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Characteristics of Medicaid Recipients Receiving Persistent Antipsychotic Polypharmacy

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Abstract

Antipsychotic polypharmacy (APP) is a common strategy despite guidelines advising against this practice. This article seeks to quantify the prevalence and correlates of APP using Medicaid Analytic eXtract files from 2003 to 2004. Nineteen percent of Medicaid recipients who received an antipsychotic were treated with APP. Individuals who received APP were more likely to be white, male, disabled, between the ages of 18–29, diagnosed with a psychotic disorder, and diagnosed with a higher number of psychiatric conditions. Geographic variation in APP rates was also observed. Quality improvement initiatives may help reduce APP for medically vulnerable patients.

Keywords

Medicaid; Antipsychotic polypharmacy; Pharmacoepidemiology; Geographic variation

Introduction

Current practice guidelines state that antipsychotic monotherapy is the most appropriate initial pharmacologic treatment approach for individuals with schizophrenia (Buchanan et al. 2010; Goodwin et al. 2009; Lehman; Lieberman et al. 2004; Moore et al. 2007). Combining two or more antipsychotics, or antipsychotic polypharmacy (APP), is common in clinical practice (Ganguly et al. 2004; Gilmer et al. 2007; Mojtabai and Olfson 2010; Nielsen et al. 2010; Suzuki et al. 2013). For individuals with psychotic disorders, rates of APP are highly variable depending on practice setting (Sun et al. 2014), but in a systematic review of 147

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Compliance with Ethical Standards

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studies published from 1970 to 2009, the median APP rate was 19.6%, with 83% of the sample having a diagnosis of schizophrenia (Gallego et al. 2012). More specifically, data from a two state Medicaid data set (1998–2000) have reported APP rates of 40% (Ganguly et al. 2004), while data from a five state Medicaid data set (1998–2003) have reported rates of 12.9% (Morrato et al. 2007). The practice of APP is highly relevant to Medicaid, as 30% of individuals with schizophrenia are Medicaid recipients (Wu et al. 2006). Medicaid spending on antipsychotics rose from \$1.65 billion in 1999 to \$3.15 billion dollars in 2009 (Verier 2013) and the high costs associated with APP have strained Medicaid budgets (Clark et al. 2002; Sabin and Daniels 2003a, b; Stahl 2002; Stahl and Grady 2006; Zhu et al. 2008). Cost-cutting strategies such as prior authorizations and formulary restrictions aimed at hedging rising expenditures on antipsychotic prescriptions have been minimally effective (Vogt et al. 2011). One explanation for continued rising Medicaid expenditures on antipsychotics is the practice of APP (Seabury et al. 2014).

Providers may resort to prescribing multiple antipsychotics to treat persistent symptoms that have failed to respond to a single agent, to accelerate the response to treatment (Stahl and Grady 2004), or to augment clozapine monotherapy. Additionally, antipsychotic polypharmacy can result from an aborted cross-titration of two antipsychotics (Tapp et al. 2003), or can result from continuation and reluctance to change an inherited pharmacologic regimen (Correll et al. 2011). Little evidence exists for the superiority of APP (Centorrino et al. 2004; Correll 2007; Freudenreich and Goff 2002; Stahl 2002) and there are significant disadvantages to this practice. APP is associated with increased sedation (Anil Yagcioglu et al. 2005), hypersalivation (Henderson and Goff 1996; Naber et al. 1992) and an increased risk of extra-pyramidal symptoms (Jeste et al. 1995; Lemmens et al. 1999). The latter concern often necessitates the addition of anticholinergic medications, which have independently been associated with APP (Carnahan et al. 2006; Chakos et al. 2006; Gallego et al. 2012; Megna et al. 2007) and can lead to increased cognitive impairments (Sweeney et al. 1991; Vinogradov et al. 2009). Additionally, APP may be associated with poorer adherence to medications (Fleischhacker and Uchida 2014). Cardiometabolic side effects are a significant concern, as APP has been associated with increased weight gain (Centorrino et al. 2004; McIntyre and Jerrell 2008), dyslipidemia (McIntyre and Jerrell 2008), as well as diabetes and metabolic syndrome (Citrome et al. 2004; Correll 2007; Kessing et al. 2010; Tirupati and Chua 2007). There have also been reports of associations between APP and increased mortality (Joukamaa et al. 2006; Waddington et al. 1998).

