Predictors of Treatment Discontinuation and Medication Nonadherence in Patients Recovering From a First Episode of Schizophrenia, Schizophreniform Disorder, or Schizoaffective Disorder: A Randomized, Double-Blind, Flexible-Dose, Multicenter Study

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Objective: To evaluate predictors of treatment discontinuation against medical advice and poor medication adherence among first-episode patients treated with olanzapine, quetiapine, or risperidone.

Method: First-episode patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder (DSM-IV) were randomly assigned to olanzapine (2.5–20 mg/day), quetiapine (100–800 mg/day), or risperidone (0.5–4 mg/day) as part of a 52-week, randomized, double-blind, flexible-dose, multicenter study. Patients were enrolled from 2002 to 2004 at one of 26 sites in the United States and Canada. Survival analysis tested for predictors of treatment discontinuation against medical advice, while mixed models tested for predictors of poor medication adherence. Significant findings from the final models were replicated in sensitivity analyses.

Results: Of the 400 patients randomly assigned to treatment, 115 patients who discontinued treatment against medical advice and 119 study completers were compared in this analysis. Poor treatment response ($p < .001$) and low medication adherence ($p = .02$) were independent predictors of discontinuation against medical advice. Ongoing substance abuse, ongoing depression, and treatment response failure significantly predicted poor medication adherence ($p < .01$). Higher cognitive performance at baseline and ethnicity (black) were also associated with lower medication adherence ($p < .05$). An association between poor medication adherence and illness insight at study entry was found at trend level ($p = .059$).

Conclusion: This study highlights the importance of treatment response in predicting discontinuation against medical advice and poor adherence to medication in first-episode patients. These results also support interventions to improve adherence behavior, particularly by targeting substance use disorders and depressive symptoms.

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Medication nonadherence in recovering first-episode patients with schizophrenia is a significant public health concern. Most patients will experience positive symptom remission with antipsychotic treatment. However, naturalistic first-episode studies show that, by 6 months of treatment, 33% to 44% of patients are nonadherent and, by 1 year, as many as 59% are nonadherent.[1–6] Suboptimal duration of treatment with an antipsychotic greatly increases the risk of relapse. With relapse, functional recovery may be derailed, the risk of suicidal or aggressive behaviors is increased, and disabling treatment-resistant symptoms may develop.[7–9] While the optimal duration of maintenance treatment in a remitted first-episode patient is not known, treatment guidelines generally recommend at least 1 year of antipsychotic treatment, and some consider indefinite maintenance treatment reasonable.[10]

Theoretical paradigms of adherence, such as the Health Belief Model (HBM), have been developed and adapted to model factors that may determine adherence behavior.[11,12] According to the HBM, a patient's decision to accept treatment is influenced by the patient's illness beliefs, such as "insight," which may include beliefs regarding whether he or she has an illness, whether

treatment is needed, and whether the prescribed treatment may benefit the illness. A recent study of recovering first-episode patients reported medication adherence to be related to beliefs that medication is beneficial and acknowledgment by the patient of having a mental disorder.[1] The choice of antipsychotic may also influence adherence; several,[13–16] but not all, studies[17–19] have demonstrated that treatment adherence is more likely if patients are prescribed atypical antipsychotics compared with conventional antipsychotics. Generally, little difference in adherence has been reported among atypical antipsychotics.[20,21]

This study aimed to evaluate predictors of medication nonadherence and discontinuation of treatment against medical advice in patients recovering from a first episode of psychosis. Potential predictor variables included illness beliefs, antipsychotic medication randomization, presence of medication side effects, objectively defined symptomatic improvement, severity of depressive symptoms, cognitive function, and substance use.

