Medication Nonadherence and Treatment Outcome in Patients With Schizophrenia or Schizoaffective Disorder With Suboptimal Prior Response

Jean-Pierre Lindenmayer, M.D.; Hong Liu-Seifert, Ph.D.; Pandurang M. Kulkarni, Ph.D.; Bruce J. Kinon, M.D.; Virginia Stauffer, Pharm.D.; Sara E. Edwards, Pharm.D.; Lei Chen, M.S.; David H. Adams, Ph.D.; Haya Ascher-Svanum, Ph.D.; Peter F. Buckley, M.D.; Leslie Citrome, M.D., M.P.H.; and Jan Volavka, M.D., Ph.D.

Objective: To examine the impact of medication nonadherence on treatment outcome in schizophrenia and potential risk factors for nonadherence.

Method: A post hoc analysis of a randomized, double-blind, 8-week, fixed-dose study comparing olanzapine 10, 20, and 40 mg/day for patients with schizophrenia or schizoaffective disorder (DSM-IV criteria) with suboptimal response to current treatment (N = 599) was conducted between September 12, 2003, and November 3, 2005, at 55 study centers in the United States. Nonadherence was defined as not taking medication as prescribed based on daily pill counts. Because there was no significant difference in nonadherence between dose groups, effects of nonadherence on efficacy and safety outcomes were examined using all 3 groups combined. Baseline demographics and symptom severity were investigated as potential risk factors for nonadherence.

Results: During the 8-week study, 34.5% of patients were nonadherent at least once. Nonadherent patients had significantly less improvement compared to adherent patients as measured by change in Positive and Negative Syndrome Scale total score (–22.57 vs. –26.84, p = .002). Longer duration of nonadherence was associated with reduced likelihood of treatment response (odds ratio = 0.94, 95% CI = 0.90 to 0.99, p = .008). The early treatment discontinuation rate was higher in nonadherent compared to adherent patients (40.8% vs. 24.5%, p < .001). Adherent and nonadherent patients had comparable outcomes in most safety measures, except for weight change, for which adherent patients had greater weight gain than nonadherent patients (2.63 kg vs. 1.96 kg, p = .02). Greater depression severity at baseline (p = .01) and greater hostility level during the study were significant risk factors for nonadherence (p = .02).

Conclusions: Medication nonadherence had a significantly negative impact on treatment response, highlighting the importance of adherence to achieve satisfactory treatment outcome. Findings may also help clinicians identify patients at risk for nonadherence and utilize interventions to improve adherence.

Trial Registration: clinicaltrials.gov Identifier: NCT00100776

J Clin Psychiatry 2009;70(7):990–996

Received March 18, 2008; accepted Aug. 22, 2008. From New York University, N.Y. (Drs. Lindenmayer, Citrome, and Volavka); Eli Lilly and Company, Indianapolis, Ind. (Drs. Liu-Seifert, Kulkarni, Kinon, Stauffer, Edwards, Adams, and Ascher-Svanum and Ms. Chen); the Medical College of Georgia, Augusta (Dr. Buckley); and Nathan S. Kline Institute of Psychiatry, Orangeburg, N.Y. (Dr. Citrome).

This study was funded by Eli Lilly and Company, Indianapolis, Ind. Financial disclosure appears at the end of the article.

Corresponding author and reprints: Jean-Pierre Lindenmayer, M.D., New York University School of Medicine, Manhattan Psychiatric Center, Wards Island, New York, NY 10035 (e-mail: lindenmayer@nki.rfmh.org).

