003. Clin Ther. 2007; 29:183–95. [PubMed: 17379060]
16. Barbui C, Ciuna A, Nose M, et al. Off-label and non-classical prescriptions of antipsychotic agents in ordinary in-patient practice. Acta Psychiatr Scand. 2004; 109:275–8. [PubMed: 15008801]
17. Weiss E, Hummer M, Koller D, Pharmd, Ulmer H, Fleischhacker WW. Off-label use of antipsychotic drugs. J Clin Psychopharmacol. 2000; 20:695–8. [PubMed: 11106144]
18. . Quality AfHR. 2007. Off-label use of atypical antipsychotic drugs: a summary for clinicians and policymakers.
19. Sikka R, Xia F, Aubert RE. Estimating medication persistency using administrative claims data. Am J Manag Care. 2005; 11:449–57. [PubMed: 16044982]
20. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. Pharmacoepidemiol Drug Saf. 2006; 15:565–74. discussion 575–7. [PubMed: 16514590]
21. Grymonpre R, Cheang M, Fraser M, Metge C, Sitar DS. Validity of a prescription claims database to estimate medication adherence in older persons. Med Care. 2006; 44:471–7. [PubMed: 16641666]
22. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. J Clin Epidemiol. 1997; 50:105–16. [PubMed: 9048695]
23. Gilmer TP, Dolder CR, Lacro JP, et al. Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. Am J Psychiatry. 2004; 161:692–9. [PubMed: 15056516]
24. Valenstein M, Copeland LA, Blow FC, et al. Pharmacy data identify poorly adherent patients with schizophrenia at increased risk for admission. Med Care. 2002; 40:630–9. [PubMed: 12187177]
25. Clozaril (clozapine) tablets [product information]. East Hanover, NJ: Novartis; 2005.
26. Zyprexa (olanzapine) tablets [product information]. Indianapolis, IN: Eli Lilly; 2006.
27. Geodon (ziprasidone HCl) capsules [product information]. New York, NY: Pfizer; 2007.
28. Risperdal (risperidone) tablet [product information]. Titusville, NJ: Janssen; 2007.
29. Seroquel (quetipine) tablets [product information]. Wilmingon, DE: AstraZenaca Pharmaceuticals; 2007.
30. Stroup TS, McEvoy JP, Swartz MS, et al. The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Project: Schizophrenia Trial Design and Protocol Development. Schizophr Bull. 2003; 29:15–31. [PubMed: 12908658]

31. Leslie DL, Rosenheck RA. From conventional to atypical antipsychotics and back: dynamic processes in the diffusion of new medications. Am J Psychiatry. 2002; 159:1534–40. [PubMed: 12202274]

32. Dolder CR, Lacro JP, Leckband S, Jeste DV. Interventions to improve antipsychotic medication adherence: review of recent literature. J Clin Psychopharmacol. 2003; 23:389–99. [PubMed: 12920416]

Table 1

Population and study sample characteristics

	All Atypical Antipsychotic Users (n = 7,141)		Study Sample (n = 830)	
Variable	**Count**	**(%)**	**Count**	**(%)**
Age, mean (SD)	42.0	(11.2)	43.3	(11.5)
Female	3,796	(53.2%)	527	(63.5%)
Race				
White	6,341	(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%)
Medicare Dual Eligible	2,792	(39.1%)	290	(34.9%)
Urban residence	5,379	(75.3%)	614	(74.0%)
Diagnoses				
Depression	2,075	(29.1%)	430	(51.8%)
Anxiety	1,394	(19.5%)	281	(33.9%)
Bipolar Disorder	1,558	(21.8%)	222	(26.7%)
Schizophrenia	2,236	(31.3%)	121	(14.6%)
Dementia	80	(1.1%)	8	(1.0%)
Personality Disorder	121	(1.7%)	17	(2.0%)
Post-Traumatic 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	6,106	(85.5%)	736	(88.7%)
Initiating Prescriber	NA			
Psychiatry			176	(21.2%)
General practice			214	(25.8%)
Nurse Practitioner			94	(11.3%)
Other			45	(5.4%)
Unidentified			301	(36.3%)
Drug*				
Quetiapine	2,715	(38.0%)	335	(40.4%)
Olanzapine	2,483	(34.8 %)	238	(28.7%)
Risperidone	2,317	(32.4%)	208	(25.1%)
Ziprasidone	592	(8.3%)	46	(5.5%)
Clozapine	352	(4.9%)	3	(0.4%)
Subtherapeutic dose	3,689	(51.7%)	348	(66.0%)

*Because patients could have used more than 1 agent, sum does not equal n among All Atypical Antipsychotic Users

