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Use of Depot Antipsychotic Medications for Medication Nonadherence in Schizophrenia

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***Objectives*: To describe factors associated with initiation of depot antipsychotic medications in psychiatric outpatients with schizophrenia and recent medication nonadherence. *Methods*: A national sample of psychiatrists reported on adult outpatients with schizophrenia who were nonadherent with oral antipsychotic medications in the last year. *Results*: In total, 17.6% of psychiatrists initiated depot antipsychotic injections. Initiation was significantly and positively associated with public insurance, prior inpatient admission, proportion of time nonadherent, average or above average intellectual functioning, and living in a mental health residence. Use was inversely associated with using second-generation antipsychotics and other oral psychotropic medications prior to medication nonadherence. Psychiatrists who were male, nonwhite, and more optimistic about managing nonadherence were more likely to initiate depot injections. *Conclusions*: Initiation of depot injections is a joint function of patient, physician, treatment, and setting factors. Use of long-acting preparations in this population is uncommon despite clinical recommendations urging their use.**

Key words: nonadherence/depot/antipsychotics

Introduction

Nonadherence with antipsychotic medications is a leading source of preventable morbidity in the community treatment of schizophrenia.[1] Approximately one-third of patients with schizophrenia are noncompliant with their prescribed medication regimen.[2] These patients are at increased risk of symptom exacerbation[3] and inpatient readmission.[4] Missing as few as 1–10 days of oral antipsychotic therapy nearly doubles the risk of hospitalization.[5] Clinical research and expert opinion[6] support the use of depot antipsychotics as a maintenance treatment for patients with a history of nonadherence with oral antipsychotics. However, in the United States, long-acting antipsychotic medications are only prescribed to between 19% and 30% of patients with known recent medication nonadherence.[2,7]

Although a number of single-site clinical studies have shown that use of depot antipsychotics varies by patient race/ethnicity and age,[7] no national study has examined the impact of the broad range of patient, physician, and treatment setting characteristics. In light of evidence that substantial numbers of patients with known medication nonadherence who might benefit from depot antipsychotic medications are not receiving this treatment, we sought to examine correlates of depot use among recently medication nonadherent patients with schizophrenia. A greater understanding of the pattern and distribution of depot antipsychotic use may help to target initiatives aimed at improving use of depot preparations. A study was conducted to assess patient, physician, treatment, and setting factors that might influence the decision to initiate depot antipsychotic medications for outpatients with schizophrenia and recent medication nonadherence. Prior to conducting this study, we hypothesized that depot antipsychotic use would be preferentially prescribed to patients with the most pervasive, persistent, and consequential medication nonadherence and to patients with fewer social supports such as those who were living alone or those with little family contact.

Methods

Psychiatrists were randomly selected from the American Medical Association (AMA) Masterfile of Physicians. The AMA Masterfile contains contact and practice information on all US physicians regardless of whether they are AMA members. Physicians listing psychiatry as a specialty were selected excluding the following groups: (1) psychiatry residents, (2) those residing outside of the 50 states and District of Columbia, (3) those over 75 years old, (4) those who did not list psychiatry as their primary

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specialty, and (5) those who did not list direct patient care as their type of practice. A random number generator function was used to select 1150 psychiatrists from the resulting list of physicians. These psychiatrists were sent a screening postcard. Psychiatrists with undeliverable addresses ($n = 109$) and psychiatrists with fewer than 4 patients with schizophrenia in their caseload ($n = 270$) were excluded, resulting in a final sample of 771. Of these, 534 (69.3%) responded to a comprehensive survey about their practice, attitudes regarding antipsychotic medications, and one selected patient who was nonadherent with his/her oral antipsychotic medication. The study was conducted between September, 2003, and January, 2004. Psychiatrists were instructed to select the most recent eligible patient who was (1) over 18 years old, (2) under the psychiatrist's care for at least 1 year, (3) nonadherent with oral antipsychotics at some point in the last year (ie, at least 2 consecutive weeks taking less than half of prescribed medications), and (4) not prescribed a depot antipsychotic 2 months prior to nonadherence episode. Three hundred ten respondents reported on a specific patient. Study procedures were approved by the New York State Psychiatric Institute and the American Psychiatric Institute for Research and Education institutional review boards.

