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Changes in Antipsychotic Use among Patients with Severe Mental Illness after an FDA Advisory

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Abstract

Purpose—A 2003 FDA advisory warned of increased hyperlipidemia and diabetes risk for patients taking second-generation antipsychotics (SGAs). Following the advisory a professional society consensus statement provided treatment recommendations and stratified SGAs into high, intermediate, and low metabolic risk. We examine subsequent changes in incident and prevalent SGA use among individuals with severe mental illness.

Methods—Retrospective, observational study using Florida Medicaid's claims from 2001–2006. We include non-Medicare eligible adults with bipolar disorder or schizophrenia who filled a SGA prescription. Among prevalent users we assess changes in overall and agent-specific use; discontinuations; interruptions; and therapeutic alternative use; among incident users, agent-

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specific use. Pre-advisory utilization was compared with utilization initially following the advisory and two subsequent periods.

Results—Among prevalent users, overall SGA use declined slightly and no increases in treatment interruptions or discontinuations were observed following the advisory and consensus statement publication. Compared with the pre-advisory period, in the months immediately following use of the highest metabolic-risk agent, olanzapine, decreased by 34% among prevalent users with bipolar disorder (adjusted risk ratio [aRR]=0.66; 95% confidence intervals [CI]=0.59–0.74) and 26% among prevalent users with schizophrenia (aRR=0.74, CI=0.72–0.76). A greater decline was estimated among incident users with bipolar disorder (aRR=0.37; CI=0.29–0.47) and schizophrenia (aRR=0.42; CI=0.35–0.51) during this period. During each subsequent post-advisory period, olanzapine use continued to decline while quetiapine, ziprasidone, and aripiprazole use increased.

Conclusions—The metabolic risk advisory and published consensus statement were associated with a selective reduction in olanzapine use without evidence of treatment disruptions among this population.

Keywords

Drug Utilization; FDA Advisory; Metabolic Risk; Second Generation Antipsychotics

INTRODUCTION

Second generation antipsychotics (SGAs) are effective treatments for bipolar disorder and schizophrenia, but have been associated with metabolic adverse effects that increase the risks for morbidity and mortality with long term use.¹ In November 2003, after early safety problems emerged, the FDA issued a warning and requested that all SGA manufacturers notify health care providers of the increased risks for hyperlipidemia and diabetes among patients using SGAs.² This advisory was followed by a February 2004 professional societies consensus statement³ recommending that prescribers screen patients for metabolic conditions, and consider metabolic risk when selecting an agent.

Clinicians may respond to the SGA safety advisory and consensus statement by more actively screening for metabolic changes in their patients, or changing their prescribing of SGAs by reducing overall rates of prescribing or substituting high metabolic risk agents (olanzapine and clozapine) with intermediate (risperidone and quetiapine) or lower (aripiprazole and ziprasidone) risk agents.³ Although prior studies suggests that metabolic screening rates have remained unchanged,^{4–10} one study⁸ identified shifts in new prescribing of some agents, notably decreases in new olanzapine use, and increases in aripiprazole use following the FDA advisory. However, assessing changes in new prescribing alone does not capture the advisory and consensus statement's impact on clinical decision-making for patients with ongoing use.¹¹

Clinicians may respond differently for new users than for existing users and we know little about how patterns of medication use have changed for patients with different medication histories. For example, clinicians' treating current antipsychotic users may hesitate to switch patients who are stabilized on a higher metabolic risk drug; particularly patients with a history of poor response or non-compliance. In essence, the tradeoff between symptom reduction and weight gain may differ between new versus ongoing antipsychotic users.

Since continuous pharmacotherapy is critical for patients with bipolar disorder or schizophrenia, and anecdotal evidence suggests that patients may be at increased risk for discontinuations or treatment interruptions following the release of drug risk

communications,¹² understanding changes in SGA utilization among prevalent users is important. We sought to identify patient-level changes in incident and prevalent SGA use among Medicaid enrollees with bipolar disorder and schizophrenia. We focus on changes in overall SGA use, treatment discontinuations, interruptions, and use of therapeutic alternatives among prevalent SGA users. To determine how responses differ among incident and prevalent SGA users, we assess agent-specific utilization among each group following the FDA advisory and consensus statement publication.

METHODS

Data Source

This study received an exemption from Harvard Medical School's Institutional Review Board. We used de-identified administrative claims from the Florida Medicaid program from July 2000–December 2006.

