ORIGINAL ARTICLE

Metabolic Testing Rates in 3 State Medicaid Programs After FDA Warnings and ADA/APA Recommendations for Second-Generation Antipsychotic Drugs

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Context: In 2003, the Food and Drug Administration (FDA) required a warning on diabetes risk for second-generation antipsychotic (SGA) drugs. The American Diabetes Association (ADA) and American Psychiatric Association (APA) recommended glucose and lipid testing for all patients starting to receive SGA drugs.

Objective: To characterize associations between the combined warnings and recommendations and baseline metabolic testing and SGA drug selection.

Design: Interrupted time-series analysis.

Setting: California, Missouri, and Oregon.

Patients: A total of 109 451 individuals receiving Medicaid who began taking SGA medication and a control cohort of 203 527 patients who began taking albuterol but did not receive antipsychotic medication.

Interventions: Prewarning and postwarning trends in metabolic testing were compared using laboratory claims for the cohort collected January 1, 2002, through December 31, 2005. Changes in SGA prescribing practices were similarly evaluated.

Main Outcome Measures: Monthly rates of baseline serum glucose and lipid testing for SGA-treated and propensity-matched albuterol-treated patients and monthly share of new prescriptions for each SGA drug.

Results: Initial testing rates for SGA-treated patients were low (glucose, 27%; lipids, 10%). The warning was not associated with an increase in glucose testing among SGA-treated patients and was associated with only a marginal increase in lipid testing rates (1.7%; $P=.02$). Testing rates and trends in SGA-treated patients were not different from background rates observed in the albuterol control group. New prescriptions of olanzapine (higher metabolic risk) declined during the warning period (annual share decline, 19.9%; $P<.001$). New prescriptions of aripiprazole (lower metabolic risk) increased during the warning period (share increase, 12.1%; $P<.001$) but may be attributable to the elimination of prior authorization in California during the same time frame. Quetiapine, risperidone, and ziprasidone use were not associated with the warning.

Conclusions: In a Medicaid-receiving population, baseline glucose and lipid testing for SGA-treated patients was infrequent and showed little change following the diabetes warning and monitoring recommendations. A change in SGA drug selection consistent with intentions to reduce metabolic risk was observed.

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In late 2003, the Food and Drug Administration (FDA) announced that it was requiring that class warnings be added to the labeling of atypical or second-generation antipsychotic (SGA) drugs describing increased risk of hyperglycemia and diabetes, and it required that all drug manufacturers mail "Dear healthcare professional" letters to inform health care providers of the new warning.[1,2] In some cases, the hyperglycemia was extreme and associated with ketoacidosis, hyperosmolar coma, or death. The first label changes were made in December 2003,[3] and the letters were mailed, according to the FDA, to "neuropsychiatric healthcare professionals" through August 2004.[4] The warning stated that glucose levels should be monitored in patients with an established diagnosis of diabetes, risk factors for diabetes, or symptoms of hyperglycemia.[2] The goal was to increase awareness of the signs and symptoms of diabetes to promote earlier detection and appropriate treatment. Concurrent with the warning, the American Diabetes Association (ADA) published a consensus statement with the American Psychiatric Association (APA) that described the metabolic risks associated with SGA drugs, including the differential risks of metabolic dis-

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turbances among individual SGA drugs.[5] The consensus statement also specified a monitoring protocol for all patients who were taking SGAs that included baseline assessment of personal/family history, weight (body mass index [calculated as weight in kilograms divided by height in meters squared]), waist circumference, blood pressure, fasting plasma glucose level, and fasting lipid profile.[5]

Individuals with serious mental illness, commonly treated with SGA drug therapy, have higher risk of diabetes and cardiovascular disease and therefore represent a vulnerable population for whom more frequent metabolic monitoring is also indicated.[6-8] The population prevalence of dyslipidemia, hypertension, obesity, and type 2 diabetes mellitus is approximately 1.5 to 2 times higher in individuals with serious mental illness compared with the general population[9,10]; other modifiable risk factors for type 2 diabetes such as physical inactivity and poor dietary choices[11] are also more common. Unfortunately, diabetes and cardiovascular risk is often underrecognized[10] and undertreated[12] in patients with serious mental illness.[6]

For these reasons, diabetes and dyslipidemia screening in patients who are starting to take SGA drugs is important; however, information on screening rates for SGA-treated patients is limited.[13-16] For commercially insured patients, the warnings have not been associated with a clinically meaningful increase in glucose and lipid monitoring.[15,16] However, the effect of the warnings on glucose and lipid testing has not been described in patients receiving Medicaid, for whom antipsychotic use is very common.[17] The aim of this retrospective, population-based cohort study was to evaluate whether glucose and lipid testing increased for patients initiating SGA medication following the FDA warnings and ADA/APA recommendations based on 4-year testing trends observed in the California, Missouri, and Oregon state Medicaid programs. Our secondary aim was to determine whether prescribing patterns changed following the warnings as an alternative to reduce metabolic risk. We hypothesized that the use of drugs with higher metabolic risk declined and that use of drugs with lower metabolic risk increased as a result of the warning.

