Excessive Antipsychotic Dosing in 2 U.S. State Hospitals

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Background: This retrospective study attempted to replicate the observation that African Americans are more prone to receive excessive doses of antipsychotics, even after variables that have not been well explored in previous studies (smoking and antipsychotic potency) are controlled for.

Method: The populations of 2 neighboring U.S. state hospitals, which were screened for patients who smoked, were included. The total sample comprised 316 patients from the first hospital (surveyed in 1990) and 447 patients from the second hospital (surveyed in 1992) who were taking antipsychotics and were either African American or white. An excessive antipsychotic dose (greater than 1000 mg of chlorpromazine equivalents per day) was the dependent variable in logistic regressions in all patients and in those patients with or without (DSM-III-R) schizophrenia.

Results: In the total sample from both hospitals, excessive dosing was associated with schizophrenia, age under 56 years, long hospitalization duration, high-potency antipsychotics, second hospital, and depot antipsychotics. The odds of being prescribed excessive doses of typical antipsychotics were 1.8 times higher for African American than for white schizophrenic patients. African American race in schizophrenic patients appeared to be associated with the prescription of high-potency antipsychotics and with excessive dosing of this type of antipsychotic. Excessive dosing did not appear to be associated with race in nonschizophrenic patients nor in schizophrenic patients taking low-potency antipsychotics.

Conclusion: Pharmacogenetic differences are not likely to explain this racial difference in prescription of excessive dosing of high-potency antipsychotics, which suggests that clinician attitudes may be a possible explanation. In future studies, pharmacogenetic tests and control for confounding factors, such as smoking, will help to establish whether racial differences in dosing are influenced by different metabolic capacities or physician biases.

(J Clin Psychiatry 2002;63:998–1003)

Received June 25, 2001; accepted April 10, 2002. From the Mental Health Research Center at Eastern State Hospital, Lexington, Ky.

The authors have no affiliations or relationships with any organization that can be considered a conflict of interest. The original collection of data was supported by internal resources. Dr. Diaz is an Associate Instructor of Statistics at the Universidad Nacional de Colombia, Medellín, Colombia. His collaboration in the statistical analyses of this article was supported by a grant (to Dr. de Leon) from the Kentucky Department of Mental Health and Mental Retardation to the Department of Psychiatry of the University of Kentucky through the University Collaboration Project.

For acknowledgments and a complete list of those who helped with data collection, please see original publications (Am J Psychiatry 1995;152:453–455 and Schizophr Res 2002;56:55–65). A blinded reviewer helped the authors to present a more balanced view of the results.

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The Patient Outcomes Research Team (PORT) recommended doses of antipsychotic medication for schizophrenia at between 300 and 1000 chlorpromazine equivalents.[1] Lehman and Steinwachs' study of 179 inpatients found that African Americans were more likely than white patients to be prescribed higher doses.[2] Walkup and coworkers[3] studied 293 inpatients from 4 hospitals. After correcting for other factors using logistic regression, they observed that the odds of African American patients receiving doses higher than 1000 chlorpromazine equivalents were significantly higher (2.7 times) than those for white patients. After correcting for the use of depot antipsychotics, the odds were 2.2 times higher, but not significant. Furthermore, the authors acknowledge that the effect of smoking and other enzyme inducers was not controlled for in their analyses.

Before the PORT recommendations, Segal and coworkers[4] described that African American patients received higher doses of antipsychotics relative to other patients. On the basis of their results, the authors stressed the importance of making efforts to engage African American patients in the treatment process and of communicating with patients to eliminate cultural distances. The effect of enzyme inducers was not controlled for in their study.

When using a pharmacokinetic approach to dosing, it can be argued that in special circumstances (including high weight and rapid metabolism), high doses may be appropriate. Thus, the presence of enzymatic inducers such as tobacco smoking and antiepileptics use may sometimes explain the use of high doses. Tobacco smok-

ing is an inducer of cytochrome P450 1A2 (CYP1A2) and glucuronidation enzymes,[5] so higher doses of many antipsychotics are required for smokers. Similarly, some antiepileptics such as phenytoin and carbamazepine induce CYP3A and glucuronidation enzymes.[6] However, no studies exploring the issue of antipsychotic dosing and race have controlled for smoking or the use of other enzymatic inducers.

