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Racial-Ethnic Differences in Incident Olanzapine Use After an FDA Advisory for Patients With Schizophrenia

Dr. Stacie B. Dusetzina, Ph.D., **Dr. Benjamin L. Cook, Ph.D., M.P.H.**, **Dr. Alisa B. Busch, M.D., M.S.G.**, **Dr. Caleb Alexander, M.D., M.S.**, and **Dr. Haiden A. Huskamp, Ph.D.**
Dr. Dusetzina and Dr. Huskamp are affiliated with the Department of Health Care Policy and Dr. Cook and Dr. Busch are with the Department of Psychiatry, all at Harvard Medical School, 180 Longwood Ave., Boston, MA 02115. Dr. Cook is also with the Center for Multicultural Mental Health Research, Cambridge Health Alliance, Cambridge, Massachusetts. Dr. Busch is also with the Alcohol and Drug Abuse Treatment Program, McLean Hospital, Belmont, Massachusetts. Dr. Alexander was with the Department of Psychiatry, University of Chicago, for the study and is now with the Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, and Department of General Internal Medicine, Johns Hopkins University School of Medicine, Baltimore

Stacie B. Dusetzina: dusetzina@hcp.med.harvard.edu

Abstract

Objective—Prior investigations suggest that olanzapine use declined rapidly after a U.S. Food and Drug Administration (FDA) communication and consensus statement warning of the drug's increased metabolic risks, but whether declines differed by racial-ethnic groups is unknown.

Methods—Changes in olanzapine use over time by race-ethnicity was assessed among 7,901 Florida Medicaid enrollees with schizophrenia.

Results—Prior to the advisory, 57% of second-generation antipsychotic fills among Hispanics were for olanzapine, compared with 40% for whites or blacks (adjusted risk difference [ARD]=.17, 95% confidence interval [CI]=.13–.20). Olanzapine use declined among all racial-ethnic groups. Although Hispanics had greater olanzapine use than whites in each period, the differences in absolute risk were only 3% by the latest study period (ARD=.03, CI=.01–.04).

Conclusions—After the FDA communication and consensus statement were issued, differences in olanzapine use between white and Hispanic enrollees narrowed considerably. Identifying high-use subgroups for targeted delivery of drug safety information may help eliminate any existing differences in prescribing.

In late 2003 the U.S. Food and Drug Administration (FDA)issued a class-wide warning on all second-generation antipsychotics about increased risks of developing hyperlipidemia and diabetes. Soon thereafter, a consensus statement was published in which agents were stratified into high (olanzapine and clozapine), intermediate (risperidone and quetiapine), and low (aripiprazole and ziprasidone) metabolic risk (1). Prior evaluations of the FDA advisory and consensus statement have focused on the impact on metabolic screening rates and suggest only small and temporary impacts of the advisories. However, two prior

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investigations of Medicaid populations suggest that there were substantial decreases in use of olanzapine, an agent with high metabolic risk, after publication of the advisory and consensus statement (2,3).

Prior evidence suggests that there are racial-ethnic differences in antipsychotic prescribing, including whether a patient receives any antipsychotic or which patients receive newer versus older antipsychotic therapies (4–6). There is also evidence in the general medical literature that patients from minority groups are more likely than white patients to receive care from providers with poorer clinical training and access to resources (7,8). Minority-serving providers may thus be less aware of important risk information, and disparities could increase as a result. It remains unclear whether or how existing racial-ethnic differences in treatment utilization might change after publication of safety information related to a specific drug. No prior studies have examined whether there are racial-ethnic differences in the response to new information about the comparative benefits or harms of a treatment. We sought to assess racial-ethnic differences in incident olanzapine use among Medicaid enrollees with schizophrenia after publication of an FDA advisory and consensus statement that highlighted the risks of olanzapine over other second-generation agents.

Methods

We used inpatient, outpatient, and pharmacy claims from the Florida Medicaid program for fiscal years 2001–2006. This study received a waiver from the Harvard Medical School Institutional Review Board.

We included Medicaid enrollees with at least one second-generation antipsychotic fill (for olanzapine, quetiapine, risperidone, ziprasidone, or aripiprazole) between January 1, 2001, through December 31, 2006. We defined the first fill date during this period as the enrollee's index prescription-fill date. We measured incident antipsychotic use during six time segments based on the timing of relevant publications, media reports, FDA regulatory activities, and Florida Medicaid policy changes. [A table outlining the time frames is available online as a data supplement to this report.]

We restricted the cohort to adults ages 18–64 not dually enrolled in Medicare or a managed care plan because such enrollment would mean we would lack access to their complete service utilization records. We identified enrollees as having schizophrenia if they had at least one inpatient or two outpatient claims indicating schizophrenia (*ICD-9-CM* code 295.x). To assess prior diagnoses that might influence an enrollee's likelihood of receiving olanzapine, we required enrollees to have continuous Medicaid enrollment for six months before their index date. Finally, we restricted the sample to incident antipsychotic users, excluding those with an antipsychotic fill in the 180 days prior to their index fill date.