METHODS

STUDY POPULATION

The study cohort was selected retrospectively from fee-for-service clients enrolled in the California, Missouri, and Oregon Medicaid programs between January 1, 2002, and December 31, 2005. Subjects were excluded if they were Medicare dual eligible or enrolled in a managed care plan because complete laboratory and medical claims were not available. Subjects had a unique encrypted identifier that allowed us to identify their medical, pharmacy, and laboratory claim records during the study period. The study received approval from the Colorado Multiple Institutional Review Board and the California Committee for the Protection of Human Subjects.

A cohort of 109 451 individuals with a new prescription claim for an SGA drug (aripiprazole, olanzapine, olanzapine/fluoxetine, quetiapine, risperidone, or ziprasidone) was selected. Individuals were excluded if they did not have continuous enrollment history 180 days before and after the first (index) SGA pharmacy claim in the study period. Given its unique neutropenia-related testing requirements, clozapine users were excluded.

A second control cohort of 203 527 patients initiating albuterol therapy, but not receiving antipsychotic medication, was identified. The asthma medication albuterol has been used as a control for other longitudinal claims-based research in psychiatry.[18] The control group was used to compare testing rates in SGA-treated patients with background rates of metabolic screening in the general Medicaid population from the same states. We hypothesized that glucose and lipid testing rates in individuals taking albuterol would not be affected by the antipsychotic warnings and therefore could provide a control for temporal trends.

ASSESSMENT OF METABOLIC TESTING

Glucose testing was identified if a medical claim with an American Medical Association *Current Procedural Terminology* (*CPT*) code for a metabolic or general health panel (80048, 80050, 80053) or glucose-specific serum test (82947, 82948, 82950, 82951) was present. Lipid testing was identified if a *CPT* code for a lipid panel (80061) or lipid-specific serum test (82465, 84478, 83721, 83715, 83700, 83716, 83701) was present. Baseline was operationalized as testing occurring 30 days before through 30 days after the index date. Sensitivity analyses were performed to evaluate testing rates in expanded windows of testing surrounding the index date.

ASSESSMENT OF BASELINE PATIENT CHARACTERISTICS

Disparities in diabetes care have been associated with the number of mental health conditions.[12] Mental health conditions were identified using diagnosis codes ascertained from medical claims in the 180 days before the index date and classified into 8 categories using Clinical Classifications Software coding developed by the Agency for Health Care Research and Quality.[19] The categories were affective disorders, alcohol and substance-related mental disorders, anxiety, somatoform, and personality disorders, preadult disorders, senility and organic mental disorders, schizophrenia and related disorders, other psychoses, and other mental conditions. The number of mental health conditions was categorized as none recorded, 1, or 2 or more.

Preexisting diabetes was defined as a recorded diagnosis code of 250 in the medical claims using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) coding scheme or a prescription claim for an antidiabetic drug (Generic Product Identifier 27) occurring in the 180 days before the index date. Dyslipidemia, hypertension, and heart disease are type 2 diabetes risk factors[20] and presumably should increase a clinician's vigilance and trigger more frequent screening. Individuals with preexisting dyslipidemia, hypertension, and recent evidence of heart disease were identified using medical and pharmacy records for the 180 days before the index date. Dyslipidemia was defined as a diagnosis of dyslipidemia (Clinical Classifications Software 53) or a prescription claim for a cholesterol-lowering drug (Generic Product Identifier 39). Hypertension was defined as a diagnosis of hypertension (Clinical Classifications Software 98 or 99) or a prescription claim for an antihypertensive drug: Generic Product Identifier code 33 (β-blockers), 34 (calcium channel blockers), 36 (ace inhibitors), or 37 (diuretics). Heart disease was defined based on Clinical Classifications Software classification for acute myocardial infarction (100), coronary atherosclerosis (101), pulmonary heart disease (103), or other heart diseases (104). These vari-

ables were used to control for differences in diabetes risk factors when comparing metabolic testing rates and trends between SGA users and albuterol control subjects.

Age (at the index date), race/ethnicity, and sex have also been associated with the likelihood of diabetes screening and were included in the analysis.[21]

STATISTICAL ANALYSIS

Comparison of select baseline characteristics in SGA vs albuterol users was performed using χ^2 tests. The SGA- and albuterol-treated patients were dichotomously classified as either having or not having received a baseline glucose or lipid test. Metabolic testing rates for each month were expressed as the number of patients receiving a baseline test divided by the number of patients initiating drug therapy during that month. The study period was segmented into 3 time periods: prewarning (January 1, 2002-November 30, 2003), warning (December 1, 2003-August 31, 2004); and postwarning (September 1, 2004-December 31, 2005). The time span for the warning period starts when labeling changes were first instituted[3] and ends in the month the last "Dear healthcare professional" letter was mailed.[4] Publication of the ADA/APA recommendations falls in the middle of this warning period.[5] Segmented regression analysis was performed by linear mixed modeling (corrected for first-order autoregression) to examine the association between monthly rates of baseline glucose and lipid testing associated with the FDA warning, including step and trend changes.[22] Regressions were performed for 3 cohorts: all SGA users (n=109 451); persistent SGA users (n=34 274), and propensity-matched pairs of albuterol and persistent SGA users (n=33 213 pairs). Persistent SGA users had a maximum gap in SGA drug therapy of no greater than 30 days during the initial 180 days of treatment.[23] We hypothesized that rates of initial screening might be higher in persistent users of SGA medication because physicians were anticipating that therapy duration would not be time limited.