METHOD

This study involved secondary analyses of a 52-week, randomized, double-blind, flexible-dose, multicenter trial that investigated the effectiveness of olanzapine, quetiapine, and risperidone in patients with a first psychotic episode of schizophrenia, schizoaffective disorder, or schizophreniform disorder. Patients were enrolled from 2002 to 2004 at one of 26 sites in the United States and Canada. Institutional review board approval was obtained at each site. The primary outcome measure of this study was discontinuation from the assigned antipsychotic for any reason (all-cause treatment discontinuation); results from the main study are reported elsewhere.[22]

Study Population

Patients were able to participate in the informed consent process or have a legal guardian available to provide informed consent. Consenting patients were from 16 to 40 years of age and met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[23] criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder. Patients could not have been ill for more than 5 years and must have been continuously ill. If a prior psychotic episode had remitted for 3 months, patients were not considered first-episode and were therefore excluded. Patients were also excluded if they had prior antipsychotic drug treatment for more than 16 cumulative weeks. All patients had a score of ≥ 4 on at least one Positive and Negative Syndrome Scale (PANSS) psychosis item (P1, P2, P3, P5, or P6)[24] and ≥ 4 (moderately ill) on the Clinical Global Impressions (CGI) Severity item[25] at the point of maximum severity of illness to date. Female participants of childbearing potential had to be using a medically acceptable form of contraception.

In this study, we compared patients who discontinued treatment to those who remained in treatment. Patients were not included in the analysis if they were (1) discontinued from the study by their study clinician (due to administrative reasons, inadequate efficacy, or side effects); (2) discontinued from the study, but stated willingness to take another antipsychotic medication; or (3) discontinued from the study, but their willingness to receive follow-up treatment was unknown. Figure 1 shows the numbers of patients in each discontinuation category.

Study Treatment

Patients were randomly assigned to olanzapine (2.5–20 mg/day), quetiapine (100–800 mg/day), or risperidone (0.5–4 mg/day). On days 1 and 2, each patient received 1 capsule daily in the evening of olanzapine (2.5 mg), quetiapine (100 mg), or risperidone (0.5 mg). At the treating physician's discretion, this dose could be increased by 1 capsule every other day; e.g., on days 3 and 4, 1 capsule in the morning and 1 in the evening; on days 5 and 6, 1 capsule in the morning and 2 in the evening, and so on, up to a maximum of 4 capsules b.i.d.

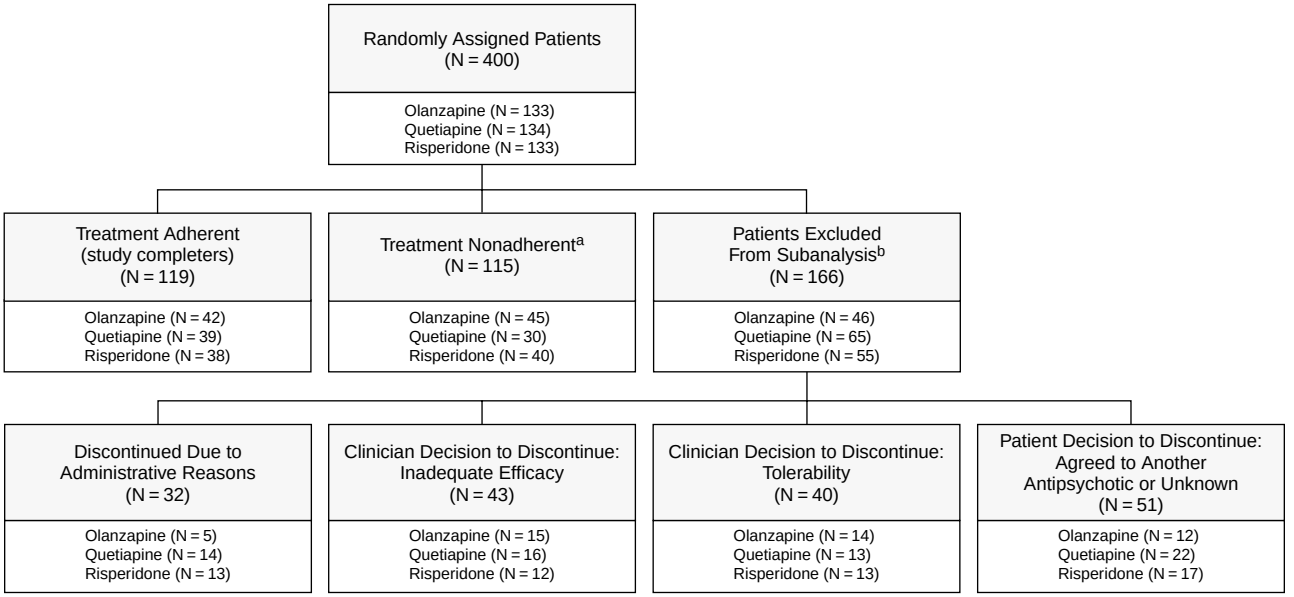
Any previous antipsychotic therapy was tapered and discontinued during the first 2 weeks of double-blind treatment, and no subsequent use of an additional antipsychotic was permitted. Treatment with an adjunctive antidepressant or mood stabilizer during the first 8 weeks of treatment was not allowed unless approved by the project medical officer. Anticholinergic medications for acute extrapyramidal symptoms (EPS) were permitted for up to a total of 2 weeks over the course of the trial. Clinicians were encouraged to lower the antipsychotic dose to relieve EPS. Otherwise, adjunctive and concomitant medications could be used without restriction. When an adjunctive or concomitant medication was prescribed, its name, modal dose, and indication (selected from forced-choice lists) were recorded.