We assessed the likelihood of initiating olanzapine versus any other second-generation antipsychotic agent among new second-generation antipsychotic users. We coded race-ethnicity as white, black, or Hispanic using Florida Medicaid enrollment files. We excluded individuals identified as "American Indian" or "Asian" because of small samples (<1%), and we excluded the 14.7% of enrollees classified as "other race" to avoid racial-ethnic misclassification.

We assessed racial-ethnic differences by implementing the Institute of Medicine (IOM) definition of health care disparity, which states that service use comparisons by race and ethnicity should adjust for racial-ethnic differences in need for services (9–11). The implementation followed a three-step process: first, using all available covariates, we estimated a regression model that best fit the data; second, we balanced racial-ethnic groups on characteristics that would influence clinical decision making for prescribing olanzapine

rather than an alternative second-generation antipsychotic (hereafter called “need” variables); and third, we estimated predictions by using coefficients from the first step to adjust values from the second step.

To complete the first step, we used modified Poisson regression models to estimate changes in olanzapine use among incident users after the advisory, estimating generalized linear models within Stata with a Poisson distribution and log link. Covariates were split into need and non-need variables. Need variables, measured in the six months before the enrollee’s index prescription-fill date, were age, inpatient mental health services use, and prior diagnoses of metabolic-related conditions and comorbid mental health conditions that could affect antipsychotic selection, complicate the treatment of schizophrenia, or indicate a specific treatment. [Programmatic definitions of covariates are provided online in a data supplement to this report.] Non-need variables were Medicaid eligibility category (Supplemental Security Income [SSI] or “other”), Medicaid district (districts 1–11, representing Medicaid-defined geographical areas within Florida), sex, and whether the enrollee was receiving care from a psychiatrist. Second, we used a rank-and-replace method (11) to equalize need across racial-ethnic groups, allowing us to match the health care needs and preferences of black and Hispanic enrollees to those of white enrollees. Third, we calculated, using the coefficients and non-need values from the original regression model and the adjusted need covariate values, the predicted risk of receiving olanzapine for each individual from a racial-ethnic minority group.

In sensitivity analyses we compared the IOM-concordant racial-ethnic differences described above with estimates of differences both with and without adjustment for all available covariates. First, we compared the unadjusted means between racial-ethnic groups. Second, we estimated the residual direct effect (RDE) of race-ethnicity. The RDE model implicitly defines a disparity as the residual racial-ethnic difference remaining after adjustment for all observable factors. Next, to test the robustness of the IOM model estimates with our selection of need-based covariates, we estimated separate models. In the first, age was excluded, and in the second, the enrollee’s sex and receipt of care from a psychiatrist before the incident drug fill were included as need-based predictors. Finally, we restricted the IOM analyses to individuals receiving Medicaid through SSI to account for differences in severity by eligibility category. We also separately restricted analyses to individuals who were not previously hospitalized to avoid misclassification of the incident prescription because medications initiated within the hospital are not observable in Medicaid claims.

Results

Our sample included 7,901 new users of a second-generation antipsychotic. Of the incident users, 45% (N=3,532) were white, 32% (N=2,518) were black, and 23% (N=1,851) were Hispanic. From the preadvisory period through the most recent study period, we observed large differences in incident olanzapine use among Hispanics compared with whites (Table 1). [Differences are also shown in a figure available as a data supplement to this report.] Before the advisory and consensus statement publication, approximately 57% (N=757) of incident second-generation antipsychotic fills among Hispanics were for olanzapine, compared with only 40% for whites (N=1,050) or blacks (N=737). The absolute difference in the risk of receiving olanzapine between white and Hispanic second-generation antipsychotic initiators was 17% during the preadvisory period (adjusted risk difference [ARD]=.17, 95% confidence interval [CI]=.13–.20). Olanzapine use declined among all groups over each subsequent time point. By the initial postadvisory period, olanzapine was initiated for only 17% of black (N=32) or white (N=38) and for 24% of Hispanic (N=32) users of second-generation antipsychotic medication.

Although the likelihood of receiving olanzapine declined significantly among all second-generation antipsychotic initiators, the relative risk of receiving olanzapine declined only slightly over the study period. For example, Hispanics were 41% more likely than whites to receive olanzapine during the preadvisory period, and an increased relative risk was observed over the study period. However, by the latest study period, the absolute difference in risk was only 3% between white and Hispanic enrollees. There were no differences between whites and blacks in the likelihood of receiving olanzapine over any period studied.

