Patients With Schizophrenia at Risk for Excessive Antipsychotic Dosing

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Background: Patient Outcomes Research Team treatment recommendations were used to investigate the relationship between patient characteristics and higher-than-recommended dosages (> 1000 chlorpromazine equivalents [CPZe]) at discharge.

Method: Inpatients who met the DSM-IV criteria for schizophrenia or schizoaffective disorder were recruited from 4 general hospitals. For those patients (N = 293) prescribed antipsychotics at discharge, chi-square tests and multiple regression analyses were used to assess the relationship between demographics, admission characteristics, comorbid diagnoses, and antipsychotic dosages. The relationship between clinical symptoms and antipsychotic dosage at discharge was also examined.

Results: Antipsychotic dosages conformed to treatment guidelines for approximately 65% of patients; 21% received doses in excess of recommended levels. African American patients and those with a history of psychiatric hospitalization were more likely to be prescribed discharge antipsychotic doses greater than 1000 CPZe. Hospital differences in antipsychotic management were also observed. Regression analyses indicated that higher-than-recommended dosages found among African American patients could not be explained by differences in symptom levels at discharge. Patients with more thought disorder were also more likely to be prescribed antipsychotic dosages in excess of the recommended range. Compared with oral administration, depot administration increased the risk of excess dosage by a factor of 30. Controlling for method of administration reduced the impact of race to nonsignificance.

Conclusion: These results replicate earlier findings that minority individuals are more likely to be prescribed dosages in excess of the recommended range and suggest that this pattern is due to higher use of depot injection in African American patients. Further research should examine how patient characteristics and institutional factors influence medication use.

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There is accumulating evidence and growing concern about the quality of medication management in the treatment of schizophrenia.[1] One aspect of medication management that has received attention is the prescribed dose of antipsychotic medication.[2,3] Research to date indicates that, beyond a certain threshold, higher antipsychotic doses generally increase side effects without contributing to clinical improvement[4] and may increase the likelihood of patients' leaving the hospital against medical advice.[5] Although prior work has investigated associations between comparatively high antipsychotic dosages and various patient characteristics, such as comorbid substance abuse,[6] history of violence and persistent illness,[7] and female gender,[8] the recent publication of treatment recommendations of the Patient Outcomes Research Team (PORT)[9] now makes it possible to study excessive dosing more precisely. Recommendations stipulate that, for an acute episode of schizophrenia, the dosage of antipsychotic medication ought to fall between 300 and 1000 chlorpromazine equivalents (CPZe) per day, that it be continued for a minimum of 6 weeks, and that the minimum effective dose be used.

In a study applying the PORT treatment recommendations to the treatment of a sample of 179 inpatients, Lehman and Steinwachs[10] found that approximately 37% of patients prescribed an antipsychotic fell outside the conformance criteria. Demographic characteristics did not influence whether a dosage fell within the recommended range, but among patients whose dosage fell outside the recommended range, minority (primarily African American) patients were more likely to be prescribed dosages in excess of the recommended range. The authors do

not speculate regarding the influences responsible for this pattern.

The present article seeks to replicate the findings of Lehman and Steinwachs,[10] as well as build on their findings. This report expands on findings to date in 4 ways. First, we examine prescribing practices at inpatient units in 4 general hospital sites over approximately 1 year; 4 sites yield a larger sample and enable us to compare sites. Second, we examine a broader set of potential correlates of excess dosages. These include not only patient characteristics, such as age, sex, weight, and race, but also the clinical characteristics of admission status (voluntary vs. involuntary), presence of a comorbid condition (substance use or depression), evidence of dangerousness, and history of prior admission to a psychiatric hospital. Third, we assess whether subgroup differences in dosage levels are a function of differences in symptom level at hospital discharge. Fourth, we assess whether subgroup differences in dosage levels are associated with neuroleptic type (typical vs. atypical) or route of administration (depot vs. oral). On the basis of the prior findings, as well as other evidence suggesting that race sometimes influences psychiatric decision making,[11] it was predicted that, among patients whose discharge antipsychotic dose fell outside the recommended range, African American patients would be more likely to be prescribed an excess dosage. Examination of other variables, as well as their relationship to race, was exploratory rather than hypothesis driven.

