Predictors of Risk of Nonadherence in Outpatients With Schizophrenia and Other Psychotic Disorders

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Abstract

We investigated the course of adherence to medication recommendations in 162 patients with psychotic disorders in ambulatory treatment. Data were collected using the clinic’s outcome assessment program, maximizing the generalizability of the study. Patients initially adherent to their medication regimens maintained their adherence for an average of 13.3 months. Patients initially nonadherent developed adherence after an average of 5.6 months of treatment. Demographic factors and illness history were unrelated to adherence. This study replicated previous findings of the concurrent association between adherence and global functioning level, substance use, and working alliance with therapist. Cox regression analyses revealed that working alliance, global functioning, and being prescribed clozapine predicted longer maintenance of adherence. Working alliance was the most significant and consistent predictor of adherence to medication recommendations.

Keywords: Psychotic disorders, schizophrenia, adherence, compliance, working alliance, clozapine.


Nonadherence to medication recommendations is a substantial problem in patients with psychotic disorders and is greater among outpatients than inpatients (Hare and Willcox 1967; Irwin et al. 1971). Nonadherence, traditionally termed noncompliance, contributes to relapse, rehospitalization (Caton et al. 1985; Curson et al. 1985; Adams and Howe 1993), increased health care costs, and increased suffering of patients and those involved in patients’ lives. Previous studies have identified factors associated with adherence to medication regimens in schizophrenia. A review by Fenton and colleagues (1997) found that nonadherence among patients with schizophrenia was consistently associated with more severe psychopathology, greater substance use, greater medication side effects, more practical barriers, less family and social support, less insight, and a less positive doctor-patient relationship. Demographic characteristics (age, gender, ethnicity, education, income), illness history variables (age of onset, duration of illness, age at first hospitalization, premorbid functioning), and cognitive variables (overall intelligence, mental status) were usually found to be unrelated to adherence.

As new-generation, or atypical, antipsychotics have been developed, it has been hypothesized that the increased effectiveness of the medications, the decreased side effects of the medications, or both types of changes will facilitate adherence. Others (Hale 1993) have rejected the notion that new antipsychotics will lead to improved adherence. Clozapine has been demonstrated to promote clinical improvement better than conventional agents, and it does so with minimal extrapyramidal symptoms (Meltzer 1992; Rosenheck et al. 1997). There is evidence to support the idea that clozapine is associated with better adherence in psychotic inpatient samples (Claghorn et al. 1987; Rosenheck et al. 1997). As with prior reports, these studies were largely cross-sectional, and causal associations between proposed predictors and nonadherence remain unclear.

This study uses a cross-sectional and a longitudinal prospective design in an attempt to investigate medication adherence in psychotic patients in an ambulatory setting at a not-for-profit community-based hospital in the suburbs. We aimed to extend prior research by addressing the following questions: (1) what treatment, clinical, and demographic factors are associated with medication nonadherence in a cohort of patients with psychotic disorders who have just been admitted to an outpatient clinic; and (2) what factors predict changes in adherence over time—that is, why do adherent patients become nonadherent, and what predicts how long it takes for nonadherent...
patients to improve adherence with medication recommendations? These latter questions will help identify patients who are at high risk for nonadherence at the onset of a course of ambulatory treatment and may lead to the development of interventions to minimize treatment nonadherence and facilitate good outcome.

This study utilized an ongoing outcomes assessment program in our Schizophrenia Disorders Program in order to address the above questions. As part of this outcomes program, therapists complete a battery of questionnaires on all patients at regular intervals. The battery assesses several variables that are relevant to an adherence study, and the longitudinal nature of the program provides the opportunity to use survival analysis, a statistical procedure that has several advantages. Because this study utilized data from an outcomes assessment program, the study should be thought of as “real-world” services research with greater generalizability than earlier, more tightly controlled studies.