Study Time Periods

Although the primary focus is on comparing SGA use prior to the advisory with use immediately following the advisory, we measure SGA use during 6 distinct periods based on the timing of relevant publications, media reports, FDA regulatory activities, and Florida Medicaid policy changes (eTable 1). The pre-advisory period consisted of two segments. The first, January 2001–January 2003, was a period when metabolic risk information was largely unknown. The second, February 2003–November 2003, captured responses to early media reports and peer-reviewed publications identifying metabolic concerns for SGAs.^{13–15} The advisory period began in December 2003 following the FDA advisory, included the February 2004 professional societies' consensus statement, and ended in August 2004 after all manufacturers sent FDA-requested "Dear Health Care Provider" letters.^{2, 16, 17} The post-advisory period consisted of three segments. The first was an initial post-advisory period (September 2004–March 2005) during which no additional changes occurred in the antipsychotic marketplace. The second period, from April 2005–September 2005, contained several events that might have impacted SGA use including a class-wide black-box warning (April, 2005),¹⁷ the publication of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) results (September, 2005)¹⁸ and the temporary implementation of a preferred drug list in Florida Medicaid that re-categorized olanzapine as a non-preferred agent and required that physicians switch patients from olanzapine to an alternative agent (July, 2005).¹⁹ Finally, the third post-advisory period from October 2005–December 2006 assessed SGA use following these events.

Cohort Identification

We included adults aged 18–64 who were not dually-enrolled in Medicare or a managed care plan during the 180 days prior to their first SGA fill. Enrollees were classified as having schizophrenia if they had at least two claims (inpatient or outpatient, on separate service dates) for schizophrenia (ICD-9-CM 295.x) from July 2000–December 2006.^{20–22} Enrollees were classified as having bipolar disorder if they did not have schizophrenia and had at least two claims for a bipolar spectrum disorder (ICD-9-CM 296.0, 296.1, 296.4–296.8).^{23, 24}

We required enrollees to have at least one SGA prescription fill between January 1, 2001 and December 31, 2006. The date of the first SGA fill during this period was considered the enrollee's index prescription-fill date. SGAs included: olanzapine, quetiapine, risperidone, ziprasidone, and aripiprazole. Clozapine was excluded due to its infrequent use (<1% of SGA fills). To assess prior diagnoses we required enrollees to have continuous Medicaid enrollment for 6 months before their index SGA date. We treated the period between July

1,2000–December 31,2000 as a pre-screening window to allow all individuals to have at least 180 days of observable time before their index prescription date.

Prevalent Users

Since we were interested in estimating how SGA use changed among current users at the time of the advisory, we required that the index SGA prescription for prevalent users be filled prior to the FDA advisory period (December 2003). We defined enrollees with any SGA fill in the 180 days prior to their index fill date as prevalent users. We required prevalent users to have at least 6 months of continuous enrollment in Medicaid following their index prescription date.

Incident Users

We defined incident users as enrollees with no SGA fills during the 180 day period prior to their index prescription fill date.²⁵ No follow-up was required for incident users as the focus was on initial medication selection.

Outcome Measures

Among prevalent medication users, we assessed the likelihood of receiving any SGA, alternative pharmacotherapy use, and the occurrence of SGA discontinuations or interruptions. We assessed monthly SGA use for each enrollee. Individuals with at least 15 days of available therapy were identified as SGA users for the month. Available therapy was calculated using the enrollees' medication fill date and days of supply (adjusted for oversupply).²⁶ Alternative pharmacotherapy was defined as first-generation antipsychotics for enrollees with schizophrenia and bipolar disorder, and use of lithium or mood stabilizing anticonvulsants that are either expert guideline approved^{27–30} or FDA indicated for bipolar disorder (lamotrigine, carbamazepine, or valproate). Among monthly SGA users we defined discontinuations as gaps of 6 months or more following the last month of available SGA therapy. We defined interruptions as gaps of one to five months between SGA fills.

Next, for prevalent and incident users, we assessed the likelihood of receiving a specific SGA among enrollees filling any antipsychotic prescription. For each model, a dichotomous variable was created where the drug of interest was compared with all other SGAs. Separate models were estimated for olanzapine, quetiapine, risperidone, ziprasidone, and aripiprazole. Because of aripiprazole's late market entry (November, 2002), we estimated the probability of its use, but not relative changes from the pre-advisory period.

Olanzapine use was the primary focus given its identification as the highest metabolic risk SGA. Because of this, in secondary analyses we also assessed the likelihood of receiving each SGA among prior olanzapine users, and enrollees with prior metabolic conditions.

Covariates

Covariates, measured in the 6 months prior to the enrollee's index prescription-fill date, included age, race, Medicaid eligibility category, inpatient mental health services use, and receipt of outpatient care from a psychiatrist. Additionally, we controlled for prior diagnoses of metabolic-related conditions³¹ since these conditions may influence prescribing decisions following the advisory. We also controlled for co-morbid mental health conditions that could impact SGA selection, complicate the treatment of bipolar disorder or schizophrenia, or indicate a specific treatment³² (eTable 2).