METHOD

Data for this study were collected as part of the Rutgers Hospital and Community Survey, whose methods and objectives are detailed elsewhere and summarized here.[12] Subjects were 18- to 64-year-old, Medicaid-eligible or newly admitted Medicaid-receiving, English-speaking inpatients in 4 general hospitals with schizophrenia or schizoaffective disorder confirmed by Structured Clinical Interview for DSM-III-R (SCID; modified for DSM-IV)[13] who were free of serious medical illness.

Measures

Patient characteristics. Each patient's age, sex, weight, and race (white vs. African American) were assessed.

Clinical factors. The measure of substance abuse had 2 components. It required that the patient meet diagnostic criteria based on the Mini-International Neuropsychiatric Interview (MINI).[14] Additionally, since we were interested in the impact of substance abuse on clinical decision making, we also required that there be at least one indication that unit staff were aware of the patient's substance abuse, either reported by the primary therapist or noted in the chart. Clinical depression was assessed with the MINI. Symptoms were assessed by a trained research assistant with the Brief Psychiatric Rating Scale (BPRS),[15] and subscales measuring disorders of thought disturbances, withdrawal, anxiety/depression, paranoia, and activation were computed. Indications that suicidal or assaultive/homicidal behavior contributed to hospitalization, that restraints were used during admission, or that seclusion was used during the hospital stay were recorded from the chart review and used as indications of dangerousness.

Antipsychotic dosage. The discharge medication and dosage were recorded from the patient's chart and converted into CPZe.[16,17] Following Lehman and Steinwachs,[10] dosages were categorized into 3 groups: less than 300 mg/day, 300 to 1000 mg/day, and over 1000 mg/day. We chose to focus specifically on predictors of excess discharge dosages, defined by PORT criteria, both because this allowed us to compare our findings to those of Lehman and Steinwachs[10] and because adverse clinical consequences have been linked to excess dosages. (Analysis of risk factors for dosages falling below PORT recommendations is currently underway and will be the subject of a separate report.) The analyses presented here are based on 293 patients for whom chart reviews were completed and who were prescribed an antipsychotic at discharge.

Logistic regressions were computed to assess the impact of these variables on excess dosage, controlling for symptomatology and length of stay. In the second step of these analyses, we entered route of administration (depot vs. oral) to assess whether it accounted for the significant associations observed in the first model. We did not distinguish between atypical and conventional oral medication in this model, because no patients who were prescribed atypical medication received excess dosages.

For 28% (N = 81) of the sample, depot discharge medication was prescribed; 14% (N = 42) were prescribed atypical oral medication, and 15.7% (N = 46) of the sample were prescribed both oral and depot medication. Approximately 58% (N = 170) of the sample were prescribed only oral conventional antipsychotics.

RESULTS

Conformance Rates

As shown in Table 1, among patients who were prescribed an antipsychotic at discharge, approximately 65% fell within the recommended dosage range. The demographic and clinical factors most strongly associated with dosage were race, previous hospitalization, and discharge hospital. While approximately equal proportions of white and African American patients' prescriptions fell within the recommended range (62.9% and 65.7%, respectively), 10% more of the African American patients were prescribed dosages in excess of the recommended range.

Table 1. Dosage Levels at Discharge by Patient Characteristics, Clinical Characteristics, and Type of Antipsychotic

Variable	N[a]	Dosage Group[b] In Range	Higher	Statistic
Sex				
Male	190	64.7	23.7	$\chi^2 = 5.67$, p = .06
Female	103	64.1	15.5	
Age, y				
< 30	75	70.7	18.7	$\chi^2 = 2.03$, p = .73
30–44	160	62.5	21.9	
45+	58	62.1	20.7	
Race[c]				
White	116	62.9	14.7	$\chi^2 = 11.8$, p = .003
African American	172	65.7	25.0	
Voluntary admission				
No	163	67.5	20.9	$\chi^2 = 2.34$, p = .31
Yes	129	61.2	20.9	
Previously hospitalized				
No	154	68.8	14.9	$\chi^2 = 6.22$, p = .05
Yes	126	59.5	26.9	
Dangerousness				
No	130	65.4	21.5	$\chi^2 = .49$, p = .78
Yes	163	63.8	20.3	
Patient weight, mean ± SD				
lb	NA	174.3 ± 35.2	174.1 ± 39.4	t = –.03, p = .97
(kg)		(78.4 ± 15.8)	(78.4 ± 17.7)	
Hospital site				
A	72	62.5	13.9	$\chi^2 = 14.5$, p = .02
B	72	68.1	16.7	
C	73	58.9	32.9	
D	76	68.4	19.7	
Comorbidity				
Major depression				
No	193	64.3	23.2	$\chi^2 = 4.17$, p = .12
Yes	99	65.7	15.2	
Substance abuse				
No	185	60.5	22.7	$\chi^2 = 3.56$, p = .17
Yes	108	71.3	17.6	
Type of neuroleptic				
Depot				
No	212	71.7	8.5	$\chi^2 = 75.9$, p = .001
Yes	81	45.7	53.1	
Oral (atypical)				
No	251	60.2	24.3	$\chi^2 = 16.2$, p = .001
Yes	42	90.5	0	
Oral (conventional)				
No	123	60.9	35.0	$\chi^2 = 37.0$, p = .001
Yes	170	67.1	10.6	
Total	293	64.6	20.8	