Method

Sample. The patients in this study represent 162 out of 180 consecutive admissions to an ambulatory psychotic disorders clinic (64% day hospital, 36% outpatient department) of our Schizophrenia Disorders Program between May 1997 and February 1999. The inclusion criteria included the presence of a psychotic disorder diagnosis by the admitting clinician and completion of a data packet by the patient’s therapist within 7 days of the admission. The 18 patients excluded did not significantly differ from the study patients in terms of age, age at first hospitalization, number of previous hospitalizations, gender, or race. Most study patients were diagnosed with either schizophrenia (47.5%) or schizoaffective disorder (45%), with the remainder having other psychotic disorders. The sample included 102 males (63%) and 60 females, and subjects ranged in age from 18 to 58 (mean [M] = 36.0, standard deviation [SD] = 9.1). Most were Caucasian (78%), a substantial minority were African-American (14%), and the remainder were Hispanic (4%), Asian (2%), or of mixed background. The average age of first hospitalization was 23 years (SD = 7.0). Twenty-two percent had 15 or more lifetime hospitalizations; 10 percent had been hospitalized 10–14 times; 27 percent had been hospitalized 5–9 times; and 39 percent had been hospitalized 1–4 times.

Instruments. Variables tracked by an ongoing clinical outcomes assessment program that have been commonly studied in previous research on adherence were selected for inclusion in this study.

Working alliance. The Working Alliance Inventory—Short Form, therapist version (WAI; Horvath and Greenberg 1989), was used to measure therapeutic alliance between patients and therapists. The measure taps three aspects of the therapeutic alliance: patient-therapist agreement regarding goals of treatment, agreement regarding tasks to be used to work toward those goals, and the degree to which a bond exists between the therapist and the patient. Scores range from 12 to 84, with higher scores indicating a stronger working alliance. In the current sample, Cronbach’s alpha was 0.82, providing support for the measure’s stability. Other studies have used this measure to demonstrate significant associations between alliance and outcome in samples of patients with serious mental illness and schizophrenia (Goering and Stylianos 1988; Gehrs and Goering 1994; Neale and Rosenheck 1995; Tyrrell et al. 1999).

Psychosis and substance use. The Basis–32 (Eisen et al. 1994) is a 32-item measure developed to evaluate psychiatric patient outcome in terms of various areas of functioning and symptoms. A positive symptoms variable was created by averaging the scores for the items “disturbing or unreal thoughts or beliefs” and “hearing voices, seeing things.” The mean score on the items “drinking alcoholic beverages” and “taking illegal drugs, misusing drugs” was used to measure substance use. These items were used in place of the subscales suggested by Eisen and colleagues because preliminary factor analyses based on the current sample did not support the use of the subscales in the present sample. Therapists completed the Basis–32 for their patients based on their clinical assessments because the patients’ clinical state would often make it difficult for them to complete a self-report form. Scores on Basis–32 items range from 0 to 4, with higher scores indicating greater difficulty.

Functioning level. Therapist ratings on the Global Assessment of Functioning Scale (GAF; American Psychiatric Association 1994) were used as a measure of overall functioning level/severity of mental illness.

Treatment adherence. The patients’ primary therapists rated medication adherence. A 4-point scale (McEvoy et al. 1989) was used: 1 = active compliance (readily takes medication at appropriate times), 2 = passive compliance (must be reminded or encouraged but does not resist when asked to take medication), 3 = resistance (“cheeks” medication but takes medications when they are repeatedly proffered or strict limits are set), and 4 = overt refusal (medications can be given only against client’s wishes or are not given). Because data were skewed, scores were dichotomized, with patients receiving a rating of “1” considered “actively adherent” and patients scoring 2, 3, or 4 classified as having “adherence difficulties.” No objective information was available to confirm the accuracy of these ratings, but to maximize validity, therapists were instructed to use all available information to make these ratings, including the patients’
Predictors of Risk of Nonadherence in Outpatients

Reports, collateral reports, and clinical observations. This measure has been successfully used in a previous study of adherence in this population (Corriss et al. 1999).

**Medication.** Patients were categorized as to whether or not they were prescribed clozapine. Patients on other antipsychotic medications and conventional agents were grouped together because preliminary analyses revealed no difference between these two groups in terms of the major study variables.

**Procedure.** Data for this study were obtained from the clinic's outcomes assessment program. Each time a patient in the clinic is admitted, is discharged, or changes level of care (i.e., is transferred from outpatient to inpatient unit), the patient's primary therapist completes a battery of questionnaires. Therapists also complete a battery monthly on all patients in day treatment and quarterly on all patients in outpatient treatment. This outcome assessment program began in May 1997 and has run continuously up to the writing of this article.