Statistical Analysis

We estimated monthly changes in SGA use among prevalent users following the advisory using a modified Poisson regression model using the sandwich variance estimator to account for the repeated observations among enrollees over time.^{33–35} We present adjusted risks, risk ratios, and 95% confidence intervals. Separate models were estimated for enrollees with bipolar disorder and those with schizophrenia. Because we focus on assessing changes associated with the FDA's metabolic risk advisory and the subsequent consensus statement recommendations, comparisons are between the pre-advisory and initial post-advisory periods unless otherwise noted.

Sensitivity Analyses

Because our results may be sensitive to the timeframes selected or changes in agent-specific use, four sensitivity analyses were conducted. The first used a previously specified pre-post-advisory period;^{7,8,10} the second excluded aripiprazole because its market entry might have biased estimates of changes in SGA use; the third explored whether increases in off-label low-dose quetiapine use (e.g., for insomnia or anxiety)³⁶ influenced our results. Finally, we restricted our sample to enrollees who were continuously enrolled in Medicaid during the entire study period to determine whether our results were influenced by individuals exiting the Medicaid system over time.

RESULTS

There were 22,998 enrollees in our final sample, including 9,437 prevalent and 13,561 incident users. Among prevalent SGA users, 1,058 (11%) had bipolar disorder, and 8,379 (89%) schizophrenia (Table 1). Although the presence of metabolic-related conditions was similar between bipolar disorder and schizophrenia enrollees, there were considerable differences between these groups on most covariates. For example, as compared with prevalent users with schizophrenia, those with bipolar disorder were less likely to be male (30% versus 46%), black (7% versus 21%), or qualify for Medicaid through Supplemental Security Income (80% versus 92%). Incident SGA users were similar to prevalent users, although the proportion of incident SGA users with bipolar disorder was higher (31% versus 11%).

Changes in prevalent SGA use

Overall SGA use decreased slightly among all enrollees following the FDA advisory (Table 2, eTable 3). As compared with the pre-advisory period, in the initial post-advisory period there was a 7% decrease (RR=0.93, CI=0.89–0.97) in SGA use among enrollees with bipolar disorder and a 2% decrease (RR=0.98, CI=0.97–0.99) among enrollees with schizophrenia. Although there were decreases in SGA discontinuations and interruptions, these events were uncommon among both groups, ranging from 2–3% from the pre-advisory through the initial post-advisory period.

Among enrollees with bipolar disorder, 22% received an alternative pharmacotherapy during the pre-advisory period, and that proportion increased by 44% during the initial post-advisory period (RR=1.44, CI=1.33–1.55).

Agent-specific use – prevalent users

Olanzapine was the most prevalently used SGA during the pre-advisory period, representing 41% of SGA fills among enrollees with bipolar disorder and 43% among enrollees with schizophrenia (Table 3). From the pre-advisory to the initial post-advisory period, olanzapine use decreased by 34% among enrollees with bipolar disorder (RR=0.66,

CI=0.59–0.74) and 26% among enrollees with schizophrenia (RR=0.74, CI=0.72–0.76). By the most recent study period, olanzapine represented 16–17% of all SGA fills.

From the pre-advisory to initial post-advisory period there was a small, but statistically significant decrease in risperidone use among prevalent users with bipolar disorder (RR=0.89, CI=0.81–0.99) and schizophrenia (RR=0.92, CI=0.89–0.95). During the same time period quetiapine use increased by 47% (RR=1.47, CI=1.30–1.66) among enrollees with bipolar disorder, and 41% (RR=1.41, CI=1.34–1.47) among enrollees with schizophrenia. Further, use of this agent continued to increase through the end of the study period.

Use among prior olanzapine users

Among prior olanzapine users, subsequent olanzapine use declined by 29% from the pre-advisory to the initial post-advisory period (RR=0.71, CI=0.69–0.73). Over the study period use continued to decline, dropping from 74% in the pre-advisory period to 27% by the end of the study period (Figure 1).

Use among patients with prior metabolic conditions

By the initial post-advisory period, olanzapine use had decreased by 31% among enrollees with prior metabolic conditions (RR=0.69, CI=0.66–0.73), and by 24% among enrollees without these conditions (RR=.76, CI=.74–.79). By the most recent period the risk of olanzapine use was 13% among those with and 17% among those without prior metabolic conditions.

Agent-specific use – incident users

Incident SGA prescribing changed rapidly, with a steady decline in olanzapine use over the study period (Table 4). As compared with the pre-advisory period, by the end of the initial post-advisory period olanzapine use decreased by 63% among incident users with bipolar disorder and 58% among those with schizophrenia. Incident use patterns for each of the other SGAs largely mirrored use among the prevalent users, although quetiapine captured a larger share of incident prescriptions by the end of the study period (38% for bipolar disorder, 33% for schizophrenia).