Clinical Assessments

Screening evaluation to determine study eligibility included a diagnostic interview (Structured Clinical Interview for DSM-IV [SCID][26]), medical history, physical examination, vital signs, and laboratory tests. Confirmation that the illness met clinical severity criteria was determined by a modified, abbreviated version of the PANSS that included items P1–P6 and rated symptom severity at the point of maximum severity of illness. Study visits occurred weekly for the first 6 weeks, every other week for the next 6 weeks, and monthly thereafter.

Primary outcomes. Primary outcome measures were (1) patient decision to discontinue from the study against medical advice with refusal to continue treatment with another antipsychotic medication based on self-report at study end and (2) clinician-rated medication adherence (based on a scale of 1–4, where 1 = the patient is taking

Figure 1. Patients Analyzed From the Randomized Clinical Trial



[a]Patients who discontinued and refused further antipsychotic treatment, against medical advice, prior to completing 1 year of treatment.
[b]Patients whose adherence status was ambiguous or not assessable were excluded from the subanalysis.

medication < 25% of the time, 2 = the patient is taking medication 25% to 50% of the time, 3 = the patient is taking medication 50% to 75% of the time, and 4 = the patient is taking medication 75% to 100% of the time).

Predictor measures. Patient beliefs about severity of illness, need for treatment, and benefit from medications were evaluated with the Insight and Treatment Attitudes Questionnaire (ITAQ).[27] The ITAQ is an interview-based assessment containing a total of 11 items. The first 9 items inquire whether the patient believes that he/she has ever had, currently has, or in the future will have (1) a mental disorder, (2) a need for treatment, or (3) a need for medication. The final 2 questions ask the patient, "Will you take the medications?" and "Do the medications do you any good?" Each item is rated on a 3-point scale, where 0 indicates low agreement, 1 indicates some agreement, and 2 indicates high agreement. Thus, the ITAQ scores range from 0 to 22.

Treatment response was defined as a score of ≤ 3 on all PANSS items and ≤ 3 (mildly ill) on the CGI Severity item during any study visit. Patients were considered in remission if they met the criteria continuously for a full month (4 weeks). Depressive symptoms were evaluated with the Calgary Depression Scale for Schizophrenia (CDSS).[28]

Clinicians evaluated on a checklist at each visit the presence of the following 19 common medication-related adverse events: orthostatic faintness, sialorrhea, skin rash, weight gain, anticholinergic side effects (dry mouth, constipation, incontinence/nocturia, and urinary hesitancy), sexual side effects (menstrual irregularities, gynecomastia, galactorrhea, sex drive, sexual arousal, and sexual orgasm), sedation-related side effects (daytime drowsiness, number of sleep hours, insomnia), and extrapyramidal side effects (akinesia and akathisia). Adverse events were rated as mild (1), moderate (2), or severe (3). The anchors for moderate and severe severity generally required some impact on function; the scale used is available upon request.