Each psychiatrist provided a detailed description of the demographic and clinical characteristics of the patient including age, gender, race, marital status, employment status, lifetime cooccurring psychiatric conditions, duration of treatment with the psychiatrist, and use of inpatient and outpatient mental health services in the past 3 months. As part of this broader survey of the management of medication nonadherence, psychiatrists were asked to report whether they started a long-acting antipsychotic injection medication to manage the patient's last episode of medication nonadherence (in the form of a yes/no question), as well as rate the effectiveness of the intervention on a 1–5 Likert-type scale. Rates at which long-acting injections were prescribed are compared across strata of patient sociodemographic and clinical characteristics and psychiatrist characteristics (table 1). For purposes of the analysis, items concerning family contact and period of nonadherence were collapsed from continuous to categorical variables. Based on its distribution, the item "Approximately how many weeks has it been since that patient spoke with a member of his/her family?" was considered as ≤ 1 or >1 week. Items concerning the number of months the patient has been under the psychiatrists' care and prescribed antipsychotic medications and concerning the number of months of nonadherence with prescribed antipsychotic medications were combined to calculate percentage of time under care, nonadherent. This variable was dichotomized as $<25\%$ or $\geq 25\%$ of the time.

Chi-square analyses tested for differences in rates between strata. A series of multiple logistic regressions examined the strength of associations between initiation of depot antipsychotic injections (dependent variable) and each patient and psychiatrist attribute. Separate forward stepwise regressions were run for each independent variable of interest where that variable was forced into the model and any of the other independent variables were included in the model if its Wald chi-square had a $P < 0.20$. This criterion was selected following the recommendation of Hosmer and Lemeshow[8] to provide broad assurance that the coefficients for variables included in the model are different from zero.

Results are presented as adjusted odds ratios (ORs) for independent variables of interest with associated 95% confidence intervals (CIs). All analyses use weights to account for survey nonresponse.

Background Patient Characteristics

Most of the schizophrenia outpatients with recent medication nonadherence were males, were white in race/ethnicity, had never been married, were currently unemployed, were living with family or friends, and were between 35 and 54 years of age (table 1). A majority also paid for medications with public insurance, had contact with their families on at least a weekly basis, and were assessed by their treating psychiatrists to be of normal or above average intelligence.

Approximately 17.6% of the patients were started on long-acting antipsychotic injections to manage their most recent episode of medication nonadherence; a majority of injections were fluphenazine decanoate (62.5%), while 37.5% were haloperidol decanoate. In bivariate analyses, patients living in mental health residences were significantly more likely to start long-acting injections as were patients who paid for their medications with public insurance or sources other than private insurance (table 1). In addition, patients who were homeless during the last month were significantly more likely to start long-acting injections, though this association fell below the level of statistical significance after controlling for relevant patient and psychiatrist characteristics. The rate of initiating long-acting antipsychotic injections did not significantly differ by patient age, sex, race/ethnicity, marital status, current employment status, or frequency of patient/family contact (table 1).

Patient Clinical Characteristics

The likelihood of starting a long-acting antipsychotic injection was significantly related to whether the most recent episode of medication nonadherence resulted in inpatient psychiatric admission and whether nonadherence had persisted for more than one-quarter of the time the patient was under the psychiatrists' care. The likelihood of starting injections was inversely related to treatment with an oral second-generation antipsychotic

Table 1. Rates of Initiating Long-Acting Antipsychotic Injections in Medication Nonadherent Outpatients with Schizophrenia, Stratified by Patient Sociodemographic Characteristics[a]