Propensity analysis was used to control for differences in patient characteristics when comparing testing between SGA users and albuterol control subjects. A nearest-neighbor 1:1 matched cohort of cases and controls was determined by year of index drug, state, sex, age, race/ethnicity, number of mental health disorders, and presence of preexisting cardiovascular risk (dyslipidemia, hypertension, or heart disease) using a greedy matching algorithm.[24] The C statistic, a summary of the overall prediction accuracy, was 0.81, indicating good discrimination between cohorts based on the selected variables.[25]

Rates of glucose and lipid testing were calculated using expanding time windows surrounding the date of drug initiation for the propensity-matched pairs of subjects who began therapy during the postwarning period and stratified by diabetes status. Comparison of testing rates in subjects with and without diabetes was performed at each time window using χ^2 tests.

Patients were also classified based on their index SGA medication. Share of new prescriptions for each month was expressed as the number of patients initiating a particular SGA medication divided by the total number of patients starting 1 of the 6 SGA drugs during that month. Patients who started taking multiple SGA medications (<2%) were exclude from this calculation. Separate time series were constructed for each drug to compare monthly prescribing share trends associated with the FDA warning using similar linear mixed modeling methods as above. Prescribing trends were evaluated for all patients who began SGA medication and for patients with a schizophrenia diagnosis, the primary approved indication during the study period for all drugs in the class.

All analyses used SAS version 9.2 (SAS Institute Inc, Cary, North Carolina).

Table 1. Selected Baseline Characteristics of Patients Who Received SGA Medication or Albuterol[a]

Baseline Characteristics	Patients by Treatment Group, %		*P* Value
	SGA	Albuterol (Control)	
Sample, No.	109 451	203 527	
Demographics			
Female	52.9	62.8	<.001
Age group, y			
6-12	11.6	20.7	
13-19	12.5	16.2	
20-29	13.6	12.4	
30-39	16.7	12.7	
40-49	21.9	13.6	<.001
50-59	16.1	13.4	
60-69	6.0	8.4	
70-79	1.0	2.1	
80-88	0.5	0.6	
Race/Ethnicity			
White	59.3	53.1	
Black	16.2	11.8	<.001
Other/unknown	24.5	35.1	
State			
California	67.2	70.8	
Missouri	25.0	24.8	<.001
Oregon	7.8	4.4	
Study period			
Prewarning, Jan 2002-Nov 2003	52.9	52.2	
Warning, Dec 2003-Aug 2004	18.6	17.7	<.001
Postwarning, Sep 2004-Dec 2005	28.5	30.1	
Mental health diagnosis			
Conditions, No.			
None recorded	22.2	67.5	
1	27.7	20.4	<.001
≥2	50.1	12.1	
Types of conditions			
Affective disorder	37.8	7.9	<.001
Anxiety disorder	29.1	10.9	<.001
Alcohol and substance abuse	20.5	10.2	<.001
Senility	4.8	1.0	<.001
Other psychosis	15.0	1.1	<.001
Preadult disorder	14.8	3.8	<.001
Schizophrenia	15.4	0.9	<.001
Other mental condition	38.9	15.0	<.001
Diabetes	10.6	11.2	<.001
Cardiovascular risk			
Any of the following	34.7	29.9	<.001
Hypertension	29.4	25.8	<.001
Dyslipidemia	13.0	13.0	.97
Heart disease	6.0	6.7	<.001

Abbreviation: SGA, second-generation antipsychotic.
[a] Data from California, Missouri, and Oregon state Medicaid programs, 2002-2005.

RESULTS

Table 1 summarizes patient characteristics of the cohort who started taking SGA medication during the study period as well as control subjects. One-fourth of the sample of SGA users were children, while the largest

Table 2. Rates and Trends of Baseline Glucose and Lipid Testing by Period[a]

Group	Prewarning[b]			Warning[b]			Postwarning[b]		
	Baseline Testing Rate First Month, % (95% CI)	Annualized Change in Testing Trends, %	*P* Value	Baseline Testing Rate First Month of Period, % (95% CI)	Step Change in Testing Rates, %	*P* Value	Baseline Testing Rate First Month, % (95% CI)	Annualized Change in Testing Trends From Period 1 to 3	*P* Value
Serum Glucose Testing									
All SGA users	26.9 (25.3-28.4)	0.2	.68	28.0 (26.0-29.9)	0.9	.20	29.5 (27.6-31.4)	0.2	.83
Persistent SGA users	30.1 (27.2-33.0)	–0.9	.09	26.7 (23.2-30.2)	1.2	.19	27.8 (24.5-31.1)	1.6	.12
Propensity-matched pairs									
Persistent SGA users	30.2 (27.3-33.2)	–1.1	.07	26.9 (23.4-30.5)	1.4	.16	27.9 (24.5-31.2)	2.1	.07
Albuterol users (control)	26.1 (23.6-28.6)	1.2	.28	23.5 (20.9-26.1)	0.1	.95	31.1 (27.5-34.8)	0.1	.97
Serum Lipid Testing									
All SGA users	10.0 (8.9-11.0)	–0.5	.23	9.2 (8.0-10.4)	1.7	.02	11.4 (10.1-12.8)	0.9	.28
Persistent SGA users	11.3 (9.3-13.3)	–0.5	.29	11.4 (8.9-13.9)	1.9	.03	11.5 (9.2-13.9)	1.1	.29
Propensity-matched pairs									
Persistent SGA users	11.4 (9.4-13.4)	–0.6	.28	11.2 (8.7-13.8)	1.9	.03	11.8 (9.4-14.2)	1.0	.65
Albuterol users (control)	11.2 (9.4-13.0)	–0.7	.36	9.1 (7.4-10.9)	–0.5	.65	10.6 (8.2-13.0)	1.2	.39