[a]Numbers do not always sum to total because of missing values.
[b]Values represent percentages of total N unless otherwise specified.
Abbreviation: NA = not applicable.
[c]Four patients who were identified as Asian/Pacific Islander were deleted from this analysis.

Patients with a history of psychiatric hospitalization were also more likely to be prescribed an antipsychotic dose that exceeded the recommended range. Finally, important differences among hospitals were observed. Hospital C shows much lower rates of conformance to PORT guidelines (58.9%), and one third of the patients discharged from this hospital were prescribed dosages in the highest range.

Table 2. Logistic Regression of Excess Dosage on Patient Characteristics, Clinical Characteristics, and Type of Antipsychotic[a]

Variable	Model I Parameter Estimate	Model I Odds Ratio	Model II Parameter Estimate	Model II Odds Ratio
Female	–0.67*	0.52	–0.31	0.73
African American	0.98**	2.67	0.77	2.17
Previously hospitalized	0.62*	1.85	1.16**	3.18
Hospital A[b]	–0.72	0.49	–1.65**	0.19
Hospital B[b]	–1.17**	0.32	–2.03**	0.13
Hospital D[b]	–0.35	0.70	–1.68**	0.19
Thought disorder	0.39**	1.48	0.25	1.28
Depot medication	...	...	3.40**	30.0

[a]Controlling for length of stay, age, voluntary admission, patients' weight, dangerousness, depression and substance use comorbidity, activation, withdrawal, depression/anxiety, and paranoia subscales of the Brief Psychiatric Rating Scale.
[b]Reference category is hospital C.
*Significant at p ≤ .10.
**Significant at p ≤ .05.

Route of administration shows the strongest association with dosage range. More than one half of those given depot medication were prescribed dosages higher than the recommended range, compared with 10.6% for those prescribed oral medication. No patient prescribed an atypical medication at discharge received an excess dosage.

As shown in the first logistic regression model, patients with a greater number of symptoms of thought disorders were more likely to receive excess dosages than patients with fewer of these symptoms (Table 2). Race remains significant in these models, suggesting that the excess antipsychotic dosage levels among African American patients do not reflect differences in symptom levels at discharge. The observed difference between hospitals B and C remained significant, although neither hospital A nor hospital D were significantly different from hospital C in these multivariate analyses. No race-by-hospital interaction was found. There was a marginal effect of sex and prior hospitalization, with men and those with a history of psychiatric hospitalization being more likely to receive excess dosages, controlling for symptomatology.

As shown in model II, patients taking depot medication at discharge were 30 times more likely to be given dosages that exceed recommendations than patients taking oral medication. Moreover, controlling for depot versus oral administration reduced the race difference to nonsignificance. Further analyses (not shown in Table 2) indicate that 33% of minority patients, as compared with 19% of white patients, were prescribed depot medication, controlling for the variation in the other relevant variables included in Table 2. African Americans were also less likely to receive atypical oral medication (11%) than white patients (19%), although this difference was not significant when we controlled for the relevant covariates.

Because male patients and those with thought disorders were more likely to be prescribed depot medication,

controlling for method of administration reduced the sex and symptom effects to nonsignificance. Moreover, depot medication was prescribed least frequently in hospital C and was slightly less likely to be given to patients with prior psychiatric hospitalizations; therefore, controlling for method of administration accentuated the hospital differences in dosage levels and the effect of prior hospitalization.