Group	% Receiving Injections	χ^2	*df*	*P*	Adjusted OR (95% CI)
Age, y		2.1	2	.35	
18–34 (*n* = 112)	14.5				1.00 (Reference)
35–54 (*n* = 156)	20.4				1.27 (0.55–2.92)
55+ (*n* = 34)	13.1				1.22 (0.29–5.10)
Sex		1.0	1	.31	
Male (*n* = 217)	19.0				1.00 (Reference)
Female (*n* = 87)	14.1				1.08 (0.45–2.57)
Race/ethnicity		2.9	1	.09	
White (*n* = 201)	14.9				1.00 (Reference)
Nonwhite (*n* = 103)	22.7				1.14 (0.53–2.46)
Marital status		2.8	2	.25	
Never married (*n* = 188)	17.7				1.00 (Reference)
Married/together as married (*n* = 52)	11.0				1.01 (0.31–3.28)
Divorced/widowed/separated (*n* = 64)	22.9				1.64 (0.68–3.94)
Employment		4.9	2	.08	
None (*n* = 228)	19.8				1.00 (Reference)
Worker for pay (*n* = 40)	5.3				0.23 (0.08–1.06)
Volunteer (*n* = 34)	17.9				1.04 (0.34–3.18)
Living situation		14.0	2	.0009	
Alone (*n* = 161)	12.2				1.00 (Reference)
Family of friends (*n* = 161)	15.4				1.09 (0.47–2.56)
Mental health residence (*n* = 31)	44.2				4.11 (1.37–12.30)
Homelessness, past month		5.0	1	.03	
Yes (*n* = 9)	45.4				1.84 (0.22–15.33)
No (*n* = 297)	16.6				1.00 (Reference)
Payment of medications[a]		12.1	2	.002	
Private insurance (*n* = 56)	1.7				1.00 (Reference)
Public insurance (*n* = 175)	22.3				19.04 (2.26–160.39)
Other (*n* = 59)	19.3				14.61 (1.58–135.43)

Note: *n*'s vary due to missing data. Percentages weighted to adjust for participant nonresponse. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) are from logistic regressions that force in the independent variable of interest and step in sequentially all variables in table 1 and psychiatrist variables (age, sex, race/ethnicity, teaching status, practice setting, therapeutic optimism, number of patients in caseload with schizophrenia, and practice guideline familiarity), retaining those with a Wald chi-square $P < .20$ in the final model. Overall, 17.6% of patients received long-acting antipsychotic injections.
[a]See text for description of associations between psychiatrist characteristics and rates of initiating long-acting antipsychotic injections.

medication just prior the episode of medication nonadherence and to treatment with oral psychotropic medications other than antipsychotics (table 2). These relationships remained significant in the multivariate analyses. After controlling for patient and psychiatrist variables, average or above average patient intellectual functioning was also significantly related to initiating long-acting antipsychotic injections.

Psychiatrist Characteristics

Rates of initiating long-acting injections were significantly greater for patients treated by nonwhite vs white psychiatrists (27.6% vs 13.1%, $\chi^2 = 3.6$, $df = 1$, $P = .002$) and psychiatrists who had higher vs lower levels of optimism concerning the effectiveness of efforts to improve medication adherence (35.3% vs 14.9%, $\chi^2 = 10$, $df = 1$, $P = .002$). In multivariate analyses, nonwhite psychiatrists and psychiatrists with higher levels of optimism remained significantly more likely to initiate long-acting antipsychotic injections, while female physician gender (OR = 3.03; 95% CI = 1.23–7.69) became significant.

Discussion

In outpatient psychiatric practice, psychiatrists use long-acting antipsychotic injections to manage fewer than 1 in 5 patients with schizophrenia having episodes of medication nonadherence. Although consideration of long-acting antipsychotic injections is recommended for patients with a history of problems with adherence on oral medication,[6] most patients in this nationally representative community sample who were not adherent with oral antipsychotic medications were not prescribed long-acting antipsychotic injections. The relatively low rate of use is broadly consistent with previous research.[2,7]

Table 2. Rates of Initiating Long-Acting Antipsychotic Injections in Medication Nonadherent Outpatients with Schizophrenia, Stratified by Patient Clinical Characteristics[a]

