Adherence Assessments and the Use of Depot Antipsychotics in Patients With Schizophrenia

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Background: Antipsychotic medications significantly ameliorate the symptoms of schizophrenia, but patients are often noncompliant with these medications. Research evidence supports the use of depot antipsychotics in noncompliant patients.

Method: Between January 9, 1991, and December 19, 1995, 1307 veterans with schizophrenia or schizoaffective disorder (ICD-9) were enrolled in a study of enhanced psychosocial programming at 14 Veterans Administration Medical Centers. All had a history of high inpatient use. At enrollment, clinicians listed patient medications, rated patient compliance, and completed a Brief Psychiatric Rating Scale (BPRS) and Global Assessment of Functioning (GAF). Patients reported medication side effects. We describe depot antipsychotic use among these patients and examine the relationship between depot use, assessed compliance, and patient characteristics.

Results: At enrollment, 18% of patients in this cohort were receiving depot antipsychotics; however, clinicians reported that 49% had been noncompliant with medication in the past year. Depot use varied significantly with treatment site; African Americans were more likely to receive depot antipsychotics and less likely to receive atypical antipsychotics than white patients. Patients on depot and oral agents had similar levels of psychiatric symptoms, but patients on depot antipsychotics were more likely to receive high doses and complain of side effects.

Conclusion: Clinicians prescribed depot antipsychotics relatively infrequently, despite high rates of noncompliance and high levels of inpatient use. Variation in use with treatment site and ethnic group suggests barriers to implementing research-based recommendations for depot use in noncompliant patients. Quality improvement programs should consider facilitating the appropriate use of depots.

(J Clin Psychiatry 2001;62:545–551)

Received Aug. 24, 2000; accepted Feb. 1, 2001. From the Department of Veterans Affairs, Serious Mental Illness Treatment, Evaluation, and Research Center (SMITREC), Health Services Research and Development (HSR&D) Field Office (Drs. Valenstein, Copeland, and Blow and Ms. Visnic); the Department of Psychiatry, University of Michigan, Ann Arbor, Mich. (Drs. Valenstein and Blow); and the Department of Veterans Affairs, HSR&D, Center for Mental Healthcare and Outcomes Research and the Department of Psychiatry and Behavioral Sciences, University of Arkansas, Little Rock (Dr. Owen).

Funded through the Department of Veterans Affairs, HSR&D Research Career Development Award, RC-98350-1, and through the Mental Health Strategic Health Group of the Veterans Administration Headquarters.

In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows: Dr. Valenstein is an employee of Veterans Affairs and has received research grant support from HSR&D Career Development Award; Dr. Copeland is an employee of Veterans Affairs and has received research grant support from Strategic Mental Health Group; Dr. Owen has received research grant support from the Department of Veterans Affairs; Dr. Visnic is an employee of Veterans Affairs and has received research grant support from Strategic Mental Health Group; and Dr. Blow has no significant commercial relationships to disclose relative to the presentation.

Presented as an abstract at the Veterans Administration HSR&D Conference; March 2000; Washington, D.C.

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Schizophrenia is a devastating and costly illness that affects 1% of the population in the United States.[1] Antipsychotic medications substantially reduce the symptoms of the illness and are an essential component of treatment. The majority of patients with schizophrenia improve with antipsychotic treatment and relapse when antipsychotics are discontinued.[2–6]

Unfortunately, investigators report that 20% to 60% of patients with schizophrenia are noncompliant with antipsychotics,[7–12] with estimates of noncompliance varying with the study's definition of compliance, the study population, and the methods used for assessing compliance. Noncompliance is more common when patients are on more complex medication regimens, disagree about the need for treatment, or have side effects.[12–17]

Depot antipsychotics address many issues that might result in noncompliance. Depot agents are administered by injection every 2 to 4 weeks, eliminating the need for daily dosing. Although depot antipsychotics do not prevent noncompliance,[8,18] they do prevent covert noncompliance. Patients who refuse or fail to come in for their scheduled injections are readily identified, and early outreach efforts can be initiated.