Abbreviations: CI, confidence interval; SGA, second-generation antipsychotic.

[a] Data from California, Missouri, and Oregon state Medicaid programs, 2002-2005 (n = 109 451 SGA users; n = 34 274 persistent SGA users; n = 33 213 propensity-matched pairs of albuterol and persistent SGA users).

[b] The prewarning period was defined as January 1, 2002, through November 30, 2003; warning, December 1, 2003, through August 31, 2004; postwarning, September 1, 2004, through December 31, 2005.

subgroup of adults was aged 40 to 49 years. Two-thirds of the SGA sample were from California (n=73 544), 25.0% from Missouri (n=27 345), and 7.8% from Oregon (n=8562). Half of the SGA users had 2 or more mental health conditions recorded. Of SGA users, 10.6% had identified diabetes; 29.4%, hypertension; 13.0%, dyslipidemia; and 6.0%, recent evidence of heart disease. Thirty-one percent of SGA users initiating SGA medication were therapy persistent for 180 days after starting to take medication.

BASELINE SERUM GLUCOSE AND LIPID TESTING TRENDS

Rates and trends of baseline glucose and lipid testing in patients who began taking SGA medication and the cohort of propensity-matched albuterol users are presented in **Table 2** for the prewarning, warning, and postwarning study periods. In January 2002, 26.9% of patients starting to receive SGA medication had baseline serum glucose testing and 10.0% had baseline lipid testing. During the prewarning period, baseline testing rates remained constant (glucose trend change, 0.2%/y; lipid trend change, –0.5%/y). Glucose testing rates did not increase during (0.9% absolute change) or after the FDA warning (trend change, 0.2%/y). A clinically small but statistically significant step change of 1.7% in baseline lipid testing rates occurred during the warning period but testing rates did not increase significantly after the warning (trend change, 0.9%/y).

Persistent SGA users did not have clinically higher rates of baseline glucose or lipid testing than patients initiating SGA medication. Rates and trends of baseline glucose and lipid testing were comparable between propensity-matched pairs of SGA and albuterol users, with the exception of a slight increase observed in lipid testing during the warning period.

TESTING RATES IN PATIENTS WITH AND WITHOUT RECOGNIZED DIABETES

Figure 1 shows the relationship between testing window definitions and serum glucose and lipid testing rates by diabetes status in propensity-matched pairs of albuterol and persistent SGA users during the postwarning study period. In SGA-treated patients with and without diabetes, glucose and lipid testing rates increased 2- to 3-fold as the defined window of testing expanded from the primary baseline definition (30 days before or after drug initiation) to 180 days before or after drug initiation ($P<.001$; Figure 1 and **Figure 2**). Glucose and lipid testing rates were approximately 2-fold higher among SGA-treated individuals with preexisting diabetes compared with those without diabetes for each of the 4 testing windows evaluated ($P<.001$; Figures 1 and 2). Although glucose and lipid testing rates for SGA-treated individuals were statistically different from matched control subjects at several testing windows, the absolute clinical differences were small and, in most cases, the albuterol cohort outperformed the SGA cohort.

INDEX SGA MEDICATION TRENDS

Figure 2A shows trends in the index SGA medication prescribed during the prewarning, warning, and postwarning study periods for patients beginning to take a single SGA drug, regardless of indication. Changes in share of prescribing for olanzapine and aripiprazole were significantly