Group	% Receiving Injections	χ^2	*df*	*P*	Adjusted OR (95% CI)
Intellectual functioning		0.4	1	.51	
Average or above (n = 237)	18.3				2.79 (1.05–7.42)
Borderline or below (n = 68)	14.9				1.00 (Reference)
Substance use disorder, past month		0.3	1	.61	
Present (n = 54)	19.6				1.30 (0.49–3.10)
Absent (n = 252)	16.9				1.00 (Reference)
Aware of mental illness		2.3	1	.13	
Present (n = 203)	14.9				1.04 (0.48–2.24)
Absent (n = 97)	22.0				1.00 (Reference)
Extent of medication, nonadherence		2.1	1	.15	
Complete (n = 209)	19.7				0.95 (0.40–2.29)
Partial (n = 95)	13.0				1.00 (Reference)
Inpatient admission, nonadherence		13.4	1	.0003	
Present (n = 121)	27.5				3.32 (1.56–7.07)
Absent (n = 183)	11.1				1.00 (Reference)
Period under care, nonadherent		6.2	1	.01	
<25% (n = 144)	11.3				1.00 (Reference)
25+% (n = 155)	22.0				2.56 (1.12–5.88)
Positive symptom severity		0.3	1	.57	
Severe (n = 167)	18.6				0.75 (0.34–1.67)
Moderate or less severe (n = 139)	16.2				1.00 (Reference)
Negative symptom severity		0.04	1	.85	
Severe (n = 71)	17.0				0.86 (0.35–2.09)
Moderate or less severe (n = 230)	18.0				1.00 (Reference)
Other psychotropic medication[b]		4.1	1	.04	
Present (n = 66)	9.2				0.30 (0.10–0.84)
Absent (n = 240)	19.8				1.00 (Reference)
Second-generation antipsychotics		13.4	1	.0003	
Present (n = 275)	14.8				0.23 (0.08–0.63)
Absent (n = 31)	41.3				1.00 (Reference)

Note: n's vary due to missing data. Percentages weighted to adjust for participant nonresponse. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) are from logistic regressions that force in the independent variable of interest and step in sequentially all variables in table 1 and psychiatrist variables (age, sex, race/ethnicity, teaching status, practice setting, therapeutic optimism, number of patients in caseload with schizophrenia, and practice guideline familiarity), retaining those with a Wald chi-square $P < .20$ in the final model. Overall, 17.6% of patients received long-acting antipsychotic injections.
[a]See text for description of associations between psychiatrist characteristics and rates of initiating long-acting antipsychotic injections.
[b]Includes antidepressants, mood stabilizers, and anxiolytics/hypnotics.

The clinical decision to initiate injection antipsychotic medications appears to rest on a clinical assessment of the risks and consequences of poor medication adherence. Patients at greater risk, specifically those who have a history of persistent nonadherence and those admitted for inpatient care during their last episode of nonadherence, were more likely to be started on injections. However, some patient groups at high risk for recurrent medication nonadherence, such as patients who live alone and younger patients,[1] had surprisingly low levels of injection use.

Depot antipsychotic medications are not widely used beyond those who are publicly insured or treated in residential or inpatient facilities. These settings presumably have staff members to facilitate delivery of depot antipsychotics and cater to the more severely ill. Innovative strategies to train more psychiatrists and their staff in the use of depot antipsychotics may help promote their use in different settings and in patients who are less severely ill but are still medication nonadherent. In general, adoption of technologies that vary from current or typical practices face significantly greater challenges in diffusing into practice, than those that rely on existing practices.[9] For this reason, greater opportunities for first-hand observation and hands-on training may be needed. One approach is to set up specialty long-acting antipsychotic injection clinics in private and public outpatient settings that accept referrals. Mobile outreach services provide another option for delivering long-acting injections.[10]

Use of long-acting antipsychotic medications was uncommon among patients prescribed antidepressants or

mood stabilizers just prior to the start of the last episode of antipsychotic nonadherence. Some psychiatrists may perceive that the marginal benefit of a long-acting antipsychotic injection is diminished when it does not obviate the need for oral medications as is the case when several classes of oral psychotropic medications are prescribed. In light of the frequency with which schizophrenia patients receive complex regimens involving oral medications other than antipsychotic medications,[11,12] this diminishing benefit of depot medications may also hinder use of newer long-acting antipsychotic preparations.

Cognitive impairment has been linked to treatment nonadherence among psychotic patients (review[13]). Although cognitively impaired patients may have a limited ability to take oral medications on their own, patients assessed as having lower than average intelligence were (after controlling for several potential confounds) significantly less likely to receive depot antipsychotic medications than were those of at least average intelligence. These results suggest that efforts are needed to improve access of depot antipsychotic medications to cognitively impaired patients.