At the inception of the program, all therapists in the Schizophrenia Disorders Program attended staff meetings that included training in completing the instruments in the assessment battery. New therapists were given individual training as part of their orientation to working in the program. Additional training was provided periodically during staff meetings when it was deemed necessary by quality improvement studies. Because of the study design, formal training of raters and formal reliability studies were not feasible. However, reliability and validity of the instruments used have been previously demonstrated.

At each single point in time, one therapist completed the entire battery of questionnaires for a particular patient. Therefore, for cross-sectional analyses, the same therapists rated adherence and other variables. Most often, the same therapist completed both the initial battery and the battery completed at the endpoint. However, a patient sometimes had consecutive batteries completed by different clinicians because of a change in therapist. Therefore, in longitudinal analyses, the endpoint adherence rating may or may not have been done by the same therapist that rated initial adherence. The therapists were social workers, psychiatric nurses, or doctoral-level psychology fellows who were the primary coordinators of the patients' care, providing individual and family counseling and treatment planning.

Data for the present study are for patients who were admitted to ambulatory treatment (day hospital or outpatient) after May 1997 and had batteries completed by their therapists within 7 days of admission. Followup data for each patient were included until one of four events occurred: (1) an initially actively adherent patient got a rating indicating adherence difficulties, (2) a patient with initial adherence difficulties received a rating of active adherence, (3) the patient left the clinic, or (4) the study period ended (February 1999). Patients were followed for an average of 7 months (SD = 5.6), ranging from a few days to more than 22 months.

**Statistical Analysis.** Data were analyzed using the Statistical Package for the Social Sciences (SPSS). Three analyses were carried out. The first investigated variables cross-sectionally related to difficulties with medication adherence at the time of admission to ambulatory treatment using Spearman and Kendall correlation coefficients. The second set of analyses, which were longitudinal and prospective, focused on patients who were rated as actively adherent at admission. The time-course of medication adherence was studied using survival analysis techniques, and predictors of the length of time active adherence was maintained were identified using the Cox proportional hazards regression model. The final analyses used the same approach to look at those patients who began treatment with adherence difficulties, describing the predictors and time-course for the development of active adherence.

Survival analysis can analyze data from subjects who enter and leave the study at different times, minimizing biases, such as history effects, that result from fixed-point data collection methods. Survival analysis also takes into account data from all subjects, no matter how long they were followed, reducing biases resulting from differential dropout rates. In sum, the procedure allowed new patients to enter the study continuously until the study ended and included data on patients who were later lost to followup. This statistical methodology has been used effectively to study the predictability of rehospitalization of patients with schizophrenia (Caton et al. 1985; Haro et al. 1994; Mortensen and Eaton 1994).

**Results**

At baseline, patients displayed low-to-moderate levels of positive psychotic symptoms (M = 1.23, SD = 1.17) and low levels of substance use (M = 0.10, SD = 0.45). There was substantial variability in GAF scores (M = 40.55, SD = 9.44) and in WAI scores (M = 59.11, SD = 12.09). Eighty percent of the patients were rated as "actively adherent" on admission. Sixty-nine patients (44%) were prescribed clozapine; 34 percent were taking atypical antipsychotics other than clozapine; 10 percent were prescribed atypicals other than clozapine with a conventional antipsychotic; and 12 percent were taking only conventional antipsychotic drugs.

**Cross-Sectional Analyses at Baseline.** To determine which variables were associated with adherence at the
time of admission to ambulatory care, correlations were performed. Eight variables were considered: age, gender, age at first hospitalization, positive psychotic symptoms, substance use, global functioning level, working alliance with therapist, and whether or not clozapine was prescribed. Kendall’s tau-b was used for correlating continuous variables with adherence, and Spearman’s rho was used for correlating categorical variables with adherence, as shown in table 1. Adherence difficulties were significantly associated with lower GAF scores, more substance use, and weaker working alliance with therapist.

To investigate whether these three variables independently contributed to the variance in adherence, they were simultaneously entered into a logistic regression model with initial adherence status as the dependent variable (full model $\chi^2 = 25.97, df = 3, p < 0.0001$). Only working alliance ($\beta = 0.07$, standard error [SE] = 0.02, $p < 0.001$) remained a significant predictor of adherence.