The present retrospective study attempted to replicate the observation that African Americans are more prone than whites to receive high doses of antipsychotics. Some unexplored variables such as high weight, smoking, and antiepileptic use were statistically controlled for. A large sample that combined 2 state hospital surveys was used. These surveys focused on tobacco smoking and have already been published.[7,8] A preliminary analysis of the data of the first of the 2 hospitals appeared in an abstract,[9] reporting a significant association between excessive dosing and African American race in a univariate analysis that did not control for the effect of potential confounding variables.

METHOD

Subjects and Variables

Two state hospitals serving Philadelphia, Pa., and the surrounding counties were screened for patients who smoked. Their catchment areas did not overlap and included different counties. All 360 patients from the first hospital were surveyed in 1990,[7] and 649 cooperative patients from the second hospital were surveyed in 1992.[8]

Since we were interested in comparing African American patients with white patients, 11 Hispanic subjects and 4 subjects from other minorities were excluded from analyses. Subjects with incomplete information were also excluded, and only those patients who had been prescribed antipsychotics at the time of the survey were included in analyses. Thus, the final sample sizes utilized in the analyses presented in this article were 316 patients from the first hospital and 447 patients from the second hospital.

Table 1 describes the samples and variables used in univariate and multivariate analyses. All variables were dichotomous, which is convenient for calculating odds ratios (ORs). Following the PORT recommendation,[1] an excessive antipsychotic dose was defined as a dose greater than 1000 mg of chlorpromazine equivalents per day. Chlorpromazine equivalents were calculated using a table.[10] When compared with 100 chlorpromazine equivalents per day, those antipsychotics with equivalent doses lower than 8 mg/day were considered high-potency antipsychotics.[10] At the time of the study, only typical antipsychotics were being prescribed at these 2 hospitals. Clinical DSM-III-R diagnoses were taken from the charts. As was done before, the diagnoses were divided into schizophrenic (schizophrenic or schizoaffective, 78%) and nonschizophrenic categories (22%).

Table 1. Description of Variables for Total Patient Sample

	First Hospital (N = 316)		Second Hospital (N = 447)	
Variable	N	%	N	%
Excessive antipsychotic dosing (> 1000 mg of chlorpromazine equivalents per day)	67	21	141	32
Schizophrenia	225	71	370	83
African American	56	18	135	30
Male	200	63	293	66
Old age (≥ 56 y)	41	13	119	27
High weight (> 90 kg [> 198 lb])	49	16	91	20
Smoking	257	81	327	73
Long hospitalization (≥ 3 y)	165	52	200	45
Depot antipsychotics	48	15	59	13
High-potency antipsychotics	193	61	220	49
Carbamazepine or phenytoin	35	11	92	21

Statistics

Schizophrenic and nonschizophrenic patients were analyzed separately. The association between excessive antipsychotic dosing and the variables of African American race, smoking, old age, hospital, gender, long hospitalization, high weight, depot and high-potency antipsychotics, and treatment with carbamazepine or phenytoin (Table 1) was examined. Odds ratios computed from 2-way cross tabulations for univariate analyses and from logistic regressions for multivariate analyses were used to measure associations between variables. Excessive antipsychotic dosing was the dependent variable in logistic regressions. The advantage of logistic regression is that the OR corresponding to an association between excessive antipsychotic dosing and a variable is adjusted for the effect of the other variables in the logistic model. Ninety-five percent confidence intervals (CIs) for ORs were computed.

To assess the impact of the high potency variable on the association between excessive antipsychotic dosing and African American race, logistic regression analyses not including the high potency variable as an independent variable were further carried out. The Statistical Package for Social Sciences, version 7.5, was used for calculations.[11] The Hosmer-Lemeshow goodness-of-fit test was used to test the fitness of the logistic models. All models fit well.

An additional multivariate analysis was performed using the total sample (schizophrenic and nonschizophrenic patients together). This time, the diagnosis of schizophrenia was also included as an independent variable in the logistic model. There was no significant association between diagnosis and race ($\chi^2 = 0.7$, df = 1, p = .41).

All analyses were repeated using high dose of chlorpromazine after controlling for weight. In this set of

analyses, a high dose was defined as a dose greater than 14.3 mg/kg/day (which corresponds to 1000 mg of chlorpromazine equivalents in an average subject of 70 kg [154 lb]). Results from these analyses are not reported since they were essentially the same as those for the excessive antipsychotic dosing without dividing by weight.