Unadjusted model estimates were similar to those generated with the IOM-concordant method, which adjusted for need variables. In the unadjusted model, Hispanics had a 16% absolute difference in the risk of receiving olanzapine in the preadvisory period compared with whites (risk difference=.16, CI=.13–.19). In the initial postadvisory period, the risk difference was 7% (risk difference=.07, CI=.03–.11).

Estimates of the residual direct effect of race show more modest differences between whites and Hispanics. Using this model, we found that the risk of receiving olanzapine was only 49% for Hispanics and 40% for whites during the preadvisory period. This resulted in an absolute risk difference of approximately 8% (ARD=.08, CI=.05–.11). As in the IOM-concordant method, olanzapine use declined among each racial-ethnic group over each subsequent period. However, the magnitude of the difference in risk between whites and Hispanics was smaller and was not statistically significant in the post-advisory periods.

Results from models using the two-alternative specification of clinical need, described previously, were largely unchanged, suggesting that the IOM-concordant method was robust to potential misspecification. In addition, sensitivity analyses restricted to individuals with SSI coverage and analyses restricted to individuals without a history of in-patient treatment were consistent with our primary analysis, although differences between groups without prior hospitalizations were more modest.

Discussion

In this sample of new second-generation antipsychotic users diagnosed as having schizophrenia, Hispanics were more likely than whites to receive olanzapine. Absolute differences were greatest in the preadvisory period and decreased over time, resulting in small absolute differences in the risk of receiving olanzapine between groups during the most recent time points. However, the relative risk of olanzapine use was similar for Hispanics and whites at each time point, suggesting that recommendations were applied uniformly across racial-ethnic groups. Although similarity across racial-ethnic groups is encouraging, this finding also suggests that targeted efforts to further reduce use among persons from racial-ethnic minority groups may help to close the gap between white and nonwhite medication users when differences in pre-advisory medication use exist.

There are several potential explanations for our findings that Hispanics were more likely than whites to receive olanzapine. First, some evidence suggests that Hispanic patients may be less likely than whites to adhere to antipsychotic treatments (12). Because olanzapine has a lower rate of discontinuation compared with other anti-psychotic agents (13), it might be preferred as a first-line treatment among patients considered at higher risk of discontinuation and nonadherence. Moreover, the physician’s assessment of illness severity and likelihood of adherence may be complicated by language or cultural barriers, potentially resulting in physicians relying on olanzapine as a primary treatment among nonnative English speakers.

Although we observed large declines in olanzapine use among all racial-ethnic groups, the metabolic risk advisory is likely only responsible for a portion of this reduction in use. Several major marketing, policy, and clinical information changes occurred after the

advisory period (specifically, a classwide black-box warning, publication of the Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE] trial [13], and a temporary change in Florida Medicaid policy), each of which may have affected drug utilization. In addition, although the decrease in olanzapine use in the early postadvisory period would suggest improved quality of care, this interpretation is less clear after the publication of the CATIE trial (where, compared with other treatments, olanzapine was associated with a longer period until discontinuation).

We found that the magnitude, and in some cases the significance, of the differences in olanzapine use varied by the method used to define racial-ethnic disparities. The primary difference between these models is that the IOM-concordant method allows for disparities estimates to include geographic differences or differences mediated by socioeconomic status, whereas the RDE model explicitly removed the influences of these factors from the racial-ethnic disparity estimate. Differences in effects estimated between these two methods suggest that socioeconomic and geographic factors may play an important role.

There were large imbalances in geographic distribution of racial-ethnic minority group enrollees within the Florida Medicaid districts. For example, approximately 85% of the Hispanic enrollees lived within one district, whereas black and white enrollees were distributed more evenly across districts. [A table showing distribution by district is available online as a data supplement to this report.] The observed differences between the risk differences and IOM-concordant estimates may be due to differences in practice patterns by district. For example, if Hispanic patients are more likely to receive care from only a few providers within a region, the differences observed may be concentrated within clinics or by physician and not widespread. If this is the case, targeting clinics serving a high percentage of minority groups may help to eliminate differences in prescribing patterns where they exist. Debate continues about whether geographic differences in prescribing or health services use should be considered in analyses of racial-ethnic disparities (9,14); nevertheless, we found that racial-ethnic prescribing differences existed even after analyses controlled for geographic variation.

Our study had several limitations. First, our sample consisted of fee-for-service Medicaid enrollees from a single state. However, Florida Medicaid provides services to one of the largest Hispanic populations in the United States, and our results are consistent with other work examining patterns of second-generation antipsychotic use among Hispanics, blacks, and whites (15).

Second, our selection of need-based variables was largely based on judgments regarding patient need. In the case of antipsychotics, metabolic conditions and disease severity can guide clinicians' agent selection within the class. However, some variables may influence prescribing decisions even where evidence of relative benefits is lacking. Because this process is subjective, we modified the need-based variables definition in sensitivity analyses and found that our estimates were robust to changes in model specification.