Effectiveness of medication treatment is determined by 3 components: treatment efficacy (symptom reduction), tolerability/safety, and adherence. Further, medication adherence is influenced by medication efficacy, safety, tolerability, and other factors. There has been increased interest in the research of adherence in the past 20 years. Understanding factors related to medication nonadherence is particularly important, as nonadherence in patients with schizophrenia continues to be a significant problem and threatens successful treatment outcomes.[1] Reported rates of nonadherence to antipsychotics range from 10% to 76%, with an estimated average rate of about 42%.[1]

Medication nonadherence is often associated with negative consequences, including symptom exacerbation, more frequent emergency room visits, rehospitalizations, and relapse.[2–4] Among patients who discontinue their medication, 75% experience significant symptom exacerbation over 1 year compared to 25% of those who adhere to their medication. In turn, symptom exacerbation can often lead to serious consequences, including dangerous behaviors, worsened prognosis of the disease, antipsychotic treatment resistance, and increased health care costs.[5] Medication status is the largest predictor of relapse risk in schizophrenia, with continuous maintenance antipsychotic medication resulting in an approximately 70% reduction in the risk of relapse.[6,7]

Most previous research has defined nonadherence as a complete discontinuation of medication. However, many patients with schizophrenia show partial adherence: they

do not completely discontinue their medication, but they do not take all that has been prescribed. Partial adherence is more difficult to define than complete nonadherence. We examined partial adherence and its relationship with treatment outcome in the context of a randomized, double-blind, 8-week, fixed-dose study comparing olanzapine 10 mg/day, 20 mg/day, and 40 mg/day for patients with schizophrenia or schizoaffective disorder (N = 599). The study sought to assess the effect of medication nonadherence on a broad range of treatment outcomes, including efficacy, safety, and treatment discontinuation. The medication nonadherence status in the current study was determined based on daily pill counts and provided an objective and direct measure of the adherence level compared with measures based on patient reports and medication prescription information used by many other studies. In addition, potential risk factors of medication nonadherence were also investigated among a range of baseline characteristics and symptom severities.

METHOD

This was a post hoc analysis of a randomized, double-blind, 8-week study comparing olanzapine 10 mg/day, 20 mg/day, and 40 mg/day for patients with schizophrenia or schizoaffective disorder with suboptimal response to current treatment. A brief description of the patient population and study design is provided here. Additional details can be found in the primary report of the trial.[8]

Patient Population

Patients screened for this study were 18- to 60-year-old outpatients or inpatients meeting the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) diagnostic criteria for schizophrenia or schizoaffective disorder. Key inclusion criteria required a baseline Brief Psychiatric Rating Scale[9] (BPRS) score ≥ 45 (extracted from the Positive and Negative Syndrome Scale[10] [PANSS]), scores on at least 2 of the 4 BPRS positive symptom items ≥ 4 (moderate), and a Clinical Global Impressions-Severity of Illness scale[11] (CGI-S) score ≥ 4. Patients were required to be experiencing less than optimal response to their current treatment in the opinion of the investigator. Key exclusion criteria included serious suicidal risk, DSM-IV diagnosis of substance dependence within the past 3 months, and antipsychotic treatment resistance. The study was conducted between September 12, 2003, and November 3, 2005, at 55 study centers in the United States. The study protocol was approved by the sites' institutional review boards, and written informed consent was obtained from all participants prior to study entry.

Study Design

This was a multicenter, randomized, double-blind, parallel, 8-week, fixed-dose study. Random assignment was performed 1:1:1 into 3 treatment groups: 10 mg/day olanzapine, 20 mg/day olanzapine, and 40 mg/day olanzapine. All patients were initiated on 10 mg/day olanzapine. Patients randomly assigned to the 20-mg/day group were titrated to that dose by the end of week 1, and patients randomly assigned to the 40-mg/day group were titrated to their assigned fixed dose by the end of week 2. Patients were titrated off prestudy medication over the same 2-week period. Concomitant medications with psychotropic activity were not permitted, with the following exceptions: benzodiazepines, hypnotics, medication for treatment of emergent extrapyramidal symptoms, and antidepressants or mood stabilizers if taken in stable doses for at least 30 days prior to enrollment and maintained throughout the study.

Outcome Measures

Medication nonadherence was defined as not taking the full dose of medication as prescribed and was determined based on a daily pill count for each patient. Patients identified as medication nonadherent could have taken a portion of the full dose or could have not taken any dose at all.