Maintaining Medication Adherence. In longitudinal analyses, patients were followed until they left the clinic, the study ended, or their adherence status changed.

Survival curve to nonadherence. Patients who were rated as “actively adherent” at baseline were included in this next set of analyses ($n = 127$). The Kaplan-Meier estimator of the survival function was used to generate a survival curve. Patients “surviving” were those who remained in the treatment program and continued to be “actively adherent.” Sixty percent of the cases in this analysis were censored—that is, they did not become nonadherent during the study period. The great majority (83%) of the censored cases in this study were “right censored,” meaning that they did not drop out of the study but completed the study without becoming nonadherent. Censored cases were followed for an average of 9.5 months (SD = 5.6).

Results indicate that 75 percent of patients remained adherent at 5.2 months (SE = 1.3) and 50 percent remained adherent at 13.7 months (SE = 2.6). The mean survival time was 13.3 months (SE = 0.9; 95% confidence interval 11.5, 15.0 months). The risk of nonadherence was consistent across the study period.

Predictors of time maintaining adherence. Cox’s proportional hazards regression model was used to identify variables that predicted the length of time adherence was maintained. The assumption of proportional hazards was tested by visual inspection of plots of baseline hazard functions for different levels of the covariates. The same variables used in the cross-sectional analyses were considered as predictors in this model: age, gender, age at first hospitalization, positive psychotic symptoms, substance use, global functioning level, working alliance with therapist, and whether each patient had been prescribed clozapine. Each of these variables was considered in separate univariate models, as presented in table 2.

Only three of the models were significant: working alliance ($p < 0.001$), global functioning ($p < 0.001$), and clozapine use ($p < 0.01$). The relative hazards for WAI and GAF scores were approximately 0.95, indicating that for every one-point increase in WAI or GAF score, the risk of nonadherence was reduced by approximately 5 percent. Being prescribed clozapine reduced the risk of nonadherence by more than half (odds ratio = 0.44).

Separate Kaplan-Meier survival curves for patients on clozapine and not on clozapine are displayed in figure 1. Patients who were prescribed clozapine ($n = 58$) remained adherent significantly longer (log rank statistic = 8.47, $p < 0.01$) than those who were not prescribed clozapine ($n = 68$). Patients were also divided into low WAI ($n = 65$) and high WAI ($n = 62$) groups, based on a median split (median = 63). Separate Kaplan-Meier survival curves are presented for these groups in figure 2. As the graph shows, patients who had better working alliances with their therapists remained adherent significantly longer than those who scored lower in this area (log rank statistic = 5.94, $p < 0.05$). Patients with higher GAF scores remained adherent significantly longer than those with scores below the median of 40 (log rank statistic = 11.92, $p < 0.001$).

To follow up on the univariate regression analyses, the significant covariates were simultaneously entered into a Cox regression model (full model $\chi^2 = 26.59, df = 3, p < 0.0001$). Results indicated that all three variables remained significant, supporting the hypothesis that GAF ($\beta = -0.04$, SE = 0.02, $p < 0.05$), WAI ($\beta = -0.60$, SE = 0.31, $p < 0.05$), and clozapine ($\beta = -0.04$, SE = 0.01, $p < 0.01$) make unique contributions to the maintenance of adherence.

Table 1. Correlations between adherence and other variables at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Medication adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>161</td>
<td>-0.03</td>
</tr>
<tr>
<td>Gender</td>
<td>162</td>
<td>0.06</td>
</tr>
<tr>
<td>Age at first hospitalization</td>
<td>156</td>
<td>0.03</td>
</tr>
<tr>
<td>GAF</td>
<td>160</td>
<td>0.20***</td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>162</td>
<td>-0.09</td>
</tr>
<tr>
<td>Substance use</td>
<td>162</td>
<td>-0.19*</td>
</tr>
<tr>
<td>WAI</td>
<td>159</td>
<td>0.30***</td>
</tr>
<tr>
<td>Clozapine</td>
<td>158</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Note.—GAF = Global Assessment of Functioning Scale; WAI = Working Alliance Inventory. Correlations are all 2-tailed.

Kendall’s tau-b.

