Guideline Implementation and Patient-Tailoring Strategies to Improve Medication Adherence for Schizophrenia

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Objective: To determine the effectiveness of an intervention to promote medication adherence.

Method: Data were collected for adults with exacerbation of schizophrenia who were treated at one of 6 U.S. Department of Veterans Affairs (VA) Medical Centers (VAMCs) in 3 regional VA networks (Veterans Integrated Service Networks [VISNs]) from March 1999 to October 2000. All 6 VAMCs received a basic guideline implementation strategy for medication management of schizophrenia using usual VA procedures. One VAMC within each VISN was randomly selected to receive an enhanced implementation strategy designed to promote guideline-concordant prescribing by physicians and medication adherence by patients. In the enhanced strategy, a research nurse worked with study participants to identify medication adherence barriers and to develop patient-specific strategies to overcome those barriers. Participants (N = 349) were interviewed at enrollment and 6 months later, using the Structured Clinical Interview for the Positive and Negative Syndrome Scale (PANSS), the Barnes Akathisia Rating Scale, and the Schizophrenia Outcomes Module (SCHIZOM). Medication adherence was measured via subjects' self-report, using the SCHIZOM, and from data abstracted from medical records.

Results: Participants were primarily male (94%) and nonwhite (69%, primarily African American) with a mean age of 46 years. Medication adherence at follow-up was modeled using logistic regression, controlling for adherence at baseline, demographic characteristics, PANSS total score, akathisia at baseline, family history of mental illness, and substance abuse. A logistic regression model for adherence at follow-up was significant (likelihood ratio = 52.72, df = 14, $p < .0001$). Patients enrolled at sites receiving the enhanced intervention were almost twice as likely to be adherent at follow-up. Those who were nonadherent at baseline were significantly less likely to be adherent at follow-up. In addition, adherence at follow-up was significantly greater at 2 of the VA networks as compared to the third network.

Conclusions: These data suggest that a patient-centered strategy to identify and overcome barriers to adherence can improve adherence to antipsychotic medications.

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Medication management with antipsychotics is one of the cornerstones of treatment for schizophrenia.[1–4] Unfortunately, nonadherence to antipsychotic regimens remains a serious problem in schizophrenia, and it is associated with poor outcomes, more hospital readmissions, and increased costs of care.[5–9] Despite the development of newer antipsychotics that cause fewer movement disorders and continued research of strategies to improve adherence, nonadherence to antipsychotic medications continues to have a major negative impact on the treatment and clinical outcomes of patients with schizophrenia.[10–12]

In a recent review of strategies to improve adherence to antipsychotic medications, Zygmunt and colleagues[13] conclude that assertive community treatment models and motivational interviewing techniques appear to be the most effective for improving adherence. Other studies have found that behavioral tailoring, self-monitoring, and reminders/cues are helpful to improve adherence.[14–16] However, many of these promising techniques are more

time- and resource-intensive than is feasible within settings providing routine clinical care. It is important to continue to develop and test strategies to improve adherence to antipsychotic medication in this population.

The present study uses data collected for the U.S. Department of Veterans Affairs (VA)–funded Schizophrenia Guidelines Project, which was a multi-site study designed to examine how strategies to implement clinical practice guidelines for schizophrenia affect subjects' care and the outcomes of that care. Specifically, we studied whether an enhanced guideline-implementation strategy that promoted guideline-concordant prescribing by clinicians and medication adherence by patients would be more effective than a basic implementation strategy in improving subjects' adherence to antipsychotic medications. This article focuses on findings related to adherence to antipsychotic medication and identifies characteristics of patients who are at risk for nonadherence.

METHOD

Project Overview

Eight eligible Veterans Affairs Medical Centers (VAMCs) within 4 Veterans Integrated Service Networks (VISNs) were selected to participate in the Schizophrenia Guidelines Project, conducted from March 1999 to October 2000. Because it is possible that network-level policies could influence the likelihood of medication adherence, we designed the study to compare facilities within VA networks (VISNs). We paired a facility receiving the enhanced intervention with a facility receiving the basic intervention within the same VISN. However, one facility was unable to complete the study because of administrative issues, and therefore data from that facility and its paired facility in that network were excluded from comparison of the adherence intervention, leaving data from 6 sites available for analysis.