RESULTS

Univariate Analyses for Patients With Schizophrenia

Among patients with schizophrenia, 41% (62/153) of African Americans versus 27% (120/442) of whites received excessive antipsychotic dosing. Thus, the odds of being prescribed excessive doses of antipsychotics were 1.8 times higher in African American schizophrenic patients than in white schizophrenic patients. Smoking, age lower than 56 years, depot antipsychotics, the second hospital, and high-potency antipsychotics were also significantly associated with excessive antipsychotic dosing in this population.

Multivariate Analysis for Patients With Schizophrenia

In the model that did not include high-potency antipsychotics as an independent variable, African American race was associated with excessive antipsychotic dosing ($\chi^2 = 4.3$, df = 1, p = .04). Smoking, age lower than 56 years, depot antipsychotics, and second hospital were also associated with excessive dosing in patients with schizophrenia (Table 2). When high-potency antipsychotics were included, the association between African American race and excessive antipsychotic dosing was no longer significant ($\chi^2 = 2.0$, df = 1, p = .16). Smoking, age lower than 56 years, depot antipsychotics, and second hospital continued to be significant.

Univariate Analyses for Nonschizophrenic Patients

Among nonschizophrenic patients, 24% (9/38) of African Americans versus 13% (17/130) of whites received excessive antipsychotic dosing. The difference between these 2 percentages was not significant ($\chi^2 = 2.5$, df = 1, p < .11). Depot antipsychotics, second hospital, and high-potency antipsychotics were significantly associated with excessive antipsychotic dosing in the nonschizophrenic population.

Multivariate Analysis for Nonschizophrenic Patients

Among nonschizophrenic patients, African American race was not significantly associated with excessive antipsychotic dosing ($\chi^2 = 0.42$, df = 1, p = .52). In contrast to schizophrenic patients, exclusion of the high potency variable from the logistic regression model did not yield a significant association between African American race and excessive dosing. Variables associated with excessive antipsychotic dosing in the nonschizophrenic population were depot antipsychotics (OR = 8.7, 95% CI = 2.6 to 29.4, p < .001), second hospital (OR = 4.3, 95% CI = 1.4 to 12.7, p = .009), and high-potency antipsychotics (OR = 3.6, 95% CI = 1.2 to 11.2, p = .02); smoking was not significantly associated with excessive antipsychotic dosing.

Table 2. Logistic Regression Analyses of Excessive Antipsychotic Dosing in Patients With Schizophrenia in 2 State Hospitals (N = 595)

	Not Including High-Potency Antipsychotics[a]		Including High-Potency Antipsychotics[b]	
Variable	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
African American	1.55*	1.02 to 2.34	1.35	
Smoking	1.85*	1.11 to 3.06	1.91*	1.13 to 3.22
Old age (≥ 56 y)	0.56*	0.33 to 0.95	0.43*	0.24 to 0.76
Depot antipsychotics	2.34*	1.45 to 3.76	2.08*	1.27 to 3.40
Second hospital	1.60*	1.07 to 2.41	2.31*	1.49 to 3.60
Male	1.13		1.11	
Long hospitalization	1.10		1.40	
High weight (> 90 kg [> 198 lb])	0.93		1.03	
Carbamazepine or phenytoin	1.19		1.20	
High-potency antipsychotics	…	…	4.24*	2.77 to 6.49

[a]Hosmer-Lemeshow goodness-of-fit test: $\chi^2 = 5.8$, df = 8, p = .7.
[b]Hosmer-Lemeshow goodness-of-fit test: $\chi^2 = 2.4$, df = 8, p = .9.
*Significant at p ≤ .05. Only significant confidence intervals are included in the table.

Multivariate Analyses for All Patients

Using all subjects (schizophrenics and nonschizophrenics together, N = 763), schizophrenia was significantly associated with excessive antipsychotic dosing (OR = 1.9, 95% CI = 1.1 to 3.1, p = .01). Other variables that were associated with excessive dosing were smoking, age lower than 56 years, long duration of hospitalization, high-potency antipsychotics, second hospital, and depot antipsychotics. African American race was not significantly associated with excessive antipsychotic dosing in the total sample ($\chi^2 = 2.6$, df = 1, p = .11). However, the association became significant when the high potency variable from the logistic model was excluded ($\chi^2 = 4.9$, df = 1, p = .03).