Some studies report that depot preparations have increased side effects compared with oral preparations, specifically noting the possibility of increased dysphoria, but most studies have found that depot agents have comparable or even fewer side effects than oral conventional agents.[18–20] Thus, depot medications appear to be as well tolerated as oral conventional agents—although all conventional agents may have more side effects than the newer atypical agents.[21,22]

Given the simplified dosing regimen, comparable levels of side effects, and the elimination of covert noncompliance, the use of depot medications would seem likely to improve compliance and decrease relapse. However, studies examining this issue have faced considerable methodological challenges and produced mixed results.[18] Patients who are willing to participate in randomized controlled trials (RCTs) are often more compliant at baseline, an enrollment bias that diminishes the likelihood that differences in compliance will be found between patients assigned to depot and those assigned to oral medications. In naturalistic studies, patients who are placed on depot medications are usually less compliant at baseline than patients continued on oral medications, again decreasing the likelihood of finding subsequent compliance differences. Finally, many studies examining the differential impact of depot and oral agents on relapse are of insufficient duration to take delayed relapse into account; relapse often develops months after medications are discontinued.[19,23]

Despite these methodological challenges, the preponderance of research evidence indicates that depot medications increase compliance and decrease relapse.[4,24] Treatment guidelines for schizophrenia, such as those published by the American Psychiatric Association,[25] the Schizophrenia Patient Outcomes Research Team (PORT),[26] and the Texas Medication Algorithm Project (TMAP),[52] recommend that clinicians strongly consider depot medications for patients who are noncompliant with oral medications. Yet, clinicians in the United States appear to prescribe depot agents relatively infrequently; in several U.S. patient populations, only 5% to 20% of patients receive depot agents,[18] compared to 40% to 60% in patient populations in the United Kingdom and other European countries.[19,27]

When depot medications are prescribed, moderate doses are recommended.[25] Many RCTs support the use of moderate doses of oral conventional agents (between 300 and 1000 mg chlorpromazine equivalents [CPZe]).[28] Doses below this range often are insufficient to control psychotic symptoms, while doses above this range produce little additional benefit but more side effects. Although depot antipsychotics cannot easily be translated into oral chlorpromazine equivalents,[18] several RCTs indicate that low doses of depot medication (less than 5–10 mg of fluphenazine decanoate every 2 weeks or less than 50 mg of haloperidol decanoate every month) are less effective than moderate doses.[29,30] High doses are also more likely to produce side effects without additional benefit. The PORT[26] recommends avoiding fluphenazine decanoate doses above 25 mg every 2 weeks or 37.5 mg every 3 weeks and haloperidol decanoate doses above 200 mg per month.

In this study, we examine the use of depot antipsychotic agents in a large cohort of veterans with schizophrenia and a history of high inpatient use. We describe the prevalence of depot use and examine the relationships between depot use and assessed patient compliance, patient characteristics, and treatment site.

METHOD

Between January 9, 1991, and December 19, 1995, 1637 seriously mentally ill veterans were enrolled in a study comparing enhanced psychosocial programming with standard care at 14 Veterans Administration Medical Centers (VAMCs). Patients were eligible for enrollment if they had a DSM-III-R diagnosis characterized by psychotic symptoms and either 150 or more days of hospitalization or 5 or more admissions in the previous 12 months. In this cohort, 1307 veterans had a diagnosis of schizophrenia or schizoaffective disorder (ICD-9 codes 295.xx).

Enrolled patients were assigned to standard care or to one of several enhanced psychosocial programs, based on the order of enrollment and clinician judgment. The enhanced psychosocial programs included day treatment, intensive community case management, or intensive inpatient rehabilitation programs designed to return patients to the community. The overall study design has been described in detail in earlier publications.[31,32]

We analyzed data gathered at baseline from the 1307 patients with a diagnosis of schizophrenia or schizoaffective disorder. These data were obtained from clinicians' assessment forms and patients' surveys that were completed at the time of assignment to specialized programs or usual care.

The clinician completed a patient assessment form that included the Brief Psychiatric Rating Scale (BPRS) and the Global Assessment of Functioning (GAF). The patient survey was administered by non-treating research staff and included patient reports of medication side effects. Both clinicians and research staff received training in completing survey items.

Study Measures

Patients' age and ethnicity (African American, white, or other) were obtained from national VA patient databases. The category "other ethnic" included small samples of Hispanic, Asian, and Native American veterans (N = 42). Patients were categorized into 3 age groups, consisting of (1) patients under the age of 45 years, (2) pa-

tients aged 45 through 65 years, and (3) patients older than 65 years.