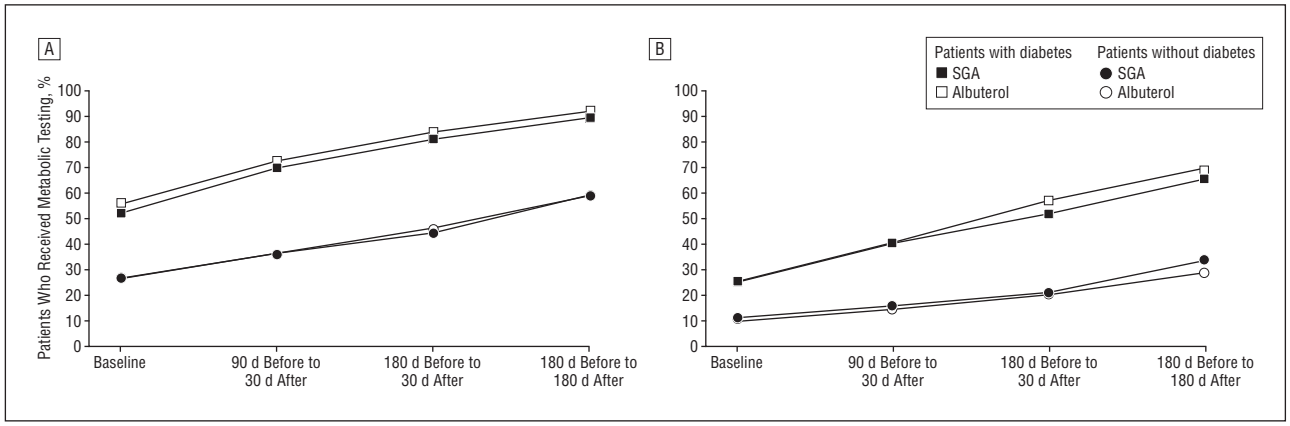

Figure 1. Serum glucose (A) and lipid (B) testing rates by diabetes status. Data are from California, Missouri, and Oregon state Medicaid programs, September 2004 through December 2005. Propensity-matched groups of albuterol and second-generation antipsychotic (SGA) persistent users are shown (n=33 213).

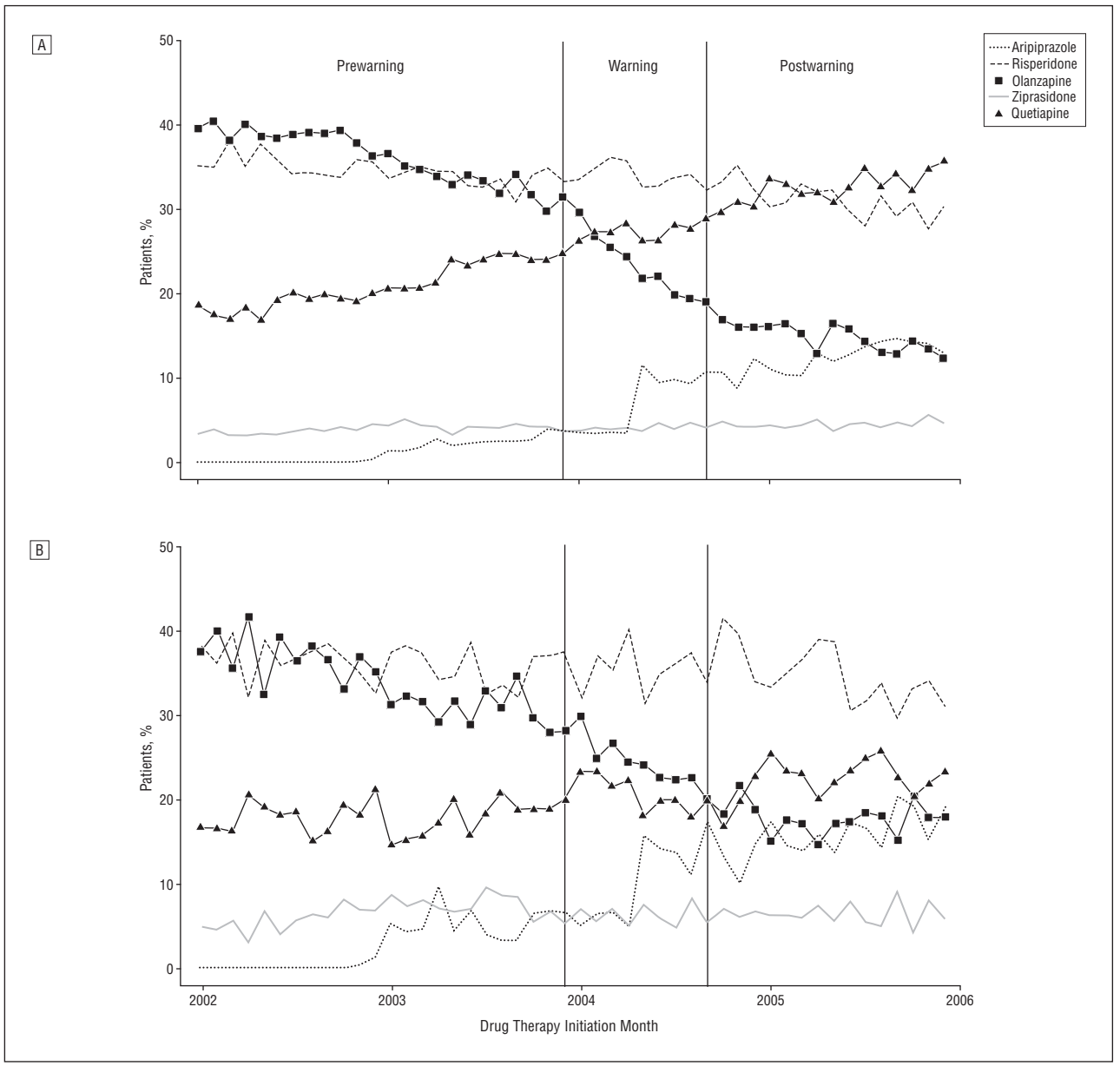

Figure 2. Trends in new second-generation antipsychotic (SGA) prescriptions during the prewarning, warning, and postwarning study periods for all SGA users (A) and SGA users with schizophrenia (B). Data are from California, Missouri, and Oregon state Medicaid programs, 2002-2005. For an explanation of the study periods see the "Statistical Analysis" subsection of the "Methods" section.