DISCUSSION

While noting the existence of individual variability in antipsychotic response, experts generally caution that dosages in the range classified here as excessive generally yield no additional clinical benefit.[18,19] This report adds to the small number of studies that examine whether high dosing is more common for certain categories of patients and in certain institutional settings.

While pharmacokinetic differences between white and African American or Hispanic patients are often viewed with skepticism,[20] it is logically possible that unmeasured physical differences might be responsible for differences in the metabolism of antipsychotics.[21] For example, smoking decreases serum concentrations of chlorpromazine[22] and fluphenazine.[23] If more African American than white patients smoke, differences might result.

Drug metabolism is mediated through the cytochrome P450 microsomal enzyme system. Small numbers of individuals lack the P450 microsomal enzyme and, consequently, are "poor metabolizers." Their plasma levels tend to be high. Recent studies have identified a larger group who are genotypically heterogeneous "slow metabolizers," perhaps because a variant gene is coded for a partially inactive enzyme. Recent estimates suggest that the prevalence of slow metabolizers of antipsychotic medications is higher among African American and Asian groups than whites.[24] If more African American than white patients are slow metabolizers, this would only accentuate the potential for excess dosing in the African American subsample. We lack the data to directly examine or control for either of these factors.

The finding that race differences in excess dosing were explained by use of depot injections is an important one. Future studies of race differences in excess dosing ought to control for oral versus depot administration, as should studies more broadly concerned with quality of care for schizophrenia. The clinical issues raised require careful consideration. Although American psychiatrists prescribe depot injections much less frequently than their counterparts in Western Europe, their use does not constitute suboptimal or disadvantaged care. On the contrary, experts commonly complain that depot is underutilized and stress its advantages,[25,26] particularly in the all-important transition from inpatient to outpatient care.[27] Survey data from the United Kingdom indicate that patients readily accept a recommendation of depot medication and that the vast majority of those taking depot medication report that, given a free choice, they would continue with it.[28] Ironically, although the frequent finding that African American patients are significantly more likely to receive depot medication[29,30] may reflect a social prejudice, any prejudice involved may also function as an access barrier for white patients, who are being denied a beneficial treatment technology.

Our data complicate the issues surrounding depot medication. Both patient race and use of depot medications have been associated with higher antipsychotic dosing. If excess dosing found for African American patients is explained by psychiatrists' greater reliance on depot administration, then future studies ought to concentrate on untangling the factors responsible for this convergence of race, depot use, and excess dosing. Efforts to exploit the advantages of depot medication must avoid the risks associated with excessive dosing. For example, other studies[31] have suggested that patients receiving both depot and oral medications are more liable to receive higher doses than patients receiving one or the other medication and that this practice may require particular attention.

This study has 3 main limitations. First, we relied on a standard conversion formula, but we should note that conversion of depot medication doses into oral equivalents is controversial.[32–34] No system enjoys universal acceptance, but Galletly[35] found that patients prescribed depot medication received higher doses even when she relied on the manufacturer's (Squibb) formula for conversion of fluphenazine decanoate, which yielded CPZe doses lower than prior studies. Second, we lack information on the full range of clinical data that influenced prescribing practices. Controlling for the influence of symptomatology does not eliminate the possibility that other clinical features, not well captured by the BPRS or our measures of comorbidity, may have influenced physicians. Third, our sample of hospitals is too small to identify hospital features that may have influenced differences in prescription practices.

Our finding that excessive antipsychotic dosing was significantly more common at one of the hospitals studied adds to the evidence suggesting that local institutional cultures may exert a powerful influence on prescribing norms.[36] That this influence may operate independent of evidence-based standards has significant implications for diffusion of treatment recommendations. Rigorous qualitative investigation of the development and maintenance of these norms may yield clues valuable for efforts to alter practices.

Other authors have reported that African American patients are more likely than whites to be treated with higher doses of antipsychotics[37] and to be treated with antipsychotics, irrespective of illness.[38] Thus, accumulating evidence points to a need to examine the impact of a patient's

minority status on optimal psychiatric care. More direct social psychological investigation of medication decision making by physicians may be required to determine how patient race exerts its influence.

Drug name: chlorpromazine (Thorazine and others).

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