In many but not all health care contexts,[14–17] patients with private insurance enjoy greater access to evidence-based treatments than publicly insured patients. For long-acting antipsychotics, patients with private insurance were less likely than publicly insured patients to receive treatment. This may reflect greater access to long-acting injections in organized treatment settings than in office-based settings favored by privately insured patients or a stronger preference for oral second-generation antipsychotics among privately insured patients. With the availability of long-acting injectable risperidone, the difference in rate of use by publicly and privately insured patients may narrow.

Psychiatrists who were more optimistic about the effectiveness of managing medication nonadherence were more likely to treat their patients with depot antipsychotics. Psychiatrists who prescribe injections may have had more opportunities to observe favorable patient outcomes than do psychiatrists who do not prescribe these preparations.[18] In this study, greater knowledge of depot medications was in turn related to more favorable attitudes toward these medications. Consequently, educational efforts to expand use of depot antipsychotics might be preferentially targeted to psychiatrist groups with low rates of use.

After controlling for several potentially confounding factors, female psychiatrists were significantly more likely to treat their medication nonadherent schizophrenia patients with depot antipsychotic medications than were their male and white counterparts. In one survey of British psychiatrists, more favorable patient-centered attitudes were reported by psychiatrists with higher depot use,[19] and in some contexts female as compared with male physicians have been found to engage in a more patient-centered style of communication.[20] Whether gender-related differences in communication style or other factors account for the psychiatrist gender difference in use of depot antipsychotic medications remains unknown.

The use of depot antipsychotic medications was not significantly related to patient age, gender, or race/ethnicity. Previous studies of psychotic patients that are not selected for recent medication nonadherence have reported that use of depot antipsychotic medications is significantly more common among males,[21,22] African Americans,[21–24] and younger patients.[25] Because these demographic characteristics also increase the risk of antipsychotic medication nonadherence (reviews[1,26]), it is perhaps not surprising that they are not significantly related to depot antipsychotic use among patients selected for recent medication nonadherence.

This study is constrained by several limitations. First, we relied exclusively on psychiatrist-reported data without independent validation of nonadherence. Because mental health professionals may fail to detect antipsychotic nonadherence,[27] depot medications may be more underutilized than the current data suggest. In addition, although the study was limited to patients who had been under the psychiatrists' care for at least 1 year, the respondent psychiatrists likely vary in their knowledge of the patients. For example, the reliability with which some psychiatrists rated variables such as living situation or family contact may be variable. Second, because the first second-generation long-acting injection was approved by the Food and Drug Administration for marketing when this study was in the field, no information is provided on long-acting risperidone injections. Third, no information was collected concerning the offer of injection. Although available evidence suggests that patients tend to have a positive attitude toward depot antipsychotic medications,[28] we do not know the extent to which study patients with medication nonadherence were offered but refused depot antipsychotic medications. Fourth, although psychiatrists were specifically instructed to report on the last patient that they saw who met the study criteria, it is possible that patient selection was biased by protocol violation. Because the survey (management of medication nonadherence) was oriented around management of medication nonadherence, psychiatrists may have tended to select patients who received more active forms of management such as initiation of depot antipsychotic medications. Finally, psychiatrist nonresponse opens the study to the possibility of selection bias at the level of the participating psychiatrist.

With the introduction of injectable long-acting risperidone, it will be important to track the extent to which patients and psychiatrists become more willing to utilize depot preparations and to assess changes in factors that influence these decisions. Early clinical research indicates that medication nonadherence with oral antipsychotic medications is the most common reason for initiating

risperidone long-acting injections,[29–33] that poor prior antipsychotic adherence predicts greater improvement on risperidone long-acting injections,[33] and that patients who are switched from another depot are much less likely to discontinue risperidone long-acting injections than those switched from oral antipsychotic medications.[34] These findings suggest that factors which have influenced use of the older depot antipsychotic medications may continue to play a role in medication management decisions with the newer injectable antipsychotic preparations.

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