Sensitivity Analyses

We assessed an alternative definition of the advisory period using previously defined timeframes and found no meaningful differences in outcomes. Additionally, we estimated separate models in which we excluded aripiprazole and found no meaningful differences in outcomes between analyses.

We next assessed whether increases in quetiapine use could be explained by off-label low-dose use³⁶ and found that low-dose quetiapine prescribing actually declined and average daily dose increased over the study period.

After restricting to those continuously-enrolled throughout the study period, approximately 67% of SGA users before the advisory were observable through the entire study period and 76% were observable through the initial post-advisory period. Results for olanzapine use were virtually identical, and although there were modest differences when examining secondary outcomes the substantive interpretation of our findings remained unchanged.

DISCUSSION

Among Florida Medicaid recipients, there were small decreases in overall SGA use after the FDA advisory and consensus statement publication. However, there were significant and sustained decreases in olanzapine use among both incident and prevalent SGA users. Our results are consistent with two prior evaluations assessing SGA prescribing, specifically regarding shifts in olanzapine use.^{8, 37} However, the current study expands upon prior efforts by evaluating the advisory and consensus statement's impact on both specific agent selection and several important and potentially unintended outcomes including changes in overall SGA use, use of therapeutic substitutes, and treatment interruptions or discontinuations.

While anecdotal evidence suggests that patients may be at increased risk for discontinuations or treatment interruptions following the release of drug risk communications,¹² we did not observe this in our sample. Instead, there were decreases in discontinuations and treatment interruptions through the initial post-advisory period. This is encouraging considering the importance of continuity of care among patients with severe mental illness.

Previous studies of the FDA advisory's impact on metabolic risk have left the impression that the advisory was largely ineffective due to the low adoption of metabolic screening recommendations.^{16, 18, 19, 38} Coupled with our finding of little change in overall SGA use, one might conclude that the advisory had little effect on providers' treatment decisions. However, there were substantial changes in drug utilization with major shifts away from olanzapine to drugs with lower known risk. Given the recent focus on preventing weight gain and metabolic syndrome in patients through selecting lower metabolic risk agents,³⁹ these results are promising.

While the importance of screening and monitoring patients for metabolic adverse effects should not be minimized, neither should the importance of agent selection. Patients taking SGAs or other agents requiring laboratory monitoring or clinical follow-up may face important barriers to monitoring, including a fragmented medical system,⁴⁰ provider discomfort or lack of knowledge about the patient's general medical conditions (for mental health clinicians)⁴¹ or mental health conditions (for primary care providers),⁴² and problems resulting from the patient's mental illness (e.g., amotivation, cognitive limitations, poverty).⁴⁰ These barriers may have led physicians to adopt a general policy of avoidance of higher metabolic risk agents. In fact, significant declines in olanzapine use occurred among enrollees with and without prior metabolic conditions, suggesting that high-risk agent use decreased among all patients, rather than among higher-risk patients alone. This explanation is supported by a recent study suggesting that selection of a lower-risk SGA was not consistently associated with abnormal laboratory values.⁷

Although olanzapine use rapidly decreased following the FDA's advisory, these decreases were offset by significant increases in quetiapine use. Recently there has been concern that quetiapine may be associated with a higher metabolic risk than originally proposed in the consensus statement.^{43, 44} Given the high proportion of incident quetiapine use in our sample, this relationship should be further clarified.

Following the initial post-advisory period, several important market impacts occurred for SGAs. For example, from April–September 2005 the CATIE trial results were published (reporting olanzapine's efficacy and association with weight gain and metabolic problems), the FDA added a black-box warning to SGAs regarding an increased risk for elderly patients with dementia, and Florida Medicaid temporarily shifted olanzapine onto a non-preferred drug list. These factors were associated with additional decreases in olanzapine use. By the

end of the study period olanzapine use had decreased by 59% among prevalent users with bipolar disorder, and 64% among prevalent users with schizophrenia, while incident olanzapine prescribing declined, 81% and 83%, respectively.

Limitations include using Medicaid claims from a single state, which may limit generalizability if SGA users systematically differ across states. In addition, one prior study showed a large effect of Florida's 2005 policy change on olanzapine prescribing.⁴⁵ Although our primary focus is on assessing changes prior to this policy change, estimates from later study periods may be lower than in Medicaid programs without similar policies. Next, while we observed changes in SGA selection following the FDA advisory and consensus statement, the effect cannot be separated from other policy and market impacts. Changes in pharmaceutical firms' promotional strategies, Medicaid policies, and publication of new safety and effectiveness information all play a part in increasing or decreasing overall utilization of a pharmaceutical product. Although we control for known Medicaid policy changes and timing of major publications, press releases, and additional advisories, other unobserved factors may have influenced our results.