Measures used to assess the effect of medication nonadherence on efficacy included the PANSS, CGI-S, Montgomery-Asberg Depression Rating Scale (MADRS),[12] Global Assessment of Functioning (GAF: Axis V assessment from the DSM-IV), and Heinrich Carpenter Quality of Life Scale (QLS).[13]

Measures used to assess the effect of medication nonadherence on safety included treatment-emergent adverse events, vital sign measurements, and movement disorders as measured by the Simpson-Angus Scale,[14] Barnes Akathisia Rating Scale,[15] and Abnormal Involuntary Movement Scale (AIMS).[16] In addition, plasma olanzapine concentrations were collected for approximately half of the study patients.[17]

Statistical Analyses

We compared the rate of nonadherence between the 3 dose groups using a Fisher exact test. Since there were no significant differences in nonadherence rates between dose groups (10 mg, 34.5%; 20 mg, 31.4%; and 40 mg, 37.6%; smallest pair-wise comparison $p > .24$), the 3 dosage groups were combined and analyzed as a pooled sample. Analyses were completed on an intent-to-treat basis unless otherwise specified and were performed using Statistical Application Software (SAS Institute Inc., Cary, N.C.). Statistical significance was defined as a 2-tailed p value less than .05.

Changes in PANSS scores and other efficacy measures were compared between adherent and nonadherent patients using analysis of covariance (ANCOVA) with terms for adherence group and baseline values. Treatment response, defined as at least 20% improvement from baseline in PANSS total scores both at the end of the study and at week 2, was also compared by adherence group using Fisher exact test. The PANSS total scores were also compared between adherent and nonadherent patients at each visit using

Table 1. Patient Characteristics and Illness Severity at Baseline in Adherent and Nonadherent Patients

Variable	Adherent (n = 381)	Nonadherent (n = 201)
Gender (male), %	68.0	69.2
Age, mean (SD), y	40.9 (10.7)	41.9 (10.9)
Race (white), %	42.8	49.3
Race (black), %	44.9	39.3
Race (other), %	12.3	11.4
Diagnosis, %		
Schizophrenia	67.7	72.6
Schizoaffective disorder	32.3	27.4
Age at onset of psychosis, mean (SD), y	23.8 (8.7)	23.4 (9.1)
Duration of illness, mean (SD), y	17.06 (10.50)	18.52 (10.98)
No. of previous schizophrenia episodes, mean (SD)	8.2 (7.0)	8.6 (8.1)
Weight, mean (SD), kg	90.4 (22.5)	87.6 (21.7)
Body mass index, mean (SD)	30.43 (7.19)	29.25 (7.26)

Table 2. Mean (SD) Changes From Baseline in Clinical Outcomes in Adherent and Nonadherent Patients

Measure	Adherent (n = 381)	Nonadherent (n = 201)	p
PANSS score			
Total	−26.84 (19.66)	−22.57 (21.20)	.002
Positive factor	−10.61 (8.07)	−8.70 (8.75)	.002
Negative factor	−5.59 (5.65)	−4.79 (6.13)	.058
Disorganized thought factor	−4.41 (4.13)	−3.84 (4.01)	.035
Hostility factor	−2.60 (3.04)	−1.87 (3.61)	< .001
Depression factor	−3.62 (3.43)	−3.23 (3.57)	.017
CGI-S score	−1.14 (1.05)	−0.96 (1.13)	.05
GAF score	12.14 (13.57)	9.54 (12.20)	.036
MADRS total score	−5.0 (6.91)	−4.29 (7.93)	.004
QLS total score	8.55 (18.81)	6.06 (18.19)	.15

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, QLS = Quality of Life scale.

a mixed-model repeated-measures analysis with terms for baseline, adherence status, visit, and interaction between status and visit.

A logistic regression analysis was performed to assess the effect of days of nonadherence on achieving response at the end of study. Safety measures were compared between adherent and nonadherent patients using Fisher exact test for categorical variables and ANCOVA with terms for baseline and group for continuous variables. Discontinuation rates due to all causes as well as due to different reasons were compared between adherent and nonadherent patients using Fisher exact test.