Substance use was evaluated at each study visit using the Alcohol Use Scale (AUS) and Drug Use Scale (DUS),[29] where a score of 0 indicates no use, 1 indicates use without abuse or dependence, 2 indicates abuse, 3 indicates dependence, and 4 indicates severe dependence requiring institutional treatment. A substance use disorder was indicated by a score of ≥ 2 on the AUS/DUS.

Neurocognitive function was based on a composite score of tests included in a comprehensive test battery, which was evaluated at baseline, week 12, and week 52. The composite score weighted tests from each of the cognitive domains (attention, verbal fluency, verbal memory, motor speed, working memory, and visuomotor speed) equally and was standardized by using data from the entire study group. The mean of each test was set to 0 and the standard deviation to 1 to allow each score to contribute to the composite irrespective of scaling.

Statistical Analyses

Baseline demographic and clinical characteristics of the study completers and the study patients who

discontinued treatment against medical advice were compared using Fisher exact (for categorical variables) and Kruskal-Wallis (for continuous variables) tests. Reported 2-tailed p values are for descriptive purposes, with no adjustment for multiple comparisons.

The primary analysis tested the time to discontinuing treatment against medical advice using the Cox regression model. Study completers were included as censors. Following the backward model selection procedure, potential predictors were excluded one at a time, starting from the least significant, until those that remained in the model had p values < .05. The initial set of predictors included both fixed and time-dependent covariates. Race; antipsychotic randomization status; treatment response over the trial; baseline measures of ITAQ, CDSS, and PANSS total score; neurocognition composite score; presence of any substance abuse; duration of illness (defined as the interval between the onset of first symptoms, according to the SCID, and the starting date of study medication); and any moderate or severe side effects were included as fixed covariates. Their follow-up measures as well as the visit-by-visit medication adherence rating and remission status were included as time-dependent covariates. Significant findings from the Cox regression model were replicated using Kaplan-Meier survival analysis by comparing survival curves of the lower and upper half of the patient population for the significant predictor.

Factors associated with medication adherence were identified using mixed models in which the outcome measure was the clinician's visit-by-visit medication adherence rating. The model selection procedure and initial set of potential predictors were the same as those employed in the Cox regression model.

For modeling purposes, missing data were filled in using information from the previous visit (including baseline), except for substance use and medication adherence rating. Some patients were hospitalized after enrollment and therefore baseline substance use information became invalid. Medication adherence information was not available at baseline.

Final models were subject to extensive sensitivity analysis to test model robustness. Interaction terms of medication with final model predictors were tested for potential drug-specific variations of the main effects. All statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, N.C.).

RESULTS

Of the 400 patients who were randomly assigned to treatment, 234 patients were included in this analysis (Figure 1). The group of 115 patients (28.8%) who discontinued treatment against medical advice prior to completing 1 year of treatment (the proportions were similar for patients randomly assigned to olanzapine [45/133, 33.8%], quetiapine [30/134, 22.4%], and risperidone [40/133, 30.1%]) were compared to the group of 119 patients (29.8%) who completed the 1-year treatment study. Treatment adherence status after study discontinuation was unknown for those patients who discontinued study participation prior to 1 year due to reasons other than the decision to stop treatment. Therefore, using Kaplan-Meier adjusted survival analysis to take into account time in the study, it was estimated that 37.1% of patients discontinued treatment against medical advice.

Table 1 summarizes the baseline characteristics of study completers and patients who discontinued against medical advice. Both groups demonstrated similar demographic and clinical characteristics, except for a greater proportion of patients of white ethnicity and less severe depressive symptoms in the completer group.