Given the limited evidence supporting the clinical benefit of APP, the documented risks to combining antipsychotics, and initiatives aimed at reducing APP practice (Baandrup et al. 2010; Becker et al. 2013; Owen et al. 2008; Thompson et al. 2008), it is clear that reducing this practice is not only an issue of minimizing the financial burden of APP, but is also an important quality of care consideration for Medicaid. It is important to understand nationwide trends and correlates of this practice in order to develop strategies to reduce APP and offer guidelines to effectively manage the treatment of patients with schizophrenia. The current study sought to examine these trends in a national Medicaid claims data set and explore correlates of APP and associated medical comorbidities.

Methods

Data for analysis came from Medicaid Analytic eXtract (MAX) files for 50 states and District of Columbia. The MAX Files include information on Medicaid eligibility, type of coverage (Fee-for-Service vs. Managed Care), health care utilization from both inpatient and outpatient, payments, and sociodemographic characteristics.

The MAX data were merged with measures from the Area Health Resource File (AHRF; US Department of Health and Human Services 2005) in order to evaluate the impact of health care resources at the county level. The AHRF is a county-level data base that aggregates publically available data from multiple sources about health care resources, economic activity, and socioeconomic and environmental characteristics. County Federal Information Processing Standard (FIPS) codes were used to merge the ARF with MAX data files.

Data were extracted for non-dual eligible enrollees who were prescribed two or more antipsychotics during the years 2003 and 2004. Analyses were restricted to antipsychotic users who were between the ages of 18 to 64 at the time of their first antipsychotic prescription claim, eligible for fee for service (FFS), and who were continuously enrolled in FFS Medicaid for 12 consecutive months following the first antipsychotic prescription. Persons 65 and above and other persons dually eligible for Medicare were excluded because they commonly have missing data for services billed to Medicare (Hennessy et al. 2003).

Data for antipsychotic users was summarized by state of residence for states where managed care penetration was less than 80% during the years 2003 and 2004. The following states with 80% managed care penetration among the antipsychotic users were excluded: Delaware, Washington, Michigan, Kentucky, Arizona, Oklahoma, Colorado, Iowa, Alabama, Oregon, Nevada, Utah, Maryland, Massachusetts, New Mexico, and Nebraska. The information from these states would not be useful since service utilization from managed care encounter data in the MAX data system are incomplete. This exclusion is typical in Medicaid analyses because claims data are typically incomplete for managed care enrollees (Crystal et al. 2007; Howell 1996; Kronick and Gilmer 2009).

The primary dependent variable was APP. Consistent with previous literature, APP was defined as two or more consecutive episodes (gap < 15 days) of different antipsychotic medications with fill dates overlapping by 14 days and lasting 60 days in duration (Morrato et al. 2007). Antipsychotic users who did not meet the above criteria were coded as no APP.

Covariates at an individual level included demographic variables (age, sex, race), Medicaid eligibility category (disability vs. poverty), a count of mental health diagnoses, and a count of comorbid medical conditions developed using the Elixhauser comorbidity index (Elixhauser et al. 1998). The latter is a validated approach for risk adjustment using claims data (van Walraven et al. 2009), using the following conditions: HIV/AIDS; cancer (lymphoma, metastatic cancer, solid tumors); rheumatoid arthritis; coagulation deficiency; obesity; weight loss; fluid and electrolyte disorders; anemia (blood loss, deficiency); renal failure; liver disease; paralysis; chronic obstructive pulmonary disease; hypothyroidism; hypertension (with/without heart failure); hypertensive renal disease (with/without renal

failure); and peripheral vascular disease. Data were deidentified before delivery to the investigators, and institutional review board approval was not sought.