2 Spearman’s rho.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$
Table 2. Univariate Cox regression analyses predicting risk of medication nonadherence in patients who were actively adherent when beginning ambulatory treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>SE</th>
<th>Relative hazard</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age (n = 127)</td>
<td>0.0049</td>
<td>0.0165</td>
<td>1.0049</td>
<td>0.9729</td>
<td>1.0380</td>
</tr>
<tr>
<td>2. Gender (n = 127)</td>
<td>0.3030</td>
<td>0.2937</td>
<td>1.3539</td>
<td>0.7614</td>
<td>2.4074</td>
</tr>
<tr>
<td>3. Age of first hospitalization (n = 124)</td>
<td>0.0149</td>
<td>0.0202</td>
<td>1.0150</td>
<td>0.9755</td>
<td>1.0561</td>
</tr>
<tr>
<td>4. Positive symptoms (n = 127)</td>
<td>0.1209</td>
<td>0.1204</td>
<td>1.1285</td>
<td>0.8913</td>
<td>1.4287</td>
</tr>
<tr>
<td>5. Substance use (n = 127)</td>
<td>-1.1628</td>
<td>1.2353</td>
<td>0.3126</td>
<td>0.0278</td>
<td>3.5199</td>
</tr>
<tr>
<td>6. GAF (n = 125)</td>
<td>-0.0469</td>
<td>0.0128</td>
<td>0.9542***</td>
<td>0.9304</td>
<td>0.9785</td>
</tr>
<tr>
<td>7. WAI (n = 124)</td>
<td>-0.0518</td>
<td>0.0130</td>
<td>0.9495***</td>
<td>0.9256</td>
<td>0.9741</td>
</tr>
<tr>
<td>8. Clozapine (n = 126)</td>
<td>-0.8317</td>
<td>0.2938</td>
<td>0.4353**</td>
<td>0.2448</td>
<td>0.7742</td>
</tr>
</tbody>
</table>

Note.—GAF = Global Assessment of Functioning Scale; SE = standard error; WAI = Working Alliance Inventory.

** p < 0.01; *** p < 0.001

Figure 1. Kaplan-Meier survival graph displaying the number of months initially compliant patients remained compliant, for patients on clozapine (n = 58) and not on clozapine (n = 68)

Figure 2. Kaplan-Meier survival graph displaying the number of months initially compliant patients remained compliant, for patients with high (n = 62) versus low (n = 65) scores on the Working Alliance Inventory

Attaining Medication Adherence

Survival curve to adherence. A Kaplan-Meier estimator of the survival function was used to generate a survival curve, presented in figure 3, which displays the length of time it took for the 35 patients who were initially nonadherent to develop “active” medication adherence. Patients “surviving” were those who continue to be rated as having adherence difficulties. Overall, 75 percent remained nonadherent after 1.0 month (SE = 0.1), 50 percent were still rated as nonadherent after 1.9 months (SE = 0.5), and 25 percent had not yet achieved active adherence by 9.1 months (SE = 3.1) after admission. It took patients an average of 5.6 months (SE = 1.3, 95% confidence interval 3.2, 8.1 months) to develop active adherence. As shown in the figure, the likelihood that a patient would become adherent decreased sharply after approximately 4 months. The nine patients who did not develop adherence within the study period (censored cases) were followed for an average of 7 months (SD = 6.9).

Predictors of time to developing adherence with medication. Cox proportional hazards regression models were used to identify predictors of the length of time it took patients to develop active adherence, with covariates again considered in separate univariate models. Because of the small sample size, the following results should be viewed as tentative and exploratory. As can be seen in table 3, only age (p < 0.01) and working alliance (p < 0.05) were significant predictors of the length of time it took for nonadherent patients to develop adherence, with
In longitudinal analyses, patients were not followed after the first changes in adherence status. Analyses were not conducted to determine the stability of the new adherence status.

**Discussion**

This study offered a comprehensive investigation of the course of medication adherence in a sample of patients with psychotic disorders in ambulatory treatment. Advantages of the methodology used include (1) longitudinal, prospective, as well as cross-sectional design; (2) statistical approach that accounts for variation in treatment lengths and dropouts; and (3) use of a services outcomes program for data collection, which avoids the problems of sample selection bias and leads to real-world generalizability.