Clinician-rated assessment of medication adherence correlated highly with pill counts (r = .92), supporting the validity of the measure. Overall, medication adherence ratings were fairly high, with patients in all 3 treatment groups demonstrating approximately 50% to 75% adherence (average score of 1.3).

Predictors of Discontinuation Against Medical Advice

Significant independent predictors of discontinuation against medical advice were poor treatment response (hazard ratio [HR] = 0.23, $\chi^2 = 41.50$, $p < .001$) and poor medication adherence (HR = 1.38, $\chi^2 = 5.19$, $p = .02$). Achieving treatment response (score of ≤ 3 on all PANSS items and ≤ 3 (mildly ill) on the CGI Severity item during any study visit) was associated with > 3 times reduction in the hazard of discontinuation. Independent of treatment response, each point improvement on the medication adherence rating scale resulted in almost a 30% reduction in the hazard of treatment discontinuation, a measure of the instantaneous risk of discontinuation against medical advice.

Kaplan-Meier plots for adherence and treatment response are illustrated in Figure 2. Clear separations of survival curves in both plots support the results from the Cox regression model. Patients with better individual mean adherence ratings or those who responded to treatment at any time during the trial were less likely to discontinue against medical advice (log-rank test, $p \leq .001$).

Predictors of Medication Adherence

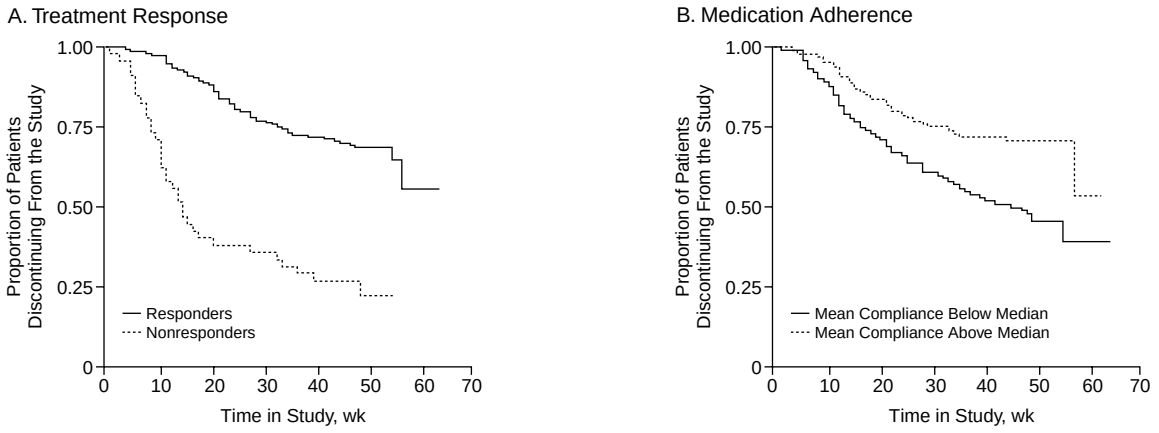
Ongoing substance abuse, ongoing depression, and treatment response failure were the strongest predictors of poor medication adherence ($p < .01$) (Table 2). Notably, poor medication adherence was also associated with ethnicity (black), higher baseline cognitive performance, and reaching remission status ($.01 < p < .05$). Insight into illness at study entry, as rated by the ITAQ, indicated an association with poor medication adherence, but at a trend level of significance ($p = .059$).