associated with the FDA warnings. During the prewarning period, olanzapine share declined 5.4%/y ($P < .001$) but began to decline at a faster rate during the warning period (–19.9%/y; $P < .001$) resulting in a 14% step reduction during the warning period. The rate of decline after the warning was not significantly different from the prewarning trend. Aripiprazole market share increased at 2.1%/y before the warning period ($P < .001$), grew significantly during the warning period (12.1%/y; $P < .001$), and returned to prewarning growth rates after the warning period. The step change during the warning period was 7.4% ($P < .001$). The increase in aripiprazole prescribing during the FDA warning period was observed in California (10.0%/y; $P < .001$) and Missouri (3.0%/y; $P = .02$) but not in Oregon. Prewarning share trends for quetiapine (growth, 4.3%/y; $P < .001$), risperidone (decline, 1.7%/y; $P = .005$), and ziprasidone (growth, 0.6%/y; $P = .002$) continued unchanged after the FDA warning.

Changes in prescribing trends among SGA users with schizophrenia (Figure 2B) were qualitatively similar to the overall prescribing trends; however, changes in prescribing share were less pronounced and the association of the warning period with prescribing was attenuated.

COMMENT

The FDA warnings and related risk communication concerning SGA drugs and risk of diabetes and dyslipidemia appear to have had no detectable effect on average baseline serum glucose or lipid testing rates for SGA-treated adults in the 3 state Medicaid populations studied. Absolute rates of baseline testing were low; on average, less than 30% of SGA-treated patients received baseline serum glucose and less than 15% received lipid testing. Rates of baseline testing did not increase following the warning. Moreover, rates of testing among SGA-treated patients appeared to be no different from general background rates of screening in this Medicaid population, as evidenced by similar rates of testing in the albuterol-treated control group, despite well-characterized increased risk of diabetes and cardiovascular disease in the SGA-treated population.[6]

Lack of awareness may be one cause behind the low rates of testing, although surveys of psychiatrists after the warning indicate high levels of knowledge concerning the need for metabolic monitoring.[26,27] Lack of resources in Medicaid-receiving mental health settings for ordering blood tests may also explain low rates of screening. For comparison, the baseline testing rates in our SGA-treated Medicaid population are comparable with SGA-treated patients in 2 commercially insured populations,[15,16] and the 6-month testing rates (data not shown) in older adults are similar to rates reported in a Veterans Affairs–based population (glucose, 57%; lipid, 39%).[14] Thus, it appears that average screening rates may be more similar between health care settings than dissimilar.

The FDA warnings were associated with changes in SGA prescribing practices. The most notable was the use of olanzapine, a drug associated with greater metabolic risk,[5,9] which declined significantly. The increase in aripiprazole prescribing is also noteworthy because it might signal an increase in the use of SGA drugs with low metabolic risk.[5,9] However, much of the spike in aripiprazole use may be owing to a concurrent California formulary change that had been under way before the warning in which the California Medicaid program added aripiprazole to its List of Contract Drugs and eliminated prior authorization. Prescribing trends for quetiapine, risperidone, and ziprasidone were not associated with the warning. Thus, the findings suggest that the main effect of the FDA warning was to accelerate a decline in olanzapine prescribing, consistent with intentions to reduce metabolic risk, rather than to increase metabolic laboratory monitoring.

Although this retrospective study was not able to identify or quantify reasons why laboratory screening did not increase after the FDA warnings, whereas prescribing practices did change, we might speculate on some possible explanations. Diffusion and behavior change theory would predict that it is easier to adopt behaviors for which the relative advantage is clear and compatible with existing experience and practices than to adopt behaviors with greater perceived complexity or that are designed to lower the probability of some unwanted future event.[28] Translating this to drug warnings, one would expect faster adoption of drug prescribing changes (eg, switching to lower-risk drugs or not treating) than the adoption of new screening or monitoring practices. This phenomenon was observed following the pediatric antidepressant suicide warning regarding an immediate decline in the pharmacological treatment of pediatric depression[29] but a lack of change in the frequency of follow-up office visits.[30]

On the other hand, the low rates of baseline blood testing observed in this study population are surprising given high awareness among psychiatrists of the metabolic risks associated with SGA medication and generally strong agreement regarding the need to screen and monitor patients.[27,31] For example, in the year following the FDA warnings, 60% to 80% of psychiatrists reported monitoring glucose and lipid levels at regular intervals.[27,31] A national survey of community mental health centers also indicated that two-thirds of the community mental health centers reported having protocols or procedures to screen for common medical problems such as diabetes and dyslipidemia.[32] Therefore, more research is needed to better understand this gap between reported monitoring behavior and observed monitoring rates before improvements can be made in diabetes and dyslipidemia screening for this at-risk population.