All 6 VAMCs received basic education about schizophrenia guidelines, with 3 facilities receiving the enhanced intervention. The present study utilizes data collected from patient interviews and from medical records at 6 VAMCs that completed the project: 2 sites within each of 3 VISNs. One of the 2 participating VAMCs per VISN was randomly selected to receive the enhanced intervention strategy, and the other site within each pair received a basic education strategy for schizophrenia guidelines. Approval for research involving human subjects was obtained from the designated institutional review board at each of the 6 VAMCs included in this study. Consistent with Veteran Health Affairs' ongoing nationwide effort to implement treatment guidelines, all 6 VAMCs received a basic guideline implementation strategy for medication management of schizophrenia using usual VA procedures consisting of dissemination of educational materials about guidelines and local development of guideline-derived clinical pathways for treatment of schizophrenia.[17] One VAMC within each VISN was randomly selected, using a random numbers table, to receive an enhanced implementation strategy designed to promote guideline-concordant prescribing by physicians and medication adherence by patients. A more extensive description of site selection methods, recruitment and follow-up rates, and other study details has been previously published.[18,19]

Sample and Data Collection

Patients were eligible for the study if they were experiencing an exacerbation of schizophrenia, were 18 to 65 years old, were able to give informed consent, and were not enrolled in another study that mandated a particular medication protocol. After giving informed consent, each participant was interviewed at baseline and 6 months later using the Structured Clinical Interview for Positive and Negative Syndrome Scales (SCI-PANSS),[20] the Barnes Akathisia Rating Scale (BARS),[21] the Schizophrenia Outcomes Module (SCHIZOM),[22–26] and the MOS 36-Item Short-Form Health Survey (SF-36).[27]

Medication adherence variables were derived from 2 data sources: the adherence measure from the SCHIZOM administered during the baseline and follow-up interviews and the medical record for the subject's inpatient or outpatient encounter closest to the baseline and follow-up dates. Trained research assistants abstracted medication adherence information from the clinic visit closest to the date of the baseline and follow-up interviews. The research assistant looked for any mention that the patient was not taking an antipsychotic medication as prescribed or needed to resume antipsychotic medication in physician history and physical or in daily notes and in intake notes from nurse practitioners and social workers. If the provider did not address adherence in the medical record, the patient was classified as adherent on the medical record measure. Chart abstractions were completed for all study participants regardless of whether they completed the follow-up interview. For those who did not complete the follow-up interview, chart abstraction data were used to assess medication adherence.

Intervention

The intervention was delivered by trained nurse coordinators who worked at least 50% of full-time employment. After each enrolled participant completed the baseline research interview with a trained research assistant, the research nurse coordinator followed the written protocol for the intervention and conducted a clinical interview lasting 20 to 60 minutes. During this interview the nurse completed a checklist of 9 domains of barriers to adherence, derived from an extensive literature review: (1) memory problems, (2) problems with the medication regimen, (3) subject's fear of medications, (4) adverse

drug reactions, (5) denial of illness, (6) stigma of taking medication, (7) lack of trust in the provider, (8) lack of social support, and (9) other issues (for barriers that were reported but not listed in the previous 8 domains). Based on the barriers identified, the nurse coordinator worked with participants to select and tailor strategies that could be used to overcome that particular barrier. For example, if a patient had difficulty remembering to take the medication, the nurse could offer an option such as a pill organizer or the nurse could use behavioral tailoring techniques to help patients remember to take medication when performing another routine task such as brushing their teeth, or work with a family member to help the patient remember to take the medication.[15,28] The nurse coordinator conducted barrier assessments at entry into the study and at each subsequent visit to the mental health provider. For individuals who did not have mental health appointments more frequent than every 6 weeks, the nurses attempted to contact the study participants in order to conduct a barrier assessment a minimum of every 6 weeks throughout the 6-month study period.

The nurse coordinators completed one-and-a-half days of training with the research team. The nurses were given a detailed manual describing the intervention protocol, which included flexible scripts and suggestions to use in conducting clinical interviews with participants and the assessment of medication adherence barriers. The protocol also specified how nurses were to maintain contact with patients during the study period and how to provide feedback to each physician about the participants' treatment preferences, reported adherence, adherence barriers, and generic information about VA clinical practice guidelines for schizophrenia. During training, role play was used to ensure that nurses understood the intervention and how to conduct it.

Forms developed by the research team were used to document specific elements of the intervention and barrier assessment. Fidelity to the study protocol was monitored by research staff in Little Rock, who received copies of all forms used for the project and logs of activities conducted for each enrolled subject and maintained regular phone contact with each the personnel at each study site.