Baseline patient characteristics including demographics, illness history, and symptom severity were compared between adherent and nonadherent patients using Fisher exact test for categorical variables and analysis of variance with terms for group for continuous variables. Further, effect of depression-related symptoms on medication adherence during the study was investigated using a Cox regression model with time-dependent covariate. Both the absolute score and the change from baseline at a postbaseline visit (x) in the PANSS depression/anxiety factor[18] were tested for their effect on medication adherence status at the next visit (x + 1). Similar tests were also conducted for each of the 4 PANSS items (depression, guilt feelings, anxiety, and somatic concern) that make up the depression/anxiety factor. In addition, the PANSS total score and the hostility item were tested as potential predictors for nonadherence. Both the absolute scores of the PANSS total score and hostility item and their changes from baseline at any visit during the study were examined in separate Cox regression models as time-dependent covariates for their effect on nonadherence at the following visit. Adverse events were also tested as possible predictors for nonadherence. A Cox regression model was constructed with the maximum severity of all reported adverse events as the time-varying covariate. A similar model was also constructed with weight change from baseline as the time-varying covariate.

RESULTS

Impact of Nonadherence on Efficacy Outcomes

Patient demographics and clinical characteristics were comparable between the 3 dosage groups (Table 1). During the 8-week study, 34.5% of patients were nonadherent with their medication at least once. At any given visit during the study, 7% to 12% of all patients were nonadherent. Nonadherent patients had significantly less improvement compared to adherent patients as measured by change in PANSS total score (−22.57 vs. −26.84, p = .002). Similar differences between adherent and nonadherent patients were also observed in all other efficacy measures except for QLS (Table 2). There was no significant interaction between adherence status and treatment dose group, indicating that the effect of nonadherence on efficacy measures was consistent across the treatment dose groups.

At the end of the study, nonadherent patients had significantly lower response rates compared to adherent patients (51.5% vs. 63.9%, p = .004). Nonadherent patients also had a lower rate of early response assessed at week 2 (31.3% vs. 42.4%, p = .01).

Impact of Duration of Nonadherence

As indicated by logistic regression, longer duration of medication nonadherence was associated with reduced likelihood of treatment response at the end of the study (odds ratio [OR] = 0.94, 95% CI = 0.90 to 0.99, p = .008). Any additional day that a patient was nonadherent during the study reduced the likelihood of achieving response at study end by 6%.

Impact on Discontinuation

The early study all-cause discontinuation rate was higher in nonadherent patients compared to adherent

Table 3. Reasons for Study Discontinuation in Adherent and Nonadherent Patients

Reason, %	Adherent (n = 381)	Nonadherent (n = 201)	p[a]
Poor efficacy[b]	5.3	5.5	1.0
Intolerability[c]	3.7	6.0	.2
Patient decision	5.0	12.4	**.003**
Lost to follow-up	5.0	3.0	.29
Protocol violation	1.8	5.5	**.02**
Criteria not met	0.0	0.5	.35
Sponsor's decision	1.6	1.5	1.0
Other	2.1	6.5	**.01**

[a]Bolded values indicate statistical significance.
[b]Poor efficacy is defined as lack of efficacy or psychiatric adverse event.
[c]Intolerability is defined as nonpsychiatric adverse event.

Table 4. Baseline Symptom Severity in Adherent and Nonadherent Patients[a]

Measure	Adherent (n = 381)	Nonadherent (n = 201)	p[b]
PANSS score			
Total[c]	92.93 (12.47)	94.50 (13.17)	.16
Lack of judgment and insight item	3.44 (1.31)	3.25 (1.29)	.09
Suspiciousness item	4.32 (0.94)	4.41 (0.98)	.31
GAF	42.89 (9.35)	42.80 (9.07)	.91
QOL	52.28 (18.0)	52.21 (19.36)	.97
MADRS			
Total	13.90 (8.80)	15.85 (8.50)	**.01**
Item 1: apparent sadness	1.56 (1.32)	1.77 (1.26)	.07
Item 2: reported sadness	1.54 (1.45)	1.81 (1.44)	**.04**
Item 3: inner tension	1.97 (1.24)	2.18 (1.26)	.06
Item 6: concentration difficulties	2.36 (1.44)	2.64 (1.38)	**.02**
Item 7: lassitude	1.45 (1.40)	1.68 (1.39)	.06
Item 9: pessimistic thoughts	1.24 (1.31)	1.55 (1.34)	**.01**

[a]All values are presented as mean (SD).
[b]Bolded values indicate statistical significance.
[c]PANSS factors were also examined, and there were no significant group differences.
Abbreviations: GAF = Global Assessment of Functioning, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, QOL = Quality of Life scale.

patients (40.8% vs. 24.5%, p < .001). This group difference appeared to be driven by greater drop-out rates in nonadherent patients due to adverse events, patient decisions, protocol violation, and other nonspecified reasons (Table 3).