The presence and the severity of psychiatric symptoms were ascertained from the 19-item BPRS scale in the clinician assessment form. The 19-item scale included 17 items from the commonly used 18-item BPRS, omitting the item for "excitement" and including items for "elation" and "psychomotor excitation." Each BPRS item was rated from 0 for "not present" to 6 for "extremely severe."[33,34]

Ratings of patient compliance were obtained from an item on the clinician assessment form that asked if patients were compliant with medication "all, most, quite a bit, some, or none" of the time during the past year. These ratings were dichotomized, whereby patients were considered compliant by strict criteria if they were taking medication all of the time and compliant by broad criteria if they were taking their medication all or most of the time. If patients were not taking medications all of the time, clinicians assessed whether their noncompliance had resulted in an increase in symptoms or in one or more hospitalizations.

Medication side effects were determined from an item in the patient survey which asked, "In the last 3 months, how much of the time have you experienced bothersome side effects from your psychiatric medication?" Patients could choose responses of "none, some, quite a bit, most, or all of the time." Responses were dichotomized, whereby patients were considered to have side effects if they reported being bothered by side effects at least some of the time.

A list of patients' medications was obtained from the clinician's assessment form.

In one exploratory analysis, the doses of depot medication were examined. In the baseline assessment form, clinicians had been instructed to record the "equivalent daily dose" of depot medications; however, clinicians continued to report over half of depot doses in the customary fashion of milligrams per injection with the interval between injections. Because there are several competing formulas for converting depot medications into daily equivalents,[20] we examined dosing only in the 175 patients whose depot doses were reported in the customary fashion or in equivalent daily doses obtained by dividing the milligrams per injection by the number of days between injections. (Dividing the milligrams per injection by number of days between injections results in readily interpretable numbers and simple conversion back to customary dose notation.) Depot doses were categorized as representing appropriate or high doses using the PORT recommendations for depot dosing.[26]

Statistical Analyses

Simple descriptive statistics were completed with univariate analysis of frequencies and means ± standard deviations. Bivariate analyses examining the relationship between the primary outcome of receiving/not receiving depot medication and categorical patient characteristics (e.g., gender or age group) were completed using chi-square analyses. Bivariate comparisons of receiving/not receiving depot medication and continuous variables were completed using Student t tests.

Logistic analyses were used to explore the relationship between the dichotomous outcome variable of depot use (yes/no) and independent variables of ethnic group, age group, and assessed compliance, producing Wald chi-squares. The Mantel-Haenszel chi-square test was used to determine if there was a significant linear trend in the proportion of patients receiving depot medications by year of enrollment. The criterion alpha level was set at .05 for all of these analyses.

In exploratory analyses, categorical comparisons of patient characteristics by all medication groups (depot antipsychotics, oral conventional antipsychotics, oral atypical antipsychotics, or none) were completed using chi-square analyses. If these comparisons were significant, descriptive statements were made based on cell chi-square values ≥ 3.84.[35] Additional post-hoc 2 × 2 chi-square analyses were then completed. For these post-hoc chi-square analyses, a criterion alpha level of .001 was adopted to adjust for simultaneous comparisons and potential inflation of the experiment-wise alpha.

Statistical analyses were completed using SAS Proprietary Software Release 6.12 TS020 (1989–1996 by SAS Institute Inc., Cary, N.C.)

RESULTS

Demographics and Clinical Characteristics

The mean age of patients in the overall cohort was 50.9 ± 12.6 years (range, 21–86 years); 96.6% of the patients were male and 3.4% were female. Most patients were white (81%), 16% were African American, and 3% were from other ethnic groups.

On average, patients were symptomatic and markedly impaired at enrollment, with a mean BPRS score of 21.5 ± 12.9 (items rated on a 0–6 scale) and a mean GAF score of 43.6 ± 14.8 (Table 1).

Depot Use

In this cohort, 234 of the patients were receiving depot antipsychotics, 936 patients were receiving oral conventional antipsychotics, 70 were receiving atypical antipsychotics (clozapine or risperidone), and 67 patients were not receiving any antipsychotic medication (Table 2). Of the 234 patients receiving depot preparations, 53% were receiving haloperidol decanoate and 47% were receiving fluphenazine decanoate.