Table 1. Baseline Characteristics of Patients Experiencing a First Episode of Psychosis: Study Completers vs. Patients Who Withdrew Against Medical Advice

Characteristic	Study Completer (N = 119)	Discontinued Against Medical Advice (N = 115)	All Patients (N = 400)	p[a]
Sex, N (%)				.566
Female	32 (26.9)	35 (30.4)	108 (27.0)	
Male	87 (73.1)	80 (69.6)	292 (73.0)	
Ethnicity, N (%)				.003
White	73 (61.3)	52 (45.2)	205 (51.3)	
Black	36 (30.3)	59 (51.3)	172 (43.0)	
Other	10 (8.4)	4 (3.5)	23 (5.8)	
Substance abuse/dependence, N (%)	11 (9.2)	10 (8.7)	45 (11.3)	1.000
DSM-IV diagnosis, N (%)				.423
Schizophrenia	71 (59.7)	62 (53.9)	231 (57.8)	
Schizophreniform disorder	33 (27.7)	41 (35.7)	115 (28.8)	
Schizoaffective disorder	15 (12.6)	12 (10.4)	54 (13.5)	
Patients drug naive, N (%)	26 (21.9)	30 (26.1)	96 (24.0)	.540
Duration of previous antipsychotic use, mean (SD), wk	5.9 (5.4)	6.5 (8.9)	6.3 (7.2)	.790
Age, mean (SD), y	24.8 (6.1)	24.5 (5.9)	24.5 (5.8)	.671
Age at onset, mean (SD), y	24.0 (5.9)	23.3 (5.7)	23.5 (5.6)	.254
Baseline ITAQ score, mean (SD)	14.2 (5.9)	13.9 (5.8)	14.4 (5.9)	.734
Baseline neurocognitive composite score, mean (SD)	0.06 (0.65)	0.02 (0.56)	0.00 (0.64)	.418
Baseline CDSS total score, mean (SD)	12.1 (3.4)	13.1 (3.9)	13.0 (4.2)	.028
Baseline PANSS total score, mean (SD)	72.3 (15.8)	74.3 (14.8)	73.8 (15.8)	.339

[a]Study completers versus patients who withdrew against medical advice, using Fisher exact test for categorical variables and Kruskal-Wallis test for continuous variables.
Abbreviations: CDSS = Calgary Depression Scale for Schizophrenia; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; ITAQ = Insight and Treatment Attitudes Questionnaire; PANSS = Positive and Negative Syndrome Scale.

Figure 2. Kaplan-Meier Survival Plots for Time to Discontinuation Against Medical Advice



The sensitivity analysis replicated all significant predictors from the main effect model. The only interaction with antipsychotic medication was the effect of reaching remission status on medication adherence. Pair-wise comparisons demonstrated that preremission adherence levels were comparable among the olanzapine, quetiapine, and risperidone treatment groups ($p > .40$). After remission was achieved, the least square mean estimated adherence level deteriorated significantly for olanzapine (from 1.13 [SE = 0.05] to 1.21 [SE = 0.04]; higher score for worse adherence, $p = .03$) and risperidone (from 1.09 [SE = 0.05] to 1.18 [SE = 0.05]; $p = .02$). However, the change in the quetiapine group was not significant ($p = .11$) and was improved from 1.17 (SE = 0.05) to 1.10 (SE = 0.05). The sensitivity analysis improved the p value associated with the baseline ITAQ score from trend level ($p = .059$) to marginally significant ($p = .049$).

DISCUSSION

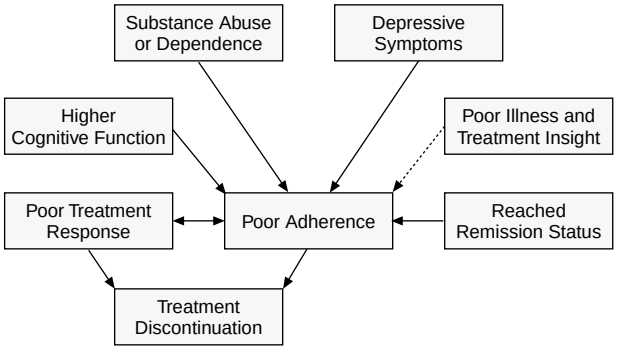
For many patients, symptomatic and functional recovery from a first psychotic episode is likely to be related to medication adherence and to remaining in treatment. Similar to results observed in routine clinical care, we