Data Analysis

Medication adherence variables were derived from 2 data sources: the adherence measure from the SCHIZOM administered during the baseline and follow-up interviews and the medical record abstraction for the subject's visit closest to the baseline and follow-up dates. If a patient was rated as nonadherent by either method, then the patient was classified as nonadherent for the combined variable used in analyses.

The SCHIZOM is the participant's self-report of medication use over the previous 30 days as follows: (1) never missed medication, (2) missed a couple of times but basically took all medications, (3) missed several times but took at least half of medications, (4) took less than half of medication, and (5) stopped taking medication altogether.[25] We converted adherence responses to a dichotomous indicator of adherence; a report of 1 or 2 was considered adherent and reports of 3, 4, or 5 were considered nonadherent.[25,29]

We identified risk for substance abuse based on patient response to the CAGE questions and to questions about recent alcohol or drug use that are embedded in the SCHIZOM. If a patient answered yes to one of the CAGE questions and had recent alcohol or drug use, that patient was classified in the analysis as being at risk for substance abuse.[22,26]

We conducted bivariate analyses using χ^2 tests, t tests, and logistic regression to compare baseline characteristics of participants enrolled at enhanced versus basic implementation sites. Logistic regression was used to model adherence at follow-up controlling for differences in subjects' baseline characteristics and for variables known to influence medication adherence (e.g., substance abuse). Casemix measures and control variables included in each model consisted of a VISN indicator variable (to control for potential regional or organizational differences), premorbid adjustment, age when first visited a mental health professional, symptom severity assessed by the PANSS, family history of mental illness, and substance abuse risk. With the exception of the VISN indicator variable and the PANSS score, each of the casemix measures is available from the SCHIZOM.

RESULTS

The majority of subjects were male (N = 328, 94%), the mean age was 46 years (SD = 7.84), 31% (N = 108) were white, and 69% (N = 241) were nonwhite, primarily African American. (See Table 1.) Most patients were not married or living with someone (86%, N = 300), and about half had completed at least some college (46%, N = 159). Of 349 patients enrolled at the 6 VAMCs, 84% (N = 293) completed both baseline and 6-month follow-up assessments. Study participants lost to follow-up were more likely to be white (45% vs. 28%, $\chi^2 = 5.8563$, df = 1, $p < .05$) and unmarried/separated (95% vs. 84%, $\chi^2 = 4.1669$, df = 1, $p < .05$), but there were no other significant demographic differences between those who did or did not complete follow-up interviews. The mean ± SD time to follow-up interviews was 187 ± 31.5 days.

In bivariate analyses, there were no significant differences between patients enrolled at basic versus enhanced implementation sites in terms of their age, gender, marital status, education, premorbid adjustment, or substance abuse risk. Patients enrolled at basic implementation sites were significantly more likely to be white (39% vs. 23%,

Table 1. Demographic Characteristics of Patients According to Implementation Strategy Received

Variable	Total, N = 349	Basic, N = 176	Enhanced, N = 173	p Value
Age, mean (SD), y	46.12 (7.95)	46.84 (7.9)	45.39 (7.96)	.088
Race, N (%)				
White	108 (31)	68 (39)	40 (23)	.0018
Nonwhite	241 (69)	108 (61)	133 (77)	
Gender				
Male	328 (94)	167 (95)	161 (93)	.5074
Married or living with someone, N (%)	300 (86)	150 (85)	150 (87)	.76
Education, N (%)				
High school or less	190 (54)	102 (58)	88 (51)	.198
Premorbid adjustment, N (%)				
Poor	98 (28)	54 (31)	44 (25)	.286
Substance abuse				
Yes	108 (31)	58 (33)	50 (29)	.413
Akathisia at baseline, N (%)				
Positive	129 (37)	63 (36)	64 (37)	.912
PANSS scores, mean				
Positive	21.7	20.16	23.22	< .0001
Negative	19.0	18.1	19.9	.0074
General	40.9	37.6	44.4	< .0001
Total	81.7	76.0	87.4	< .0001
Adherent at baseline, %	44.1	45.5	42.8	.667

Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Table 2. Proportion of Study Participants Assessed as Adherent to Medication at Baseline and Follow-Up

Site	Participants Adherent at Baseline, N (%)	Participants Adherent at Follow-Up, N (%)
VISN A, enhanced	22 (55)	34 (85)
VISN A, standard	34 (47)	45 (63)
VISN B, enhanced	22 (36)	37 (61)
VISN B, standard	22 (38)	36 (62)
VISN C, enhanced	30 (42)	42 (58)
VISN C, standard	24 (52)	25 (54)

Abbreviation: VISN = Veterans Integrated Service Network.

p = .0018) and had significantly lower baseline PANSS scores compared with enhanced sites.