There was a significant variation in depot use among treatment sites ($\chi^2 = 45.2$, df = 13, $p < .001$), with depot

Table 1. Characteristics of the Overall Cohort of Schizophrenic Patients and by Medication Delivery Method

Measure	Overall Cohort (N = 1307)	Patients on Depot Antipsychotics (N = 234)	Other Patients (Not on Depots) (N = 1073)
Male, %	96.6	96.6	96.6
Female, %	3.4	3.4	3.4
Race, %*			
White	81.1	76.1*	82.2*
African American	15.7	20.9	14.5
Other ethnic	3.2	3.0	3.3
Age, y*			
Mean ± SD	50.9 ± 12.6	47.8 ± 10.8	51.6 ± 12.9
Range	21–86	29–80	21–86
Age group, %			
< 45 y	39.5	44.4	38.4
45–65 y	42.6	47.4	41.6
> 65 y	17.9	8.1	20.0
BPRS score	21.5 ± 12.9	21.2 ± 13.6	21.5 ± 12.7
GAF score	43.6 ± 14.8	44.2 ± 15.1	43.4 ± 14.7
% Not compliant in past year[a]			
By strict criteria	48.8	53.0	47.9
By broad criteria	27.8	36.3	25.9
Experienced adverse consequences of noncompliance (excludes always compliant), %	83.2	90.2	81.5
Reported side effects in last 3 mo, %*	45.5	52.2	44.0

[a]Strict criteria for noncompliance = compliant less than "all of the time"; Broad = compliant less than "all or most of the time."
*Significant at $p < .05$.

Table 2. Characteristics of Patients on Depot, Oral Conventional, Atypical, or No Antipsychotic Medication

Measure	Patients on Depots (N = 234)	Patients on Oral Conventional (N = 936)	Patients on Atypical (N = 70)	Patients on No Antipsychotic (N = 67)
Male, %	96.6	96.8	97.1	92.5
Female, %	3.4	3.2	2.9	7.5
Race*				
White	76.1	81.2	91.4	86.6
African American	20.9	15.6	2.9	11.9
Other ethnic	3.0	3.2	5.7	1.5
Age, y				
Mean ± SD	47.8 ± 1.8	51.7 ± 12.8	44.5 ± 9.1	57.3 ± 14.6
Range	29–80	21–86	28–72	29–83
Age Group, %†				
< 45 y	44.4	37.6	60.0	26.9
45–65 y	47.4	42.5	35.7	34.3
> 65 y	8.1	19.9	4.3	38.8
BPRS score	21.2 ± 13.6	21.7 ± 12.8	22.1 ± 12.9	18.3 ± 11.3
GAF score	44.2 ± 15.1	42.9 ± 14.7	45.2 ± 12.3	48.8 ± 16.9
% Not compliant in past year				
By strict criteria	53.0	48.9	44.3	38.8
By broad criteria	36.3	26.5	20.0	23.9
Reported side effects in last 3 mo, %‡	52.2	43.4	55.9	39.2

*$p = .05$ for patients on depots compared with other patients by ethnic group.
†$p < .001$ for patients on depots compared with other patients by age group.
‡$p < .05$ for patients on depots compared with other patients for side effects.

use varying from 2% to 28% of patients at the different sites. The percentages of patients receiving depot medications did not vary significantly by year of enrollment (from 1991 to 1995).

Compliance

Estimated rates of noncompliance were high. Clinicians reported that 49% of the overall cohort had been noncompliant in the past year by strict criteria (compliant less than all of the time) and that 28% had been noncompliant by broad criteria (compliant less than all or most of the time). Of the patients who were judged to be noncompliant in the past year by strict criteria, 83% were felt to have had adverse consequences resulting from their noncompliance.

There were significant differences in estimated compliance among ethnic groups ($\chi^2 = 6.6$, df = 2, $p < .05$) and among age groups ($\chi^2 = 49.8$, df = 2, $p < .001$). Clinicians were more likely to consider white and older patients to be compliant with medications than African American or younger patients.

In this cross-sectional study, there were no differences in estimated levels of compliance in the past year by medication group at enrollment ($\chi^2 = 4.9$, df = 3, $p = .18$). Fifty-three percent of patients on depot medications were thought to have been noncompliant in the previous year compared with 48% of other patients in the cohort.

Patient Factors Associated With Depot Use

There were no significant differences in the likelihood of depot use by gender, but there were significant differences by ethnic group ($\chi^2 = 5.9$, df = 2, $p = .05$). When the 2 ethnic groups with significant representation (African Americans and whites) were examined, African Americans were more likely to be receiving depot antipsychotics than whites ($\chi^2 = 6.0$, df = 1, $p = .05$). Differences in depot use between African Americans and whites remained in logistic regression analyses that controlled for clinician-rated compliance (Wald $\chi^2 = 5.2$, $p < .05$; OR = 1.5 for African Americans compared with whites).