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Results

The total sample included 379,796 individuals (42% male and 58% female) between the ages of 18–64 who were continuously enrolled in FFS Medicaid for 12 consecutive months. These individuals resided in 35 states across the United States and all had been prescribed an antipsychotic medication. Of the total sample, 71,149 (19%) met criteria for APP. Table 1 presents characteristics of the final sample, broken down by cases with at least one episode of APP versus those with no episodes of APP. The mean age of group prescribed APP was 40.89 years ($SD = 11.53$), and with no episodes of APP was 41.16 years ($SD = 11.82$). Persons diagnosed with schizophrenia and schizoaffective disorder accounted for 74% of those prescribed APP. Thirty-two percent of individuals with schizophrenia and 24% of individuals with schizoaffective disorder had at least one episode of APP.

Characteristics of APP Episodes

The mean number of APP episodes during the 2-year period under analysis was 1.51 ($SD = 0.76$). During an episode of APP, individuals tended to remain on polypharmacy for an average of 240 days, although significant variation in APP episodes was observed ($SD = 197.44$, range = 60–816, median = 162 days). The total time on APP during the 2 year study period was 327 days ($SD = 226.74$, range = 60–816, median = 266 days). Intraclass antipsychotic prescription was more common than interclass antipsychotic prescription. Most cases of APP consisted of more than one atypical antipsychotic (70%), followed by atypical and conventional pairing (52%), and two or more conventional antipsychotics (4%). Only 9% of cases of APP consisted of clozapine plus another antipsychotic medication.

Comorbidities

No significant differences were detected between the groups on the basis of the Elixhauser Comorbidity Index, ($p = 0.42$), however there were significant differences in individual Elixhauser comorbidities, as represented in Fig. 1. Hypertension without complication (31% APP and 29% no APP), chronic pulmonary disease (24% APP and 22% no APP), and diabetes without complication (21% APP and 17% no APP) were all significantly more common in persons who had at least one episode of APP.

Geographic Variation

Geographic variation in prescriptions practices with regard to APP is pictorially represented in Fig. 1. Among the 35 states included in the current analyses, APP practice was most prevalent ($> 28\%$ of the sample) in California, Florida, Louisiana, Idaho, South Dakota, Minnesota, Wisconsin, Illinois, New Jersey and Connecticut (Fig. 2).

Demographic and Clinical Correlates of APP

When adjusting for individual state effects, Elixhauser comorbidity score, age, and race, individuals who received APP were more likely to be between the ages of 18–29, male, white, disabled, and with a diagnosis of schizophrenia or schizoaffective disorder. The higher the number of diagnosed psychiatric comorbidities, the higher the likelihood of APP (Table 2).

Discussion

The current study characterized demographic features of Medicaid recipients prescribed antipsychotic medication in the United States and examined the national prevalence of APP. Nineteen percent of Medicaid patients prescribed an antipsychotic medication were treated with APP, and 32% of individuals with schizophrenia had at least one episode of APP. This rate is at the high end or slightly higher than rates previously reported (Constantine et al. 2010; Covell et al. 2002; Ganguly et al. 2004; Gilmer et al. 2007).

During the 2 year study period, the mean length of time of APP was just under 1 year, suggesting a duration longer than expected for cross-titration of two antipsychotic medications. The range of APP episodes was between one and eight; however, the median number of APP episodes was one, suggesting that antipsychotic switching was not routine practice within the period under review. The combination of two second generation antipsychotic agents was the most common occurrence, followed by the combination of first and second generation antipsychotics and a small minority of two or more first generation antipsychotic agents.