Overall, there were significant shifts in SGA use among Medicaid enrollees with severe mental illness following the FDA advisory and consensus statement publication. Although metabolic screening and monitoring recommendations have not been effective, sweeping changes in higher-risk metabolic agent use suggest that many clinicians and patients were aware of and responded to the metabolic risks associated with these medications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- There were large shifts in olanzapine use following the FDA advisory and consensus statement publication.
- Overall antipsychotic use declined only slightly among enrollees with schizophrenia or bipolar disorder.
- Treatment discontinuations did not increase among prevalent users following the advisory.
- Decreases in olanzapine use suggest that many clinicians and patients were aware of and responded to the metabolic risk messages.

Figure 1. Atypical Antipsychotic Market Share among Prior Olanzapine Users

P/C/D = Period including the Medicaid Preferred-Drug List policy change, publication of the CATIE trial results, and the FDA's black box warning for the risk of mortality among elderly patients with dementia.

Table 1
 Characteristics of Prevalent and Incident Second Generation Antipsychotic Users with Severe Mental Illness

Sample Characteristics	Prevalent Users N = 9,437				Incident Users N = 13,561			
	Bipolar Disorder		Schizophrenia		Bipolar Disorder		Schizophrenia	
	N	%	N	%	N	%	N	%
Age								
18 – 29 Years	210	19.8	1,319	15.7	1,020	24.1	1,734	18.6
30 – 39 Years	262	24.8	1,794	21.4	1,139	26.9	1,910	20.5
40 – 49 Years	319	30.1	2,704	32.3	1,243	29.3	2,858	30.7
50 – 59 Years	205	19.4	1,947	23.2	687	16.2	2,127	22.8
60 – 64 Years	62	5.9	615	7.3	150	3.5	693	7.4
Sex								
Male	323	30.5	3,861	46.1	1,046	24.7	4,355	46.7
Female	735	69.5	4,518	53.9	3,193	75.3	4,967	53.3
Race								
White	682	64.5	3,736	44.6	2,941	69.4	3,532	37.9
Black	72	6.8	1,782	21.3	334	7.9	2,518	27.0
Hispanic	128	12.1	1,355	16.2	529	12.5	1,851	19.9
Other	176	16.6	1,506	18.0	435	10.3	1,421	15.2
Medicaid Eligibility Category								
SSI	851	80.4	7,750	92.5	2,733	64.5	8,038	86.2
Other	207	19.6	629	7.5	1,506	35.5	1,284	13.8
Received Care from a Psychiatrist								
Yes	782	73.9	6,924	82.6	2,431	57.3	6,397	68.6
Disease Severity								
Any Inpatient Mental Health Visits	173	16.3	1,930	23.0	1,068	25.2	2,717	29.1

	Prevalent Users N = 9,437		Incident Users N = 13,561	
	Bipolar Disorder	Schizophrenia	Bipolar Disorder	Schizophrenia
Sample Characteristics	N = 1,058	N = 8,379	N = 4,239	N = 9,322
	N	%	N	%
Prior Mental Health Diagnoses				
Alcohol and/or Substance Abuse	77	7.3	588	7.0
Diagnoses that Modify Treatment				
Epilepsy	82	7.7	698	8.3
Dementia	16	1.5	122	1.5
Complicating Conditions	267	25.2	1,785	21.3
Metabolic-Related Conditions				
Diabetes	103	9.7	1,059	12.6
Hyperlipidemia	99	9.4	934	11.1
Hypertension	168	15.9	1,714	20.5
Heart Disease	67	6.3	648	7.7
Obesity	29	2.7	261	3.1
Index Prescription Fill Period				
Pre-Advisory Period (Jan 01 – Jan 03)	1,058	100	8,379	100
Early- Advisory (Feb 03 – Nov 03)	--	--	--	--
Advisory Period (Dec 03 – Aug 04)	--	--	--	--
Initial Post-Advisory (Sept 04 – Mar 05)	--	--	--	--
PDL / CATIE / Dementia Warning ^a (April 05 – Sept 05)	--	--	--	--
Post-PDL/CATIE / Dementia Warning (Oct 05 – Dec 06)	--	--	--	--

^a PDL / CATIE / Dementia Warning = Period including the Medicaid Preferred-Drug List policy change, publication of the CATIE trial results, and the FDA's black box warning for the risk of mortality among elderly patients with dementia.