This study described the time-course of the maintenance of medication adherence in initially adherent patients and the development of medication adherence in initially nonadherent patients. At baseline, 80 percent of patients were rated as "actively adherent," which is consistent with previous reports in similar populations (Owen et al. 1996; Garavan et al. 1998) but higher than other reports using more objective measures (Willcox et al. 1965; Irwin et al. 1971). In general, reported levels of adherence tend to vary by type of sample and measurement. It is likely that the high level of adherence reported here is due to the fact that most of the patients admitted to ambulatory treatment in our program are transferred from an inpatient stay, during which adherence is emphasized and closely monitored.

Over half of the patients who began ambulatory treatment actively adherent maintained that level of medication adherence for more than a year. The risk of becoming nonadherent was fairly even across the 22-month study period. For the patients who began ambulatory treatment with at least some adherence difficulties, many achieved active adherence fairly quickly, with about half becoming actively adherent within 2 months. The likelihood of patients becoming adherent decreased as time went on. Future research is indicated to explore whether patients who slipped into the nonadherent status according to this study's criteria (a relatively low threshold) experienced negative consequences or were able to regain their active adherence soon enough to thwart poor outcomes. It is also unknown whether initially nonadherent patients who became actively adherent were then able to maintain active adherence or whether they had difficulties later.

**Table 3. Univariate Cox regression analyses predicting chance of becoming actively adherent with medication in patients who were nonadherent when beginning ambulatory treatment**

<table>
<thead>
<tr>
<th>Variable</th>
<th>( \beta )</th>
<th>SE</th>
<th>95% Confidence Interval for Relative Hazard</th>
<th>Relative Hazard</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.  Age ((n = 34))</td>
<td>-0.0649</td>
<td>0.0237</td>
<td>0.9371**</td>
<td>0.8947</td>
<td>0.9816</td>
<td></td>
</tr>
<tr>
<td>2.  Gender ((n = 35))</td>
<td>0.2263</td>
<td>0.4119</td>
<td>0.7975</td>
<td>0.3557</td>
<td>1.7879</td>
<td></td>
</tr>
<tr>
<td>3.  Age of first hospitalization ((n = 32))</td>
<td>0.0111</td>
<td>0.0328</td>
<td>1.0111</td>
<td>0.9481</td>
<td>1.0783</td>
<td></td>
</tr>
<tr>
<td>4.  Positive symptoms ((n = 35))</td>
<td>-0.1577</td>
<td>0.1595</td>
<td>0.8541</td>
<td>0.6247</td>
<td>1.1676</td>
<td></td>
</tr>
<tr>
<td>5.  Substance use ((n = 35))</td>
<td>0.0787</td>
<td>0.2988</td>
<td>1.0819</td>
<td>0.8046</td>
<td>1.3957</td>
<td></td>
</tr>
<tr>
<td>6.  GAF ((n = 35))</td>
<td>0.0047</td>
<td>0.0218</td>
<td>1.0047</td>
<td>0.9826</td>
<td>1.0488</td>
<td></td>
</tr>
<tr>
<td>7.  WAI ((n = 35))</td>
<td>0.0353</td>
<td>0.0175</td>
<td>1.0359*</td>
<td>1.0011</td>
<td>1.0720</td>
<td></td>
</tr>
<tr>
<td>8.  Clozapine ((n = 32))</td>
<td>-0.8076</td>
<td>0.4515</td>
<td>0.4459</td>
<td>0.1841</td>
<td>1.0804</td>
<td></td>
</tr>
</tbody>
</table>

Note.—GAF = Global Assessment of Functioning Scale; SE = standard error; WAI = Working Alliance Inventory.

* \( p < 0.05 \); ** \( p < 0.01 \)
Our use of a longitudinal design generated interesting findings regarding the evolution of adherence problems in this population. Of note, it appears that different factors predict concurrent versus future adherence.

Most of our results were consistent with prior findings. Demographics and illness history were unrelated to adherence (except for younger nonadherent patients developing adherence more quickly), and better functioning and stronger working alliance were associated with better adherence. Less substance use was associated with better adherence at baseline. Being prescribed clozapine was found to be unrelated to adherence at baseline but significantly predicted the length of time adherence was maintained in initially adherent patients.