In an exploratory analysis examining the relationship between ethnic group and all medications groups (depot, oral conventional, atypical, or no antipsychotics), significant differences ($\chi^2 = 16.0$, df = 6, $p = .01$) resulted from African Americans being both more likely to receive depot preparations and less likely to receive atypical agents than whites. Differences in atypical use were significant in a post-hoc 2 × 2 chi-square analysis ($\chi^2 = 10.2$, df = 2, $p < .001$).

There were also significant differences in the likelihood of depot use among age groups ($\chi^2 = 18.6$, df = 2, $p < .001$). Twenty percent of patients 65 years of age or younger were on depot preparations, whereas only 8% of patients over the age of 65 were on depot preparations. Older patients were less likely to receive depot prepara-

tions on the basis of logistic regression analyses that used dummy variables for age groups and adjusted for assessed compliance (Wald $\chi^2 = 15$, $p < .0001$; OR = 0.36 for patients > 65 years compared with patients aged 44–65 years).

In an exploratory analysis examining the relationship between age groups and all medication groups, older patients (> 65 years) were significantly less likely than younger patients to receive depot preparations or atypical agents and significantly more likely to receive no antipsychotic medication ($\chi^2 = 53.0$, df = 6, $p < .001$). Differences in atypical use were significant in a post-hoc 2 × 2 chi-square analysis ($\chi^2 = 16.4$, df = 2, $p < .001$) as were differences in receiving no antipsychotic medication ($\chi^2 = 18.6$, df = 2, $p < .001$).

Patients on depot preparations did not differ from other patients in the cohort in levels of psychiatric symptoms or functioning as measured by BPRS or GAF scores.

Relationship Between Depot Use and Side Effects

Patients on depot medications reported significantly more medication side effects than other patients in the cohort, with 52% of patients on depot medication reporting side effects in the last 3 months versus 44% of other patients ($\chi^2 = 4.5$, df = 1, $p < .05$).

Depot Dose

In an exploratory analysis, we found that 57% of the 175 patients with interpretable depot doses were receiving doses above PORT guidelines. Patients receiving fluphenazine decanoate were more likely to receive high doses than patients receiving haloperidol decanoate ($\chi^2 = 3.6$, df = 1, $p < .0001$); 81% of patients on fluphenazine decanoate received high doses compared with only 33% of patients on haloperidol decanoate.

DISCUSSION

Consistent with earlier studies on compliance in patients with schizophrenia,[7,9–12] clinicians reported that a large percentage of patients in this sample were noncompliant with antipsychotic medication.[9–12] Patients in this population were among the highest users of inpatient services in the VA; however, despite high rates of noncompliance and high use of inpatient services, clinicians prescribed depot medications relatively sparingly.

Forty-nine percent of patients in the sample were thought to have had problems with compliance during the past year, and the great majority of these patients suffered adverse consequences from their noncompliance. However, only 18% of patients were receiving depot medication by the time of enrollment. Although the reasons for infrequent use of depot medication are unclear, the large variation in depot use among treatment sites in this and earlier studies[36] suggests barriers to consistently applying recommendations for depot use in noncompliant patients.

As noted in previous studies,[36,37] we found significant variation in depot use by ethnic group in addition to treatment site. African Americans were more likely to receive depot medications than whites and less likely to receive atypical agents. A recent study has reported similar findings among Medicaid recipients in Pennsylvania.[38]

Previous studies have reported differences in diagnostic patterns and the pharmacologic management of African Americans and whites with schizophrenia.[39–43] African Americans are more likely to be diagnosed with schizophrenia than whites,[40,41] and once diagnosed, African Americans are more likely to receive high doses of antipsychotic medication.[42] African Americans presenting to emergency rooms are also more likely to receive injections and high doses of antipsychotics.[44,45]

There may be several reasons that clinicians use depot medications more frequently in African Americans than whites, including differential symptom presentation, acceptability of injections, tolerance of medication side effects, access to other intensive mental health services, clinician perceptions of patient compliance, or other aspects of the clinician-patient relationship. African Americans with schizophrenia have been reported to have more severe psychotic symptoms and to express more hostility and suspiciousness than whites[46,47]; clinicians may be more likely to prescribe depot medications to patients with these symptoms. Injections may be more acceptable to African Americans, or they may be more tolerant of the side effects from these medications.[37] Clinicians may perceive African Americans as being less compliant with medication, and these patients may have different levels of access to other services that address poor compliance, such as frequent outpatient visits, intensive case management, or "eyes on" medication administration.