Table 2
Impact of FDA Warning on Prevalent Second Generation Antipsychotic Users, by Diagnosis

Modeled Outcome ^a	Bipolar Disorder			Schizophrenia		
	Risk	Risk Ratio	95% Confidence Interval	Risk	Risk Ratio	95% Confidence Interval
Second Generation Antipsychotic Use						
Pre-Advisory Period (Jan 01 – Jan 03)	.66	REF	REF	.70	REF	REF
Early- Advisory (Feb 03 – Nov 03)	.64	.96	.93–.99	.70	1.00	1.00–1.01
Advisory Period (Dec 03 – Aug 04)	.62	.94	.91–.98	.69	.99	.99–1.00
Initial Post-Advisory (Sept 04 – Mar 05)	.61	.93	.89–.97	.68	.98	.97–.99
PDL / CATIE / Dementia Warning (April 05 – Sept 05)	.61	.92	.88–.96	.67	.96	.95–.97
Post-PDL/CATIE / Dementia Warning (Oct 05 – Dec 06)	.52	.78	.74–.82	.60	.87	.85–.88
Alternative Medication Use^b						
Pre-Advisory Period (Jan 01 – Jan 03)	.22	1.00	REF	.07	1.00	REF
Early- Advisory (Feb 03 – Nov 03)	.31	1.38	1.31–1.45	.07	1.02	.99–1.06
Advisory Period (Dec 03 – Aug 04)	.31	1.38	1.29–1.47	.07	1.02	.98–1.07
Initial Post-Advisory (Sept 04 – Mar 05)	.32	1.44	1.33–1.55	.07	1.00	.95–1.05
PDL / CATIE / Dementia Warning (April 05 – Sept 05)	.31	1.39	1.28–1.51	.07	1.00	.95–1.06
Post-PDL/CATIE / Dementia Warning (Oct 05 – Dec 06)	.30	1.33	1.22–1.46	.07	.96	.91–1.02
Second Generation Antipsychotic Discontinuations^c						
Pre-Advisory Period (Jan 01 – Jan 03)	.03	1.00	REF	.03	1.00	REF
Early- Advisory (Feb 03 – Nov 03)	.02	.75	.60–.94	.02	.75	.69–.82
Advisory Period (Dec 03 – Aug 04)	.02	.74	.58–.95	.02	.79	.71–.87
Initial Post-Advisory (Sept 04 – Mar 05)	.02	.73	.55–.98	.02	.80	.72–.90
PDL / CATIE / Dementia Warning (April 05 – Sept 05)	.02	.88	.66–1.18	.03	.96	.86–1.08
Post-PDL/CATIE / Dementia Warning (Oct 05 – Dec 06)	.04	1.37	1.11–1.68	.04	1.46	1.35–1.58
Second Generation Antipsychotic Interruptions^d						
Pre-Advisory Period (Jan 01 – Jan 03)	.09	1.00	REF	.08	1.00	REF
Early- Advisory (Feb 03 – Nov 03)	.08	.81	.74–.90	.07	.82	.80–.85
Advisory Period (Dec 03 – Aug 04)	.08	.80	.72–.89	.07	.82	.79–.85

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Modeled Outcome ^a	Bipolar Disorder				Schizophrenia			
	Risk	Risk Ratio	95% Confidence Interval	Risk	Risk Ratio	95% Confidence Interval	Risk	Risk Ratio
Initial Post-Advisory (Sept 04 – Mar 05)	.08	.82	.72–.93	.07	.82	.78–.85		
PDL / CATIE / Dementia Warning (April 05 – Sept 05)	.07	.80	.70–.91	.08	.90	.86–.93		
Post-PDL/CATIE / Dementia Warning (Oct 05 – Dec 06)	.07	.77	.68–.86	.07	.82	.80–.85		

^a Generalized estimating equations were used to account for the repeated measures on each subject. We estimated each model using PROC GENMOD (SAS, 9.1) with a Poisson distribution, log link. The correlation structure was unspecified. Control variables included sex, age, race, Medicaid eligibility status, and the presence of the following during the 6 months prior to the index prescription date: receipt of care from a psychiatrist, inpatient mental health treatment, dementia, alcohol or substance abuse, epilepsy, complicating conditions, diabetes, hyperlipidemia, hypertension, heart disease, or obesity. PDL / CATIE / Dementia Warning = Period including the Medicaid Preferred-Drug List policy change, publication of the CATIE trial results, and the FDA's black box warning for the risk of mortality among elderly patients with dementia.

^b Medication alternatives included first generation antipsychotics (for enrollees with schizophrenia or bipolar disorder), and lithium, lamotrigine, carbamazepine, or valproate (for enrollees with bipolar disorder).

^c Discontinuations were defined as 6 or more months of no second generation antipsychotic use following a month of second generation antipsychotic use.

^d Interruptions were defined as a gap in second generation antipsychotic fills of 1 to 5 months with second generation antipsychotic use before and after the gap.