Excessive Dosing of High-Potency Antipsychotics in Schizophrenic African Americans

Our data suggest that complex interactions involving diagnosis, high-potency antipsychotics, and hospital may contribute to the association between African American race and excessive dosing. To analyze this interaction, schizophrenic patients were divided into 4 nonoverlapping groups corresponding to the 4 combinations of hospital and with/without high-potency antipsychotics. Four further logistic regressions were thus performed. A significant association was observed between African

American race and excessive antipsychotic dosing only among patients from the first hospital who were prescribed high-potency antipsychotics (controlling for other variables, OR = 2.4; 95% CI = 1.0 to 5.6, p = .04).

In schizophrenic patients taking high-potency antipsychotics in the second hospital, there was a nonsignificant trend of African American race being associated with excessive antipsychotic dosing (controlling for other variables, OR = 1.6; 95% CI = 0.8 to 3.2, p = .15). Without controlling for other variables, the trend was significant (OR = 2.0, 95% CI = 1.1 to 3.6, p = .03). In contrast, significant associations between race and high dose were not observed within schizophrenic patients not taking high-potency antipsychotics. When other variables were controlled for, the ORs were 1.0 (95% CI = 0.1 to 9.5, p = .97) in the first hospital and 0.6 (95% CI = 0.2 to 1.6, p = .33) in the second hospital. Therefore, our study suggests that schizophrenic African Americans in these 2 hospitals tended to be treated with higher doses of antipsychotics when prescribed high-potency antipsychotics.

Exploring whether African American race was associated with high-potency antipsychotic prescription was deemed appropriate, since the association between race and high doses appeared to be restricted to patients taking high-potency antipsychotics. In effect, schizophrenic African Americans appeared more likely to receive high-potency antipsychotics. Without controlling for other variables, the odds that an African American patient with schizophrenia was on high-potency antipsychotic treatment were 2.3 times higher than those for a white patient in the second hospital (95% CI = 1.0 to 5.3, p = .05) and 1.6 times higher in the first hospital (95% CI = 1.0 to 2.5, p = .04). The OR for the 2 hospitals together was 1.5 (95% CI = 1.0 to 2.2, p = .03).

There was a nonsignificant trend of African American race being associated with prescription of depot antipsychotics (without controlling for other variables, OR = 1.5; 95% CI = 0.9 to 2.4, p = .11 for the combined sample; p = .5 for the first hospital and p = .10 for the second hospital).

Lack of Excessive Dosing in Nonschizophrenic African Americans

To analyze a possible interaction between excessive dosing with race and antipsychotic potency, the nonschizophrenic sample was also divided into 4 nonoverlapping groups corresponding to the 4 combinations of hospital and with/without high-potency antipsychotics. Four logistic regressions were thus performed. Controlling for other variables, African American race was not significantly associated with high doses in any of the 4 groups (all p values > .4).

There was no association between African American race and high-potency antipsychotics in nonschizophrenic patients (without controlling for other variables, OR = 1.3; 95% CI = 0.6 to 2.7, p = .5; p = .2 for the first hospital and p = .8 for the second hospital).

Among nonschizophrenic patients, there was a nonsignificant trend of African American race being associated with prescription of depot antipsychotics (without controlling for other variables, OR = 2.4; 95% CI = 0.9 to 6.8, p = .08 for the combined sample; p = .4 for the first hospital and p = .1 for the second hospital).

DISCUSSION

Limitations and Strengths

This article examines prescription practices of some years ago. Thus, this study explored the hypothesis that in the early 1990s, African Americans received systematically higher doses of typical antipsychotics because of their racial background. It cannot be ruled out that some of the negative findings of this study may be due to an insufficient sample size, particularly in the nonschizophrenic group.

This study may be limited because of the lack of control for clinical variables. However, Walkup et al.[3] found that these variables were not significant after correcting for the effect of depot antipsychotics. Since this current study corrected for the effect of depot antipsychotics, the lack of control for clinical variables does not appear to be a serious limitation. Moreover, the effect of clinical variables was probably controlled for by the variable measuring long hospitalization.

This current study also took into account variables such as smoking, antiepileptics, high weight, and high-potency antipsychotics, none of which were studied by Walkup and coworkers.[3] In addition, we studied the issues of race and antipsychotic dosing in nonschizophrenic patients.

African American Race and Excessive Antipsychotic Dosing

Like Walkup and coworkers,[3] we found no evidence of a significant association between African American race and excessive dosing when controlling for other variables. The results suggest a complex picture. African Americans did not consistently receive high doses of antipsychotics. In nonschizophrenic patients and schizophrenic patients taking low-potency antipsychotics, race was not associated with excessive dosing. If one assumes that psychiatrists in these hospitals had racial preferences when prescribing high doses of antipsychotics, one expects that such racial preferences were manifested to all patients regardless of their diagnosis status, including nonschizophrenic patients.