Of all the variables considered in this study, working alliance was most consistently related to medication adherence. It was cross-sectionally associated with adherence and was a predictor of both maintenance of active adherence and development of active adherence. It is noteworthy that working alliance acted as a significant predictor above and beyond global functioning. This supports previous cross-sectional findings (Marder et al. 1983) and extends them with positive longitudinal results in an outpatient sample. While a good working alliance between therapists and psychotic patients may be challenging to develop (Frank and Gunderson 1990), this study suggests that developing an appreciative, trusting bond and agreement regarding what the patient’s problems are and how they should be worked on is a crucial component of outcome. Further investigation is required to explore how such an alliance can be facilitated. Frank and colleagues (1995) provide guidelines for how education and collaboration can be used in an outpatient treatment program to do so.

In the present study, substance use was associated with nonadherence at baseline but did not significantly predict future nonadherence. Even cross-sectionally, substance use did not remain significantly related to adherence after working alliance was accounted for. It may be that using substances negatively affects adherence by weakening the relationship with the therapist. However, there are other explanations for this lack of replication of previous findings (Owen et al. 1996; Miner et al. 1997). In this study, substance use was very mild, which may be consistent with expectations in an ambulatory treatment setting in a suburban, privately run hospital where patients typically are healthier and have more supports than in public sector settings. It is possible that if use is infrequent it affects adherence only at the time of use without lasting effects.

Being prescribed clozapine significantly lengthened the amount of time patients maintained medication adherence. It has been hypothesized that clozapine increases adherence because its effectiveness in reducing symptoms and improving cognition leads to increased insight into and appreciation of the necessity of medication (Marder 1998). According to the Health Belief Model (Rosenstock 1974), it is also probable that the medication’s lack of extrapyramidal side effects combined with its effectiveness facilitates adherence by lowering the perceived risk-benefit ratio (Rosenheck et al. 1997). An alternative explanation is that rather than the physiological effects of the drug, it is the close monitoring that clozapine patients require that encourages adherence. The frequent clinical contact that coincides with obligatory frequent blood work may also contribute to increased adherence. Frequent visits may facilitate adherence by strengthening working alliance, but it should be noted that this study found an effect of clozapine independent of level of relationship with therapists. Patients may also comply more readily because they often (mistakenly) believe that blood levels of the medication are being checked along with their white blood cell counts. Finally, the relationship between clozapine and adherence is likely influenced by the fact that patients are often informally preselected for adherence before they are prescribed clozapine, because cooperation of the patient is crucial to obtaining the necessary monitoring while taking the medication. While this is the case in our treatment program, it does not seem that the effect of clozapine was solely the result of such a selection bias in this study, as clozapine status and adherence status were unrelated at baseline.

Surprisingly, in this study, severity of positive psychotic symptoms (hallucinations and delusions) was not found to be significantly related to adherence status. The nature of the present sample, a stable group of outpatients reporting moderately low levels of these symptoms, may explain this. Additionally, our rather simple measure of psychopathology does not capture the full range of symptoms that may be affecting these patients. However, other studies of outpatients have reported results similar to ours (Ayers et al. 1984). Severity of disturbance has been identified as a factor important to long-term outcome in more seriously ill samples (Renton et al. 1963).

This study is a novel contribution to the literature on medication adherence in schizophrenia. The division of the sample into subgroups based on initial adherence level is unique and illustrative. Both the strengths and weaknesses of this study stem from the source of the data, an ongoing clinical outcomes assessment program that allows for adequate sample size and high external validity but introduces drawbacks such as lack of formal reliability training of the raters and restricted choice of instruments. Other limitations include the single item, nonobjective measure of adherence; lack of patient perspective on adherence and working alliance; large percentage of censored cases; small sample of initially nonadherent patients; and adherence ratings and other ratings done by one therapist, which may
have led to rater bias. In addition, this study looked at only baseline and endpoint data rather than considering how the baseline variables fluctuated between those two times. However, we believe that the results of this study can be used to further our understanding regarding adherence and nonadherence over time, better identification of patients who are at risk for becoming nonadherent and who will have difficulty developing adherence, and interventions to prevent such problems. Future research is indicated to better understand patient perspectives on the working alliance and adherence issues, and the most important components of the working alliance.

References


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