Table 3
Impact of the FDA Warning on Agent-Specific Use among Prevalent Antipsychotic Users, by Diagnosis

Agent-Specific Utilization ^a	Bipolar Disorder			Schizophrenia		
	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval
Olanzapine Use^b						
Pre-Advisory Period (Jan 01–Jan 03)	.41	1.00	.43	1.00	REF	REF
Early- Advisory (Feb 03–Nov 03)	.37	.90	.42	.96	.95–.98	.95–.98
Advisory Period (Dec 03–Aug 04)	.33	.80	.38	.88	.86–.90	.86–.90
Initial Post-Advisory (Sept 04–Mar 05)	.27	.66	.32	.74	.72–.76	.72–.76
PDL/CATIE/Dementia Warning (April 05–Sept 05)	.22	.52	.23	.54	.52–.56	.52–.56
Post-PDL/CATIE/Dementia Warning (Oct 05–Dec 06)	.17	.41	.16	.36	.34–.38	.34–.38
Quetiapine Use						
Pre-Advisory Period (Jan 01–Jan 03)	.14	1.00	.16	1.00	REF	REF
Early- Advisory (Feb 03–Nov 03)	.17	1.15	.20	1.20	1.16–1.25	1.16–1.25
Advisory Period (Dec 03–Aug 04)	.19	1.28	.21	1.28	1.23–1.34	1.23–1.34
Initial Post-Advisory (Sept 04–Mar 05)	.21	1.47	.23	1.41	1.34–1.47	1.34–1.47
PDL/CATIE/Dementia Warning (April 05–Sept 05)	.24	1.63	.27	1.65	1.58–1.73	1.58–1.73
Post-PDL/CATIE/Dementia Warning (Oct 05–Dec 06)	.24	1.64	.30	1.83	1.74–1.92	1.74–1.92
Risperidone Use						
Pre-Advisory Period (Jan 01–Jan 03)	.45	1.00	.42	1.00	REF	REF
Early- Advisory (Feb 03–Nov 03)	.44	.98	.38	.91	.89–.92	.89–.92
Advisory Period (Dec 03–Aug 04)	.41	.90	.37	.89	.86–.91	.86–.91
Initial Post-Advisory (Sept 04–Mar 05)	.41	.89	.39	.92	.89–.95	.89–.95
PDL/CATIE/Dementia Warning (April 05–Sept 05)	.42	.92	.40	.95	.92–.98	.92–.98
Post-PDL/CATIE/Dementia Warning (Oct 05–Dec 06)	.42	.92	.41	.97	.94–1.00	.94–1.00
Ziprasidone Use						
Pre-Advisory Period (Jan 01–Jan 03)	.02	1.00	.05	1.00	REF	REF
Early- Advisory (Feb 03–Nov 03)	.04	1.65	.10	1.85	1.71–1.99	1.71–1.99
Advisory Period (Dec 03–Aug 04)	.04	2.00	.11	2.06	1.88–2.25	1.88–2.25

Agent-Specific Utilization ^a	Bipolar Disorder			Schizophrenia		
	Risk	Risk Ratio	95% Confidence Interval	Risk	Risk Ratio	95% Confidence Interval
Initial Post-Advisory (Sept 04–Mar 05)	.05	2.31	1.73–3.26	.13	2.46	2.24–2.71
PDL/CATIE/Dementia Warning (April 05–Sept 05)	.06	2.67	2.03–3.71	.15	2.76	2.51–3.04
Post-PDL/CATIE/Dementia Warning (Oct 05–Dec 06)	.06	2.58	1.88–3.58	.15	2.76	2.50–3.06
Aripiprazole Use^c						
Pre-Advisory Period (Jan 01–Jan 03)	.00	--	--	.00	--	--
Early- Advisory (Feb 03–Nov 03)	.03	--	--	.08	--	--
Advisory Period (Dec 03–Aug 04)	.05	--	--	.12	--	--
Initial Post-Advisory (Sept 04–Mar 05)	.07	--	--	.15	--	--
PDL/CATIE/Dementia Warning (April 05–Sept 05)	.09	--	--	.17	--	--
Post-PDL/CATIE/Dementia Warning (Oct 05–Dec 06)	.12	--	--	.20	--	--

^aModels were estimated using PROC GENMOD (SAS, 9.1) with a Poisson distribution and log link. Control variables included sex, age, race, Medicaid eligibility status, and the presence of the following during the 6 months prior to the index prescription date: receipt of care from a psychiatrist, inpatient mental health treatment, dementia, alcohol or substance abuse, epilepsy, complicating conditions, diabetes, hyperlipidemia, hypertension, heart disease, or obesity. PDL / CATIE / Dementia Warning = Period including the Medicaid Preferred-Drug List policy change, publication of the CATIE trial results, and the FDA's black box warning for the risk of mortality among elderly patients with dementia.

^bHigh metabolic risk agent = Olanzapine. All other agents classified as lower metabolic risk agents.

^cRisk ratios are not provided for aripiprazole since it was introduced late in the pre-advisory period.