Table 2. Predictors of Poor Medication Adherence

	Main Model			Sensitivity Analysis		
Predictor	df	F Ratio	p	df	F Ratio	p
Race	2,192	3.71	.026	2,190	3.80	.024
Baseline neurocognition score	1,192	5.39	.021	1,190	6.01	.015
Baseline ITAQ score	1,192	3.60	.059	1,190	3.93	.049
Ongoing substance use	1,3008	17.78	< .0001	1,3006	17.36	< .0001
Ongoing depression	1,3008	9.60	.002	1,3006	9.91	.002
Treatment response failure	1,192	14.67	< .001	1,190	12.06	.001
Achieving remission status	1,3008	4.14	.042	1,101	1.93	.17
Treatment	…	…	…	2,190	0.23	.79
Achieving remission status × treatment	…	…	…	2,101	4.84	.01

Abbreviation: ITAQ = Insight and Treatment Attitudes Questionnaire.
Symbol: … = not applicable.

Figure 3. Factors Associated With Poor Adherence and Treatment Discontinuation[a]



[a]All relationships significant except as indicated with dotted line, in which p value = .059.

estimate that 37% of patients in this study discontinued treatment against medical advice prior to completing 1 year of treatment. It is of interest, however, that specialized first-episode treatment programs report 1-year treatment discontinuation rates from 8% to 20%, suggesting that intense treatment early in the course of the illness may improve treatment adherence.[2,30,31]

It is clear that the reasons why patients adhere to a prescribed medication regimen and remain in treatment are complex and variable. In clinical care, it is often assumed that poor adherence and treatment discontinuation in patients with schizophrenia are due to "poor insight," in that the effects of the illness on the brain limit the patient's ability to understand the true benefits of treatment. While this assumed relationship between "poor insight" and treatment discontinuation may be true for patients with chronic schizophrenia,[12] the results of this study suggest that a more complex relationship between treatment response and treatment adherence exists for first-episode patients (Figure 3). We found that the likelihood of treatment discontinuation was related to poor symptomatic response to treatment, even when controlling for medication adherence. Thus, rather than having "poor insight" and therefore rejecting medication and treatment, recovering first-episode patients may be aware of treatment benefits, and this awareness may be reflected in their choice to remain on medication and in treatment. Other studies in first-episode populations have found that medication adherence positively influences the rate of remission and functional outcome.[32,33] It may be that treatment adherence and treatment response interact in such a way that good adherence leads to better response, which in turn leads to better adherence. In contrast, poor adherence may lead to poor response, which may further discourage treatment adherence and increase the likelihood of treatment discontinuation. That medication adherence and treatment response are dynamic processes may also be reflected in the finding that subjects who met response criteria also were at increased risk for poor adherence. While willing to take medications to achieve symptom relief, the same recovering first-episode patient may not recognize the importance of maintenance treatment to prevent relapse. Thus it may be that recovering first-episode patients may have different predictors of medication and treatment adherence than patients with more chronic illness.

Ongoing substance abuse/dependence and depressive symptoms were directly associated with poor adherence and were significant predictors of treatment discontinuation when tested alone without medication adherence in the model. These findings indicate that adherence may be the mediator for any relationship between these factors and staying in treatment (Figure 3). Substance use disorders have been associated with poor adherence in other studies of first-episode patients.[2,34] As observed in this study, depressive symptoms impact medication adherence in a number of medical conditions, including heart disease, diabetes, osteoporosis, and infectious disease.[35–38] These results support the investigation of treatment interventions designed to reduce substance use disorders and depressive symptoms and their effects on medication adherence.

In this study, side effects did not impact medication adherence or likelihood of treatment discontinuation.

These findings are similar to other recent first-episode studies that also found a lack of association between perceived side effects and treatment nonadherence[1,4] but are in contrast to studies of patients with chronic schizophrenia.[12,39] Thus, disease stage and experience with antipsychotic medication may influence the importance of medication side effects on adherence to treatment.

Unlike patients with chronic schizophrenia, first-episode patients with higher cognitive function at baseline were actually associated with a lower level of medication adherence. The reason for this is unclear.