There was no significant difference in baseline adherence for patients enrolled at basic versus enhanced implementation sites (45.5% vs. 42.8%, respectively; p = .902). Overall, 44.1% of the entire sample was assessed as adherent to antipsychotic medications in the 4 weeks prior to study enrollment (baseline). At follow-up, the proportion of participants at enhanced sites who were assessed as adherent had increased to 65.3%, a 22.5% increase, whereas the increase in adherence (to 60.6%, a 15.1% increase) was less dramatic at basic implementation sites. The extent of improvement in adherence at the 3 enhanced sites, in comparison to the matched basic sites, differed. As displayed in Table 2, there was relatively greater improvement in medication adherence rates at enhanced sites in VISNs A and C, whereas there was essentially no difference in adherence rates in VISN B.

Table 3. Logistic Model[a] of Likelihood of Adherence at Follow-Up

Variable	χ^2	OR	95% Confidence Interval	p Value
Age	2.91	1.03	1.00 to 1.06	.09
Race (white vs nonwhite)	1.62	1.43	0.82 to 2.49	.20
Sex (female vs male)	1.88	2.99	0.63 to 14.26	.17
Adherence at baseline	21.74	0.28	0.17 to 0.48	< .01
Site type (enhanced vs basic)	4.97	1.94	1.08 to 3.48	.03
VISN	6.94	2.19	1.09 to 4.37	.03
Akathisia at baseline	0.38	1.18	0.70 to 1.99	.54
Premorbid adjustment (good vs poor)	1.06	0.74	0.43 to 1.30	.30
Substance abuse (no vs yes)	0.0036	1.02	0.60 to 1.73	.95
Positive family history for mental illness (no vs yes)	0.26	1.14	0.69 to 1.87	.61
PANSS total scores	2.66	0.99	0.97 to 1.00	.10
LOS, d	0.62	1.00	0.99 to 1.01	.43
Age at first treatment	3.00	0.97	0.94 to 1.00	.08

[a]Hosmer and Lemeshow goodness of fit, $\chi^2 = 3.20$, df = 8, p = .9214.
Abbreviations: LOS = length of (inpatient) stay, OR = odds ratio, PANSS = Positive and Negative Syndrome Scale, VISN = Veterans Integrated Service Network.

A logistic regression model for adherence at follow-up is presented in Table 3 and was significant (likelihood ratio = 52.72, df = 14, p < .0001). Patients enrolled at sites receiving the enhanced intervention were significantly more likely to be adherent at follow-up (odds ratio = 1.94, 95% CI = 1.08 to 3.48), controlling for baseline adherence and other clinical and demographic variables. In addition, those who were nonadherent at baseline were significantly less likely to be adherent at follow-up. Compared with participants in VISN C, participants in VISNs A and B were more likely to be adherent at follow-up.

To further explore differences in adherence, clinical and demographic characteristics of patients who were adherent (N = 220) were compared with those who were nonadherent (N = 129) at follow-up using a χ^2 test for categorical variables and a Student t test for continuous variables. At follow-up, female patients were significantly more likely to be adherent as compared with males (88% vs. 62%, $\chi^2 = 5.27$, df = 2, p = .037). Patients who were classified as adherent at follow-up were more likely to have been adherent at baseline (79.7% vs. 48.7%, $\chi^2 = 33.06$, df = 1, p < .0001) and to have a negative baseline diagnosis for akathisia (67% vs. 46%, $\chi^2 = 3.87$, df = 1, p = .049) compared with patients who were classified as nonadherent at follow-up. Patients who were adherent at follow-up also had significantly lower baseline total PANSS scores (80 vs. 84, p = .0081, SD = 19.23, t = 2.66) than nonadherent patients. Premorbid adjustment, family history of mental illness or risk of substance abuse, age at first mental health treatment, or age at study enrollment were not associated with differences in adherence at follow-up. Nonwhite patients were slightly less likely to be adherent compared with white patients,

although this difference was not statistically significant (59.6% vs. 70.4%, $\chi^2 = 3.71$, df = 1, p = .054).

DISCUSSION

The intervention in this study used a practical, patient-tailored approach to identify and overcome barriers to medication adherence. In a recent review of interventions to improve medication adherence in schizophrenia, Zygmunt and colleagues[13] similarly noted that concrete problem-solving or motivational techniques to target nonadherence were more likely to result in improved adherence. In our intervention, barriers to medication adherence were identified for each individual, and strategies to overcome those barriers were offered. The participants worked with the nurse coordinators at sites receiving the enhanced intervention to select strategies that would best fit their particular situation and needs.