One hypothesis could be that psychiatrists, who frequently prescribe SGA drugs and who were the primary target audience for risk communication, may be aware of the warnings but primary care providers, who would generally order the necessary laboratory tests and provide general medical care, may have lower awareness. Diffusion theory predicts that it is difficult to make a change that is partly dependent on someone else to execute (eg, a psychiatrist ordering monitoring that is best accomplished in the primary care setting). In a commercially insured private practice population, patients who were prescribed SGA medication by a psychiatrist were less likely to receive testing than if the drug was prescribed by a primary care provider.[15] We could not directly as-

sess the effect of prescriber specialty on testing rates within our data. The effect of prescriber specialty and the health care setting in which they practice on the likelihood of testing warrants further investigation.

This study identified metabolic testing based on laboratory claims from multiple outpatient settings; however, it was not possible to confirm whether tests were ordered by, or were available to, the clinicians responsible for SGA treatment decision making. It is almost certain that some proportion of testing was performed for purposes other than the recommended evaluation of SGA effects on blood glucose or lipid levels, and that the results were not available to psychiatric treatment decision makers within these health systems. The fact that screening rates for SGA-treated patients were not different from general screening in a group of patients starting albuterol treatment supports this interpretation. Therefore, the absolute rates of glucose and lipid testing we observed for SGA-treated patients are likely overestimates of actual metabolic monitoring performed specifically in relation to SGA treatment. However, the data also suggest that more patients receive some glucose and lipid testing at some point in time, even if not in close temporal relation to the SGA prescription event. Because the results of these tests reside somewhere in the patient health records, optimizing the availability and sharing of that information between mental and medical care providers could contribute to improvements in medical decision making.

The results of this research are subject to limitations. One limitation of using outpatient administrative claims records is that we could not evaluate the effect of the FDA warnings on unbilled metabolic screening occurring during the visit (eg, family history of diabetes, height and body weight, finger-stick glucometer-based glucose testing, waist circumference) or testing occurring during a hospital admission. We also could not determine compliance with fasting requirements. We were not able to determine where the tests were ordered, the results of the tests, or whether these results were effectively communicated between SGA prescribers and primary care providers. There are also limitations to using claims data to define medical comorbidities. We identified comorbidities based on pharmaceutical claims and diagnoses, and this does not capture patients with unrecognized or untreated disease. In addition, some antidiabetic and cholesterol-lowering drugs are prescribed for people without diabetes or hyperlipidemia.

Our results reflect care in a Medicaid fee-for-service environment and patients with Medicaid who receive care within a capitated plan may have more integrated and comprehensive care. Although we observed similar results between the 3 state programs, caution should be applied in generalizing our findings to other state Medicaid programs or other care settings. Anecdotal evidence suggests that some local mental health treatment centers have been successful in increasing rates of glucose and lipid testing using incentives (eg, financial compensation to the ordering clinician) or disincentives (eg, sharing individual clinician performance rates among a peer group).

In summary, our study of laboratory claims offers little evidence that Medicaid-receiving patients who are taking SGA medication typically receive baseline serum glucose and lipid testing. Moreover, the FDA warning and ADA/APA consensus statement recommendations were not associated with an increase in baseline testing rates. Instead, clinicians were more likely to reduce their use of olanzapine, an SGA drug with higher metabolic risk. More effort is needed to ensure that patients who receive SGA drugs are screened for diabetes and dyslipidemia and monitored for potential adverse drug effects, beginning with baseline testing of serum glucose and lipids, so that patients can receive appropriate preventive care and treatment.