Table 2

Therapy Characteristics of Atypical Antipsychotic Medication Use

	Clozapine (n=3)		Olanzapine (n=238)		Quetiapine (n=335)		Risperidone (n=208)		Ziprasidone (n=46)		p-value
Length of Therapy											0.0543
<=30 days	0	(0.0%)	98	(70.0%)	135	(67.5%)	84	(67.7%)	18	(64.3%)	
>30 and <=180 days	0	(0.0%)	86	(61.4%)	107	(53.5%)	70	(56.5%)	14	(50.0%)	
>180 days and <=360 days	0	(0.0%)	20	(14.3%)	34	(17.0%)	19	(15.3%)	8	(28.6%)	
>360 days	3	(100.0%)	34	(24.3%)	59	(29.5%)	35	(28.2%)	6	(21.4%)	
Augmentation											
mood stabilizer	0	(0.0%)	19	(13.6%)	29	(14.5%)	23	(18.5%)	5	(17.9%)	0.7221
antidepressant	2	(66.7%)	54	(38.6%)	57	(28.5%)	50	(40.3%)	8	(28.6%)	0.0623
Average Daily Dose (SD)	433.33		10.15		140.21		1.68		78.25		
Established therapeutic range	300–900mg		10–30mg		300–800mg		2–6mg		80–160mg		
Underdosed (%)	0	(0.0%)	115	(48.3%)	287	(85.7%)	122	(58.7%)	24	(52.2%)	<.0001
Medication Possession Ratio * (>30 days of therapy)		n=3		n=140		n=200		n=124		n=28	0.2748
<0.8	0	(0.0%)	15	(10.7%)	34	(17.0%)	12	(9.7%)	4	(14.3%)	
>=0.8	3	(100.0%)	125	(89.3%)	166	(83.0%)	112	(90.3%)	24	(85.7%)	

* Note: An MPR < 0.8 indicates poor adherence; an MPR >= 0.8 indicates full or over-adherence.

Table 3

Characteristics of Subjects on Sub-therapeutic and Therapeutic Doses of Atypical Antipsychotic Medication

	Subtherapeutic dose		Therapeutic dose		p-value
	n=548	(%)	n=282	(%)	
Age, mean (SD)	43.9	(11.5)	42.2	(11.4)	0.0431
Female	364	(66.4%)	163	(57.8%)	0.0145
Race					0.4504
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/uknown	2	(0.4%)	4	(1.4%)	
Medicare Dual Enrollment	189	(34.5%)	101	(35.8%)	0.7042
Rural residence	147	(26.8%)	69	(24.5%)	0.4636
Diagnoses					
Depression	298	(54.4%)	132	(46.8%)	0.0387
Anxiety	194	(35.4%)	87	(30.9%)	0.1895
Bipolar Disorder	134	(24.5%)	88	(31.2%)	0.0374
Schizophrenia	58	(10.6%)	63	(22.3%)	<.0001
Dementia	5	(0.9%)	3	(1.1%)	0.8325
Personality Disorder	11	(2.0%)	6	(2.1%)	0.9077
Post-Traumatic Stress Disorder	86	(15.7%)	36	(12.8%)	0.2593
Insomnia	47	(8.6%)	17	(6.0%)	0.1924
Other Psychiatric Diagnoses	44	(8.0%)	15	(5.3%)	0.1501
Any of Above Diagnoses	483	(88.1%)	253	(89.7%)	0.497
Initiating Prescriber					0.0081
Psychiatry	107	(19.5%)	69	(24.5%)	
General practice	158	(28.8%)	56	(19.9%)	
Nurse Practitioner	68	(12.4%)	26	(9.2%)	

	Subtherapeutic dose		Therapeutic dose		p-value
	n=548	**(%)**	**n=282**	**(%)**	
Other	24	(4.4%)	21	(7.4%)	
Unidentified	191	(34.9%)	110	(39.0%)	
Augmentation					
Antidepressant	106	(19.3%)	65	(23.0%)	0.2111
Mood Stabilizer	35	(6.4%)	41	(14.5%)	0.0001
Medication procession ratio					0.0502
<0.8	60	(10.9%)	19	(6.7%)	
>=0.8	488	(89.1%)	263	(93.3%)	
Length of Therapy					0.0034
<=30 days	238	(43.4%)	97	(34.4%)	
>30 and <=180 days	187	(34.1%)	90	(31.9%)	
>180 days and <=360 days	43	(7.8%)	38	(13.5%)	
>360 days	80	(14.6%)	57	(20.2%)	

Table 4

Multivariate Logistic Regression Model Of Sub-therapeutic Dosing

Variable	OR	95% CI		p-value
Diagnosis of schizophrenia	0.43	0.28	0.67	<0.001
Diagnosis of bipolar	0.69	0.48	0.99	0.044
Drug (versus risperidone)				
Clozapine	<0.001	<0.001	>999.999	0.986
Olanzapine	0.53	0.35	0.79	0.002
Quetiapine	4.76	3.08	7.35	<0.0001
Ziprasidone	0.87	0.44	1.72	0.684
Mood stabilizer augmentation	0.39	0.22	0.68	<0.001
Prescriber type (versus psychiatry)				
General practitioner	2.74	1.67	4.51	<0.0001
Nurse practitioner	1.73	0.93	3.23	0.083
Other	0.71	0.33	1.53	0.385
Unidentified	1.19	0.77	1.85	0.430
Length of therapy (versus >360 days)				
<=30	1.737	1.063	2.839	0.028
>30 and <=180	0.783	0.416	1.474	0.449
>180 and <=360	1.531	0.938	2.5	0.089