Overall, patients in this study who were treated at a site receiving an enhanced guideline implementation intervention that promoted medication adherence were significantly more likely to be adherent at 6-month follow-up, controlling for baseline adherence and other clinical and demographic factors. In addition, adherence at follow-up was also significantly associated with adherence at baseline. The effectiveness of the enhanced implementation strategy with regard to improving medication adherence, in comparison to the basic strategy, was not uniform across the 3 enhanced sites, with a dramatic improvement at the enhanced site in VISN A and a moderate improvement in VISN C. This difference may represent unmeasured differences in care among VA networks or differences in the delivery of the intervention at each enhanced site. A nurse supervisor from the research team reviewed the intervention with each nurse on a weekly basis and reviewed all barrier assessment forms for each patient. Every effort was made to standardize the enhanced intervention across sites. However, the mean (SD) number of clinical barrier assessment forms completed by nurse coordinators per patient during the 6-month follow-up period was 7.0 (3.2), 3.4 (2.0), and 2.5 (1.6) for the enhanced sites in VISNs A, B, and C, respectively. That is, the VISN with the most improvement in adherence was also the VISN with the most active nurse. This difference in adherence may also represent variations in skill and experience among the nurses who implemented the intervention. Although all the nurses in the study had extensive clinical experience in mental health care, the nurse in VISN A had more research experience.

Our finding that past adherence influenced future adherence is consistent with the work of others. In a review of studies evaluating risk factors for treatment nonadherence in patients with schizophrenia, Lacro and colleagues[6] noted that previous nonadherence was associated with future nonadherence. Strategies that can identify past nonadherence may be a useful tool to help clinicians identify patients at risk for future nonadherence and should be explored further.

In our data, the network in which the patients received care was also associated with adherence to antipsychotic medications. Patients treated in networks A and B were more likely to be adherent at follow-up than those treated in network C, controlling for baseline adherence, other clinical characteristics, and demographic characteristics, regardless of whether they received the adherence intervention. This association suggests that there are quite likely additional characteristics, such as differences in patient populations or site characteristics, that affected change in adherence over time. This variation is consistent with our previous work and that of others, which found geographic and racial variations in care.[30–32] It is possible that variations in medication management by the providers across sites could have affected change in adherence over time. However, as we report in a currently unpublished paper, we found that antipsychotic dose, an important aspect of medication management, was not significantly different in enhanced compared with basic sites in this study (unpublished data, R.R.O., P.T., C.R.T., et al., 2006). The organization of VAMCs may also account for VISN-level differences. VAMCs are grouped in networks. Policies for the provision of clinical care, especially mental health care, are often developed at the network level. Differences in the VISN-level leadership in mental health care may have also influenced the outcomes in this study.

This study has several limitations. It is always difficult to measure medication adherence; each method of measurement is associated with a variety of limitations,[33,34] and electronic monitoring is often considered the gold standard. However, we were interested in designing an intervention that would be feasible to use in routine clinical care. Because the costs of electronic monitoring can be quite expensive, it may not be feasible in routine care. Therefore, we did not include this measurement strategy in our intervention. We used a combination of self-report and provider assessment, which may overestimate adherence (e.g., underestimate nonadherence). In order to be as conservative as possible, we combined the measures and used the most conservative estimate.[29] That is, if either measure suggested the patient was nonadherent, he/she was classified as nonadherent. Because this study was conducted in VA facilities, the findings may not be generalizable to women with schizophrenia and to non-VA settings. More research will be needed to determine the effectiveness of such interventions in women with schizophrenia and in diverse practice settings.

Despite the limitations of this study, the results have several implications relevant to clinical care. First, the results suggest that a practical, tailored intervention that identifies and addresses adherence barriers can improve

adherence to antipsychotic medication. A central aspect of the intervention employed in this study was the use of trained nurses who used patient-centered strategies to identify and help patients overcome barriers to medication adherence. Second, our approach focused on intervening with both the clinician and patients to promote guideline-concordant treatment, to address patient preferences in treatment decisions, and to integrate the patients' daily routine and social supports into developing strategies for improving medication adherence. In our study, nonadherence at the time of an acute exacerbation of schizophrenia was strongly associated with nonadherence 6 months later. Therefore, availability of information about past adherence may be useful to identify which patients are most likely to benefit from an intervention to improve medication adherence.

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