Antipsychotic randomization did not significantly impact adherence or treatment discontinuation against medical advice. This may be explained by the previously reported finding that treatment response was similar among antipsychotics in first-episode patients.[22] A retrospective study of a state Medicaid claims database[40] also found that treatment adherence was similar in patients with schizophrenia prescribed olanzapine, quetiapine, or risperidone. The quetiapine group, however, showed better persistence than the olanzapine and risperidone groups.[40] The only difference associated with antipsychotics in this study was in the differential deterioration in medication adherence after remission. As our finding was observed only in the secondary sensitivity analysis, and the effect sizes were relatively small, it will be of interest to evaluate the interaction of drug treatment and treatment response with adherence in future studies.

Design Limitations

Patients consented to participate in a randomized, double-blind clinical trial and are not an epidemiologic sample. Allowing prior antipsychotic treatment of up to 16 weeks may bias our sample against patients who respond rapidly to antipsychotics. Therefore, the results of this study may not apply to the general population of patients experiencing a first episode. In addition, clinical care may be different in drug trials than in routine treatment; for example, study visits are more frequent than is often possible in routine care, and the type of clinical care provided at study sites may not necessarily include specialized first-episode care, which has been shown to positively influence adherence.[2,30,31] Measurement variation between study sites may have the potential consequence of increasing measurement error and thus reducing the estimated magnitude of effect.[41] In addition, as discussed in the method section, only a subset (about 60%) of the patients who participated in the clinical trial were included in this analysis. Patients who discontinued against medical advice but were willing to take another antipsychotic and patients who were discontinued by their treating clinician due to inadequate efficacy or tolerability were excluded. Thus, our findings may be generalized primarily to patients who have adequate response to and tolerability of the antipsychotic.

Several strategies to evaluate adherence exist, each with their own advantages and disadvantages (e.g., clinician, family, and/or patient report; monitoring drug levels in blood or urine; pharmacy refill; Medication Event Monitoring System; electronic medication vial caps). Clinician assessment of adherence is reported to underestimate nonadherence,[42] but in this study, the high correlation between clinician assessment of adherence and pill counts suggests that clinician assessment was valid. In addition, poor adherence was significantly associated with fewer side effects and more symptoms, which would be likely if a patient had stopped taking his or her medication. However, it is probable that the method used to estimate medication adherence in this study underestimated medication nonadherence.

The lag between the causal events and date of discontinuation obscures the link between them. A side effect might be the direct cause for a patient's decision to discontinue, but the severity of the side effect may have abated by the date the discontinuation actually occurred. This lag may vary significantly from patient to patient, resulting in limited statistical power to capture the association.

Implications

Improving treatment adherence of the recovering first-episode patient is clearly critical, particularly given that, in this study, treatment adherence and treatment response appeared to be mutually reinforcing, such that good adherence led to better response and in turn to better adherence. In addition, the likely consequence of stopping antipsychotic treatment is relapse, with subsequent risk of hospitalization and impact on symptomatic, social, and vocational recovery.[2,43] The results of this study support the development of interventions that directly improve adherence behavior, especially those targeting substance abuse and depressive symptoms. In addition, patients with black ethnicity and those with higher cognitive function may be at particularly high risk for poor medication adherence and thus deserve targeted interventions. Finally, patients may also be vulnerable to poor adherence after achieving remission and therefore may benefit from targeted interventions at this time.

Drug names: olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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Eli Lilly and Pfizer. **Dr. Lieberman** has received grant/research support from Acadia, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Merck, Organon, and Pfizer; is a consultant for Eli Lilly and Pfizer; has participated in advisory boards for AstraZeneca, Eli Lilly, GlaxoSmithKline, Lundbeck, Organon, and Pfizer (**Dr. Lieberman** has not received any financial compensation or salary support for participation as consultant or member of an advisory board); and holds a patent with Repligen. **Drs. Gu and Hamer** report no additional financial or other relationships relevant to the subject of this article.

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