Our data suggest that the preferential use of depot preparations among African Americans is not likely to be fully explained by greater tolerance for depot medications. In this sample, African American patients on depot medications were just as likely to complain of side effects as white patients ($\chi^2 = 0.035$, df = 1, $p = .851$).

Our data also indicate that clinician perception of compliance does differ with ethnic group, but this differential assessment also does not fully explain differences in depot use. Clinicians in this sample were more likely to perceive African Americans as noncompliant; however, differences in depot use remained when analyses adjusted for assessed compliance. Interestingly, given the possible underuse of depot agents in this cohort, depots may have been used more appropriately among African Americans than among whites.

Congruent with earlier reports,[36,37] we found that clinicians were less likely to prescribe depot antipsychotics for patients over the age of 65 years. Although this may be partially explained by clinicians' more frequent assessment of good compliance among older patients, differ-

ences in depot use remained when analyses adjusted for assessed compliance. As older patients are more likely to experience side effects on antipsychotic medications, we suspect that clinicians may have been more concerned about the prolonged washout period of depot medications.

Interestingly, despite the low overall prevalence of depot use, when used, depot medications were often prescribed in high doses. In this cohort, 57% of patients on depot medication received doses above PORT recommendations. We found that high doses were particularly likely if fluphenazine rather than haloperidol decanoate was used, possibly due to prescribing habits that were established at the time of release and the peak use of these medications. Fluphenazine decanoate was released in the 1960s and used throughout the period when high antipsychotic doses were in favor (the late 1970s through the mid-1980s), whereas haloperidol decanoate was released in 1986 when the literature supporting moderate doses of antipsychotics was beginning to have an impact. Once established, prescribing patterns may be difficult to change.

Patients on depot antipsychotics were more likely to receive high doses than patients on oral conventional agents; just 28% of patients on oral conventional antipsychotics received high doses. Other investigators have reported that depot antipsychotic agents are more likely to be used in high doses than oral conventional agents.[48] The relatively high doses of depot agents may explain, in part, why patients receiving depot preparations were more likely to complain of medication side effects.

In this cross-sectional study, levels of psychopathology and estimated levels of compliance during the last year did not differ significantly between patients on oral and patients on depot medications. The lack of association between depot use and assessed compliance may arise from the fact that patients' medications were reported at the time of enrollment, but medication compliance was judged for the past year. Some patients may have been noncompliant with oral medications during the past year but were switched to depot medications by the time of study enrollment; others may have been on depot medications throughout the year but continued to be noncompliant. Clinicians rating patient compliance may have had varying levels of familiarity with their patients and may have more accurately judged the compliance of patients on depot medications. (Clinicians tend to overestimate compliance with oral medication[49]; noncompliance with depot medications is more easily discerned.) Longitudinal data are needed to further delineate the relationship between depot use and subsequent compliance.

Several limitations should be considered when interpreting our findings. First, we are unable to comment on why clinicians did not prescribe depot medications for patients who had difficulty complying with oral medications. Clinicians may have perceived injections to be coercive, patients may have refused depot injections, or depot medications may have been used unsuccessfully in the past. As outlined above, we are also unable to comment on whether depot agents improved subsequent compliance among these seriously ill patients.

Lastly, our data reflect prescribing practices from 1991 to 1995; atypical antipsychotic agents have become more widely used since that time. Because atypical agents have fewer side effects than conventional agents, noncompliance may be less of an issue when patients are prescribed atypical antipsychotic agents and the need for depot medication may have declined since 1995. Clinicians may delay prescribing depot medication until they try one or more of the newer antipsychotics to see if this increases patients' willingness to comply with antipsychotic medication. Still, many investigators and clinicians note continuing problems with compliance despite the advent of atypical agents and have called for the development of depot preparations of these agents.[50] A depot preparation of risperidone is currently being tested.[51]

In conclusion, our data suggest that depot antipsychotics may be an underused treatment option for patients with schizophrenia. Low use of depot medication in the face of high rates of noncompliance and significant variations in use by treatment site and ethnic group suggest barriers to consistently implementing depot medication in noncompliant patients. Unfortunately, when patients do receive depot medications, they may receive unnecessarily high doses. Quality improvement programs should consider encouraging depot use for noncompliant patients, developing systems that facilitate depot use, and educating providers about appropriate dosing.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), risperidone (Risperdal).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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