Table 4
Impact of the FDA Warning on Incident Second Generation Antipsychotic Drug Use, by Diagnosis

Agent-Specific Utilization ^a	Bipolar Disorder			Schizophrenia		
	Risk Ratio	95% Confidence Interval	Risk Ratio	Risk Ratio	95% Confidence Interval	
Olanzapine^b						
Pre-Advisory Period (Jan 01–Jan 03)	.66	1.00	REF	.48	1.00	REF
Early- Advisory (Feb 03–Nov 03)	.59	.88	.78–1.00	.41	.87	.79–.94
Advisory Period (Dec 03–Aug 04)	.44	.66	.56–.77	.30	.63	.56–.71
Initial Post-Advisory (Sept 04–Mar 05)	.24	.37	.29–.47	.20	.42	.35–.51
PDL / CATIE / Dementia Warning (April 05–Sept 05)	.12	.17	.12–.25	.10	.22	.16–.30
Post-PDL/CATIE / Dementia Warning (Oct 05–Dec 06)	.12	.19	.12–.29	.08	.17	.11–.27
Quetiapine						
Pre-Advisory Period (Jan 01–Jan 03)	.18	1.00	REF	.16	1.00	REF
Early- Advisory (Feb 03–Nov 03)	.24	1.38	1.19–1.60	.20	1.21	1.07–1.36
Advisory Period (Dec 03–Aug 04)	.26	1.49	1.27–1.75	.23	1.37	1.19–1.57
Initial Post-Advisory (Sept 04–Mar 05)	.34	1.91	1.62–2.26	.31	1.86	1.59–2.17
PDL / CATIE / Dementia Warning (April 05–Sept 05)	.37	2.11	1.77–2.52	.31	1.86	1.55–2.23
Post-PDL/CATIE / Dementia Warning (Oct 05–Dec 06)	.38	2.13	1.73–2.63	.33	1.98	1.60–2.46
Risperidone						
Pre-Advisory Period (Jan 01–Jan 03)	.06	1.00	REF	.33	1.00	REF
Early- Advisory (Feb 03–Nov 03)	.04	.72	.60–.86	.25	.77	.70–.85
Advisory Period (Dec 03–Aug 04)	.04	.70	.57–.86	.27	.83	.74–.94
Initial Post-Advisory (Sept 04–Mar 05)	.04	.70	.55–.89	.26	.81	.69–.94
PDL / CATIE / Dementia Warning (April 05–Sept 05)	.04	.64	.49–.85	.31	.94	.79–1.11
Post-PDL/CATIE / Dementia Warning (Oct 05–Dec 06)	.05	.74	.54–1.02	.29	.88	.71–1.09
Ziprasidone						
Pre-Advisory Period (Jan 01–Jan 03)	.01	1.00	REF	.08	1.00	REF
Early- Advisory (Feb 03–Nov 03)	.01	.79	.55–1.14	.09	1.12	.91–1.37
Advisory Period (Dec 03–Aug 04)	.02	1.35	.96–1.91	.12	1.48	1.19–1.85

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Agent-Specific Utilization ^a	Bipolar Disorder			Schizophrenia		
	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval
Initial Post-Advisory (Sept 04–Mar 05)	.02	1.59	1.11–2.28	.12	1.56	1.19–2.05
PDL / CATIE / Dementia Warning (April 05–Sept 05)	.03	1.98	1.36–2.89	.14	1.80	1.33–2.44
Post-PDL/CATIE / Dementia Warning (Oct 05–Dec 06)	.01	.59	.27–1.28	.16	1.98	1.39–2.82
Aripiprazole^c						
Pre-Advisory Period (Jan 01–Jan 03)	.00	--	--	.00	--	--
Early- Advisory (Feb 03–Nov 03)	.01	--	--	.12	--	--
Advisory Period (Dec 03–Aug 04)	.02	--	--	.13	--	--
Initial Post-Advisory (Sept 04–Mar 05)	.02	--	--	.16	--	--
PDL / CATIE / Dementia Warning (April 05–Sept 05)	.02	--	--	.16	--	--
Post-PDL/CATIE / Dementia Warning (Oct 05–Dec 06)	.03	--	--	.18	--	--

^aModels were estimated using PROC GENMOD (SAS, 9.1) with a Poisson distribution and log link. Control variables included sex, age, race, Medicaid eligibility status, and the presence of the following during the 6 months prior to the index prescription date: receipt of care from a psychiatrist, inpatient mental health treatment, dementia, alcohol or substance abuse, epilepsy, complicating conditions, diabetes, hyperlipidemia, hypertension, heart disease, or obesity. PDL / CATIE / Dementia Warning = Period including the Medicaid Preferred-Drug List policy change, publication of the CATIE trial results, and the FDA's black box warning for the risk of mortality among elderly patients with dementia.

^bHigh metabolic risk agent = Olanzapine. All other agents classified as lower metabolic risk agents.

^cRisk ratios are not provided for aripiprazole since it was introduced late in the pre-advisory period.