Third, an ascertainment bias (for example, if persons from racial-ethnic minority groups are less likely to receive treatment for metabolic-related conditions) might influence our model estimates. However, we found little evidence of such a bias, given that racial-ethnic minority groups in our sample had higher rates of metabolic conditions than whites. Fourth, categorization of Hispanic ethnicity was based on Medicaid enrollment files, and details regarding culture of origin were not available. It will be important for future work in this area to identify Hispanic cultural differences in prescribing and the role of patient preferences in medication use decisions.

Fifth, although patient preferences should be measured and included in the IOM disparities estimate, we are unable to measure these in Medicaid claims. Although this remains a limitation of our study, patient preferences are more likely to influence initiation of pharmacotherapy as opposed to agent selection, which we studied in this analysis. Finally, this study focused on second-generation antipsychotic agent switching in response to the metabolic risk messages, but physicians might have used other strategies for managing metabolic risks. Future research is needed to explore the fuller array of management strategies that providers may use to address metabolic risks for patients who are taking antipsychotic medications.

Conclusions

Our findings suggest that even among individuals receiving the same class of therapies, there may be clinically important differences in individual agent use. An important finding was that although there were large declines in olanzapine use among all racial-ethnic subgroups, statistically significant differences in the use of olanzapine were observed even after the FDA advisory and consensus statement were published. This study highlights the importance of communication and dissemination of drug safety information, specifically to underserved and vulnerable populations. As the nation moves toward evaluating and making treatment recommendations based on the relative benefits or harms of available treatments, it will be important to monitor the adoption of these recommendations across diverse patient populations.

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Table 1

Analyses of racial-ethnic differences in use of antipsychotic agents with high metabolic risk after a U.S. Food and Drug Administration advisory

	Risk of receiving olanzapine			Black versus white		Hispanic versus white	
Estimate of olanzapine use over time[a]	**White**	**Black**	**Hispanic**	**Risk difference**	**95% CI**	**Risk difference**	**95% CI**
Institute of Medicine definition of health care disparity (rank-and-replace method)							
Preadvisory period (Jan 2001–Jan 2003)	.40	.40	.57	.00	−.03 to .03	.17	.13 to .20
Early advisory period (Feb 2003–Nov 2003)	.35	.35	.49	−.01	−.03 to .02	.14	.11 to .17
Advisory period (Dec 2003–Aug 2004)	.25	.25	.35	.00	−.02 to .02	.10	.08 to .12
Initial postadvisory period (Sept 2004–Mar 2005)	.17	.17	.24	.00	−.02 to .01	.07	.05 to .08
PDL/CATIE/dementia warning (April 2005–Sept 2005)	.08	.08	.11	.00	−.01 to .00	.03	.02 to .04
Post-PDL/CATIE/dementia warning (Oct 2005–Dec 2006)	.07	.07	.09	.00	−.00 to .00	.03	.01 to .04
Unadjusted estimate							
Preadvisory period (Jan 2001–Jan 2003)	.41	.40	.56	.00	−.03 to .02	.16	.13 to .19
Early advisory period (Feb 2003–Nov 2003)	.35	.35	.49	.00	−.03 to .03	.14	.11 to .17
Advisory period (Dec 2003–Aug 2004)	.25	.25	.35	.00	−.03 to .03	.10	.07 to .13
Initial postadvisory period (Sept 2004–March 2005)	.17	.17	.24	.00	−.03 to .03	.07	.03 to .11
PDL/CATIE/dementia warning (April 2005–Sept 2005)	.08	.08	.11	.00	−.03 to .03	.03	.00 to .06
Post-PDL/CATIE/dementia warning (Oct 2005–Dec 2006)	.07	.07	.09	.00	−.03 to .03	.03	−.01 to .06
Residual direct effect definition							
Preadvisory period (Jan 2001–Jan 2003)	.40	.39	.49	−.01	−.04 to .02	.08	.05 to .11
Early advisory period (Feb 2003–Nov 2003)	.35	.34	.42	−.01	−.05 to .02	.06	.03 to .11
Advisory period (Dec 2003–Aug 2004)	.25	.24	.30	−.01	−.04 to .03	.05	.02 to .08
Initial postadvisory period (Sept 2004–March 2005)	.17	.17	.21	−.01	−.04 to .03	.03	−.01 to .07
PDL/CATIE/dementia warning (April 2005–Sept 2005)	.08	.08	.09	.00	−.04 to .03	.01	−.02 to .05
Post-PDL/CATIE/dementia warning (Oct 2005–Dec 2006)	.07	.06	.08	.00	−.03 to .03	.01	−.02 to .05

[a]PDL/CATIE, temporary implementation of a preferred drug list (PDL) in Florida Medicaid (July 2005) and the publication of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) results