Nonetheless, the results of patients taking high-potency antipsychotics very likely suggest that African American race may be associated with excessive dosing. Moreover, the prescription of high-potency antipsychotics appears to be associated with race.

Two main factors may explain racial differences in prescription: pharmacogenetic differences and/or clinician attitudes. An example of pharmacogenetic differences is that African Americans, as a group, appear to smoke less and have slower cotinine metabolism than whites, possibly due to differences in glucuronidation.[12] As discussed below, it is unlikely that excessive dosing of high-potency antipsychotics may be explained by pharmacogenetic metabolic differences. Therefore, this may suggest that a physician bias regarding the prescription of high-potency antipsychotics to African Americans may explain our results.

Pharmacogenetic Differences Do Not Appear to Explain Results

Cytochrome P450 2D6 (CYP2D6) appears to be the main metabolic pathway for most typical antipsychotics.[13–16] Ultrarapid metabolizers with multiple copies of an active CYP2D6 gene have recently been described to constitute 1% to 7% of whites in Europe.[17,18] It is believed that ultrarapid metabolizers will have subtherapeutic concentrations of CYP2D6 substrates when receiving "average" doses of these substrates.[19] In our experience in Lexington, Ky., the ultrarapid metabolizer frequencies in whites and African Americans are very similar (7% and 6%, respectively).[14] This suggests that racial differences in the use of high doses of CYP2D6 substrates may not be explained by differences in ultrarapid metabolizer frequencies. Future studies should include pharmacogenetic testing to eliminate the possibility of a metabolic difference[20,21] that may explain racial differences in prescription of high medication doses or the complex interactions that we found.

Clinician Attitudes

Extensive literature suggests that African Americans tend to be treated more frequently with higher doses and depot antipsychotics.[22,23] Studies in this area are difficult to conduct; cultural variables such as clinicians' biases and patients' beliefs and willingness to comply with treatment are not easy to measure. As discussed in the introduction, many excessive dosing studies may not have controlled for such confounding biological factors as smoking or comedication. As in prior literature,[22,23] our results suggest that clinician attitudes may contribute to the prescription of excessive antipsychotic doses in African American patients, at least in some groups of patients. Excessive dosing of high-potency antipsychotics may be another sign of the problems affecting severely mentally ill African Americans who have limited access to the mental health system or receive suboptimal treatment.[23] More recently, it has been suggested that African Americans may be less likely to receive atypical antipsychotics.[23]

Finally, we would like to point out that clinician biases are probably not homogenous and consistent across hospitals or individual psychiatrists. Our results are not suggestive of a generalized clinician bias, but suggest a bias with regard to African American schizophrenic patients treated with high-potency antipsychotics.

Other Factors Influencing Excessive Antipsychotic Dosing

Like Walkup and coworkers,[3] we found that some hospitals are more prone to use excessive doses than others. This suggests that "hospital cultures" may contribute to the use of high doses; this is an important finding that requires more research. Moreover, it suggests that "peer review" from psychiatrists from other hospitals that are not inclined to excessive dosing may be better than "peer review" by psychiatrists from within the same hospital who may also be used to excessive dosing.

This study suggested that schizophrenia may be associated with higher doses of antipsychotics. Additionally, schizophrenic smokers tended to receive higher doses of antipsychotics. In the first hospital, the mean ± SD chlorpromazine equivalents for schizophrenic smokers taking antipsychotics, 859 ± 720 mg/day, was nearly significantly higher than that for nonsmokers, 660 ± 630 mg/day ($z = 1.5$, 1-tailed $p = .07$). In the second hospital, the mean chlorpromazine equivalents for schizophrenic smokers, 1033 ± 801 mg/day, was significantly higher than that for nonsmokers, which was 782 ± 705 mg/day ($z = 2.7$, 1-tailed $p = .003$). Finally, the type of antipsychotic should be taken into account in studies about high doses. Both depot and high-potency antipsychotics tended to be prescribed in high doses. The odds of being prescribed excessive dosing were 8.8 times higher ($8.8 = 4.24 \times 2.08$, see Table 2) in schizophrenic patients taking high-potency depot antipsychotics than in schizophrenic patients taking neither depot nor high-potency antipsychotics.

Drug names: carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), phenytoin (Dilantin and others).

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