Significant differences were found between those who were treated with APP and those who were not. Individuals who were white and male were also significantly more likely to be treated with APP in this study. An analysis of a similar national sample of Medicaid recipients (Stroup et al. 2014) and a separate analysis of New York State Medicaid recipients (Manuel et al. 2012) both found that individuals who were white and male were also more likely to receive a prescription for clozapine. Taken together, these findings may suggest that white males are more likely than other demographic groups to be offered a range of treatment approaches for refractory symptoms. In fact, previous studies have found that racial minorities are less likely to receive second generation antipsychotics (Mallinger et al. 2006) and more likely to receive long acting injectable antipsychotics, suggestive of provider attitudes that minority patients may be less adherent to medication regimens (Aggarwal et al. 2012). Previous studies of Medicaid claims has shown that less money is spent on minority patients for psychotropic drugs as well as overall mental health services (HorvitzLennon et al. 2009). More recently, a study of Medicaid datasets for four states showed racial disparities between states as well as between counties within state, with African Americans receiving lower quality care across both states and counties (Horvitz-Lennon et al. 2015). Further research is needed to evaluate disparities in prescription practices for mental health consumers of color.

Consistent with previous findings that APP is associated with weight gain, metabolic syndrome, and diabetes (Centorrino et al. 2004; Citrome et al. 2004), individuals in the

current sample who received APP were 1.56 times more likely to be obese and 1.26 times more likely to have uncomplicated diabetes than the group who did not receive APP. All individual receiving an antipsychotic should receive baseline and follow-up measurements of weight, waist circumference, blood pressure, lipids, and glucose (American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, & North American Association for the Study of Obesity 2004). Individuals prescribed multiple antipsychotics should receive more frequent and vigilant monitoring of metabolic side effects. It is unknown whether more frequent metabolic monitoring was occurring among those individuals in the current sample who were prescribed APP regimen.

The study demonstrated pronounced geographic variation in APP practices among Medicaid enrollees. Efforts to reform APP practice may be best directed toward the states where APP was most prevalent. Diagnostically, individuals with psychotic disorders and comorbid psychiatric diagnoses were more likely to be treated with APP, suggesting that multiple medications may be used in patients with the most serious conditions. In 2008, after the years assessed by this dataset, the Joint Commission established core measures for hospital-based inpatient psychiatric services (HBIPS) including two measures specific to antipsychotic polypharmacy (The Joint Commission 2013). Participating freestanding psychiatric hospitals report the overall rate of APP, as well as the number of cases with appropriate justification of APP at discharge. Clinically appropriate justifications include: (1) a minimum of three failed prior trials of monotherapy, (2) a plan to taper onto monotherapy or cross taper in progress, (3) augmentation of clozapine, or (4) documentation in the medical record of a justification for APP other than the prior three. It is unclear what effect these measures have on the rates of APP.

The use of cross-sectional claims data (1) limits the ability to fully distinguish the clinical rationale for use of APP and (2) limits the ability to draw casual inferences from the sample. Other limitations include the exclusion of 16 states with 80% managed care penetration, and the inclusion only of fee for service Medicaid enrollees. Although the percentage of individuals enrolled in managed care has increased steadily since 2003 and is a rationale for using older data when more enrollees were FFS (Centers for Medicare & Medicaid Services 2017), the age of the data is a limitation. Since the time of data collection, prescribing practices have likely changed, at least to some extent, and several new second-generation antipsychotics were released. Also, unknown is the pharmacologic rationale for the higher rates of atypical antipsychotic polypharmacy rather than the more accepted practice of combining first and second generation antipsychotics when undertaking APP. Based on statistical correlates of APP in this sample, both psychiatric and medical comorbidity appears to play a role in the rationale for APP. Evidence-based treatment guidelines recommend APP be restricted to situations in which multiple attempts of antipsychotic monotherapy were unsuccessful, including the use of clozapine monotherapy (Lehman et al. 2004; Miller et al. 2004). The extent to which this practice occurred among the Medicaid recipients who were being treated with APP in the current dataset is largely unknown. Based on the low prevalence of clozapine prescriptions among Medicaid patients with schizophrenia in the US (Stroup et al. 2014) and the low rates of clozapine polypharmacy in the current sample, it is unlikely that clozapine monotherapy precipitated APP among the

Medicaid patients included in the current analysis. In another Medicaid sample, individuals with schizophrenia who received APP when compared with clozapine monotherapy were more likely to have disease-specific emergency department use and higher overall health care costs (Velligan et al. 2015). Taken together, these findings raise concern for both quality of care and cost effectiveness in light of previous research cautioning against APP.