Impact on Safety Measures

Adherent patients and nonadherent patients had comparable outcomes in the mean change from baseline in AIMS, Barnes Akathisia Rating Scale, Simpson-Angus Scale, and most of the vital signs with the exception of weight change, for which adherent patients had greater weight gain than nonadherent patients (2.63 kg vs. 1.96 kg, p = .02). Treatment-emergent adverse events that occurred significantly more often in nonadherent patients than in those who were adherent were increased appetite (9% vs. 4.5%, p = .04) and hemorrhoids (2.5% vs. 0.3%, p = .02). There were no treatment-emergent adverse events that occurred more often in adherent patients.

Of the patients who had plasma concentration data collected at week 4 and 8, those who were adherent to their medication had greater concentration levels compared to those who were not adherent (week 4: 44.97 ng/mL vs. 29.57 ng/mL, p = .02; week 8: 43.86 ng/mL vs. 29.97 ng/mL, p = .19).

Predictors of Nonadherence

None of the baseline patient characteristics, including demographics, illness characteristics, baseline weight, and history of substance abuse, appeared to be significant predictors of medication nonadherence (data available on request). Among the baseline symptom measures (MADRS, PANSS, CGI-S, GAF, and QLS), only the MADRS scores were a significant risk factor for medication nonadherence during the study (Table 4). Patients with greater depressive symptoms, especially sadness, concentration difficulties, and pessimistic thoughts, were more likely to be nonadherent with their medication (Table 4).

The MADRS data were collected at baseline and at the end of the study only; thus, it was not possible to assess the effect of depressive symptoms as measured by the MADRS on nonadherence during the study. To explore this issue further, we examined change in the PANSS depression factor scores[18] at each visit during the study for its predictive value for medication nonadherence during the following visit. Each individual item in the depression factor (somatic concern, anxiety, guilt feelings, and depression) was also tested as a potential risk factor of nonadherence. Data showed that at any given visit, worsening in somatic concern from baseline was associated with increased risk of medication nonadherence during the following visit (hazard ratio [HR] = 1.2, 95% CI = 1.06 to 1.35, p = .003). The absolute score of somatic concern was not found to be a significant predictor of nonadherence (p = .69). Other examined items of the depression factor were not significantly associated with risk of medication nonadherence.

Level of hostility, as measured by the absolute score of the PANSS hostility item, was found to be a significant predictor of nonadherence during the study. Greater level of hostility at any visit was associated with a greater likelihood of nonadherence at the following visit (HR = 1.14, 95% CI = 1.02 to 1.26, p = .02). Change from baseline in the PANSS hostility item did not predict adherence status at the following visit (p = .9).

Overall treatment efficacy, as measured by the change in PANSS total score at any visit, was not a significant predictor of nonadherence at the following visit (p = .38). Both overall tolerability, as measured by the maximum severity of adverse events, and weight change from baseline at any visit were not significant predictors of nonadherence at the following visit (p = .47 and p = .16, respectively).

© Copyright 2009 Physicians Postgraduate Press, Inc.

DISCUSSION

Approximately one third of the patients were nonadherent with their prescribed medication at least once during the 8-week study. Nonadherent patients achieved significantly less clinical improvement compared to patients who were adherent to their medication. There was a significant relationship between longer duration of nonadherence and reduced likelihood of achieving response at the end of the study. Depressive symptoms and hostility appeared to be risk factors for medication nonadherence.