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REFERENCES

1. Rosack J. FDA to require diabetes warning on antipsychotics. *Psychiatric News*. 2003;38:1.
2. Show 28: warning about hyperglycemia and atypical antipsychotic drugs [webcast]. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=28. *FDA Safety News*. June, 2004.
3. Janssen Pharmaceutica Inc. Risperdal (risperidone) revised label. Washington, DC: US Food and Drug Administration, Medwatch; 2003.
4. Pfizer. Geodon (ziprasidone): Dear Healthcare Practitioner letter, August 2004. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm154977.htm#. Accessed November 28, 2005.
5. American Diabetes Association, American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *J Clin Psychiatry*. 2004;65(2):267-272.
6. Newcomer JW, Hennekens CH. Severe mental illness and risk of cardiovascular disease. *JAMA*. 2007;298(15):1794-1796.
7. Marder SR, Essock SM, Miller AL, Buchanan RW, Casey DE, Davis JM, Kane JM, Lieberman JA, Schooler NR, Covell N, Stroup S, Weissman EM, Wirshing DA, Hall CS, Pogach L, Pi-Sunyer X, Bigger JT Jr, Friedman A, Kleinberg D, Yevich SJ, Davis B, Shon S. Physical health monitoring of patients with schizophrenia. *Am J Psychiatry*. 2004;161(8):1334-1349.
8. van Winkel R, van Os J, Celic I, Van Eyck D, Wampers M, Scheen A, Peuskens J, De Hert M. Psychiatric diagnosis as an independent risk factor for metabolic disturbances: results from a comprehensive, naturalistic screening program. *J Clin Psychiatry*. 2008;69(8):1319-1327.
9. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs*. 2005;19(suppl 1):1-93.
10. McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L, Meltzer HY, Hsiao J, Scott Stroup T, Lieberman JA. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res*. 2005;80(1):19-32.
11. Goff DC, Cather C, Evins AE, Henderson DC, Freudenreich O, Copeland PM, Bierer M, Duckworth K, Sacks FM. Medical morbidity and mortality in schizophrenia: guidelines for psychiatrists. *J Clin Psychiatry*. 2005;66(2):183-194.
12. Frayne SM, Halanych JH, Miller DR, Wang F, Lin H, Pogach L, Sharkansky EJ, Keane TM, Skinner KM, Rosen CS, Berlowitz DR. Disparities in diabetes care: impact of mental illness. *Arch Intern Med*. 2005;165(22):2631-2638.
13. Morrato EH, Newcomer JW, Allen RR, Valuck R. Prevalence of baseline serum glucose and lipid testing in users of second-generation antipsychotic drugs: a retrospective, population-based study of Medicaid claims data. *J Clin Psychiatry*. 2008;69(2):316-322.
14. Hsu C, Ried LD, Bengtson MA, Garman PM, McConkey JR, Rahnavard F. Metabolic monitoring in veterans with schizophrenia-related disorders and treated with second-generation antipsychotics: findings from a Veterans Affairs-based population. *J Am Pharm Assoc (2003)*. 2008;48(3):393-400.
15. Haupt DW, Rosenblatt LC, Kim E, Baker RA, Whitehead R, Newcomer JW. Prevalence and predictors of lipid and glucose monitoring in commercially insured patients treated with second-generation antipsychotic agents [published online ahead of print January 15, 2009]. *Am J Psychiatry*. 2009;166(3):345-353.
16. Morrato EH, Newcomer JW, Kamat S, Baser O, Harnett J, Cuffel B. Metabolic screening before and after the ADA Consensus Statement on antipsychotic drugs and risk of diabetes and dyslipidemia [abstract]. *Diabetes*. 2008;57(suppl 1):A3946.
17. Zuvekas SH. Prescription drugs and the changing patterns of treatment for mental disorders, 1996-2001. *Health Aff (Millwood)*. 2005;24(1):195-205.
18. Ma J, Vaillancourt R, Boddam R, Auger S, Sampalis J. Association between antidepressant use and prescribing of gastric acid suppressants. *Can J Psychiatry*. 2006;51(3):178-184.
19. Clinical classifications software (CCS) for ICD-9-CM fact sheet. Agency for Healthcare Research and Quality, Healthcare Cost and Utilization Project (HCUP) Web site. http://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccsfactsheet.jsp. Accessed August 1.
20. American Diabetes Association. Standards of medical care in diabetes: 2007. 2007; 30(suppl 1):S4-S41.
21. Rifas-Shiman SL, Forman J, Lane K, Caspard H, Gillman M. Diabetes and lipid screening among patients in primary care: a cohort study. *BMC Health Serv Res*. 2008;8:25.
22. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther*. 2002;27(4):299-309.
23. Sikka R, Xia F, Aubert RE. Estimating medication persistency using administrative claims data. *Am J Manag Care*. 2005;11(7):449-457.
24. Parsons LS. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. Paper presented at: 26th Annual SAS Users Group International Conference; April 2001; Cary, NC.
25. Baser O. Too much ado about propensity score models? comparing methods of propensity score matching. *Value Health*. 2006;9(6):377-385.
26. Buckley PF, Miller DD, Singer B, Arena J, Stirewalt EM. Clinicians' recognition of the metabolic adverse effects of antipsychotic medications. *Schizophr Res*. 2005; 79(2-3):281-288.
27. Suppes T, McElroy SL, Hirschfeld R. Awareness of metabolic concerns and perceived impact of pharmacotherapy in patients with bipolar disorder: a survey of 500 US psychiatrists. *Psychopharmacol Bull*. 2007;40(2):22-37.
28. Rogers EM. *Diffusion of Innovations*. 5th ed. New York, NY: Free Press; 2003.
29. Libby AM, Brent DA, Morrato EH, Orton HD, Allen R, Valuck RJ. Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs. *Am J Psychiatry*. 2007;164(6):884-891.
30. Morrato EH, Libby AM, Orton HD, Degruy FV III, Brent DA, Allen R, Valuck RJ. Frequency of provider contact after FDA advisory on risk of pediatric suicidality with SSRIs. *Am J Psychiatry*. 2008;165(1):42-50.
31. Ketter TA, Haupt DW. Perceptions of weight gain and bipolar pharmacotherapy: results of a 2005 survey of physicians in clinical practice. *Curr Med Res Opin*. 2006;22(12):2345-2353.
32. Druss BG, Marcus SC, Campbell J, Cuffel B, Harnett J, Ingoglia C, Mauer B. Medical services for clients in community mental health centers: results from a national survey. *Psychiatr Serv*. 2008;59(8):917-920.