Conclusion

These limitations notwithstanding, the study findings indicate substantial rates of APP nationwide. Data published subsequent to the years from which the current dataset were attained reflect a pervasive trend of APP despite insufficient evidence supporting its efficacy, effectiveness, or safety (Correll et al. 2009). Results of the current investigation suggest that divergence from antipsychotic prescribing guidelines remains common (Nielsen et al. 2010; Sneider et al. 2015; Thompson et al. 2008; Van Duin et al. 2013). Geographic, demographic, and diagnostic differences suggest inconsistencies in APP practice that do not appear to be clinically driven or evidence-based. Education and quality improvement initiatives are needed to reduce multiple antipsychotic prescribing, particularly for patients receiving Medicaid services who may be at increased risk for medical comorbidities.

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Fig. 1.

Odds ratio of Elixhauser comorbidity by antipsychotic polypharmacy (APP) or no APP.

*Errors bars represent 95% confidence interval

Fig. 2.
Antipsychotic poly-pharmacy rate by state among antipsychotic users

Table 1

Characteristics of 379,796 individuals prescribed antipsychotics, by antipsychotic polypharmacy (APP) or no APP

Characteristic	At least one episode of APP (N = 71,149)		No. episodes of APP (N = 308,647)	
	N	%	N	%
Age				
18–29	14,052	19.8	60,748	19.7
30–39	16,190	22.8	69,893	22.6
40–49	22,806	32.1	94,064	30.5
50+	18,101	25.4	83,942	27.2
Gender				
Male	34,698	48.8	124,278	40.3
Female	36,451	51.2	184,369	59.7
Race				
White	35,146	49.4	167,421	54.2
Black	18,981	26.7	75,921	24.6
Other	17,022	23.9	65,305	21.2
Eligibility				
Disabled	67,355	94.7	261,942	84.9
Poverty	3,794	5.3	46,705	15.1
Mental health diagnoses				
No mental health diagnosis	4,055	5.7	42,511	13.8
Schizophrenia	44,763	62.9	97,316	31.5
Schizoaffective	8,149	11.5	27,616	8.9
Bipolar	7,001	9.8	57,311	18.6
Depression	5,363	7.5	73,755	23.9
Other psychotic diagnosis	1,714	2.4	9,219	3.0
Anxiety	104	0.1	919	0.3
Count of number of mental illness diagnoses				
One	17,072	24.0	98,551	31.9
Two	17,498	24.6	83,574	27.1
Three	13,134	18.5	53,544	17.3
Four or more	22,028	31.0	54,761	17.7
Comorbidity score				
Elixhauser comorbidity score	3.43		3.41	

Table 2

Adjusted odds of antipsychotic polypharmacy among 379,796 Medicaid recipients prescribed antipsychotics

Patient group	OR ^a	OR ^b	95% CI ^b
Age (reference: 18–29)			
30–39	0.98	0.96	0.94–0.99
40–49	1.01	0.92	0.90–0.94
50+	0.87	0.82	0.79–0.84
Gender (reference: female)			
Male	1.37	1.09	1.07–1.11
Race (reference: white)			
Black	1.13	0.83	0.81–0.84
Other	1.0	0.92	0.90–0.94
Eligibility (reference: poverty)			
Disabled	3.06	2.06	1.98–2.14
Mental health diagnoses (reference: no diagnosis)			
Schizophrenia	4.30	3.32	3.20–3.44
Schizoaffective	2.74	2.19	2.10–2.28
Bipolar	1.17	0.99	0.94–1.03
Depression	0.68	0.63	0.60–0.66
Anxiety	1.05	0.91	0.74–1.12
Count of number of mental illness diagnoses (reference: one)			
Two	1.28	1.18	1.15–1.21
Three	1.52	1.24	1.21–1.28
Four	2.48	1.46	1.42–1.50

^aAdjusted for individual state effects using conditional logistic regression (stratified by individual state)^bAdjusted for individual state effects, Elixhauser comorbidity score, and all other covariates