Rates of medication nonadherence with antipsychotic drugs in schizophrenia patients have been reported previously based on different measures of adherence, including self-reports, clinician judgment, prescription fill records, and pill counts. Evaluation of nonadherence based on self-report and clinician judgment may be subjective and not reliable. Pill counts may provide a more accurate approach to determine degree of medication adherence. In addition, there may be differences in the definitions and degrees of nonadherence used for analysis in different studies, for example, complete or partial adherence to treatment doses.

In the current study, daily data on medication adherence to full dose based on pill counts were collected and entered into the reporting database for every patient during the entire study. We do not have data on the actual daily pill counts to further characterize whether a patient was partially or completely compliant with the daily dose. Our rate of nonadherence was low compared to the study of Mahmoud et al.,[19] who used a pill count method and reported that 94.8% of patients taking atypical antipsychotics missed at least a day of medication during their observation period.

Using the prescription refill rate method, Dolder et al.[20] found that there were only 57.4% of adherent refills by patients followed over 6 months who were taking atypical antipsychotic medication. Our relatively lower rate of nonadherence may have been due to the short duration of the study and the frequent required research visits. Csernansky et al.[21] reported an even lower rate of nonadherence (3%–4%) in a relapse prevention study using pill count. The low rates may be partially explained by the relatively stable patient population that was recruited for the relapse study, including the requirement that all patients had received a stable dose of antipsychotic medication for at least 30 days before entry and were judged clinically stable by the principal investigator at each site. Thus, these relatively stable patients might be expected to have a higher rate of compliance than has been seen in other trials and settings.

Patients who did not follow the prescribed medication regimen had less clinical response compared to their adherent counterparts in a broad range of clinical domains, including positive, negative, disorganization, depression, and hostility symptoms. The latter difference is particularly noteworthy given the potential negative effects of hostility on the patients' immediate environment. These symptom domain differences were further supported by a differential effect on the overall level of functioning as measured by the GAF. Conversely, patients with less clinical response may experience their treatment as less beneficial and, therefore, be less adherent. However, there is no evidence in this study to suggest that treatment response may have affected adherence, as change in PANSS total was not a significant predictor for subsequent nonadherence.

Furthermore, nonadherent patients had a lower rate of early response by week 2 (31.3% vs. 42.4%), suggesting that the relationship between adherence and response began early in the study. This finding may indicate that nonadherence started early for these patients. Alternatively, the decreased early response rate of nonadherent patients may result from nonpharmacologic factors, such as a negative expectation toward taking medication[22] or negative subjective response to medication.[23] The "healthy adherer effect" may also contribute to the relationship between adherence and response. This hypothesis states that good adherence may be a trait, and individuals who exhibit adherent behaviors may lead healthier lives and have better outcomes regardless of treatment.[24] Nevertheless, the cumulative negative effect of nonadherence on clinical response was evident with each incremental day of medication nonadherence associated with a 6% reduction of likelihood of response. However, the difference in functional outcomes as measured by the QLS was not significant between adherent and nonadherent patients. It is possible that the duration of the current study did not allow sufficient time to observe the long-term outcome in patient quality of life as evidenced by a recently published long-term study that reported the association between nonadherence and poor functional outcomes during a 3-year follow-up period.[25]

Patient baseline characteristics were explored as potential risk factors for medication nonadherence. Greater depressive symptoms at baseline, particularly sadness, concentration difficulties, and pessimistic thoughts, were found to be associated with increased risk of not adhering to the prescribed medication regimen during treatment. Ascher-Svanum et al.[26] also found that one of the predictors for nonadherence was prior treatment with antidepressants, likely a marker for presence of depression. Before a medication is prescribed, the identification of greater baseline depression may help clinicians identify patients who may be at risk of medication nonadherence. Appropriate interventions such as concomitant antidepressant treatment may then be considered to enhance better medication adherence and consequently better treatment outcome.

Due to the infrequent collection of MADRS data, we used the PANSS depression factor to study the predictive value of depressive symptoms for nonadherence from one visit to another. One of the items, somatic concern, showed a predictive value. The PANSS somatic concern item rates the degree of physical complaints or beliefs about bodily illness or malfunctions and may reflect somatic side effects

or subjective negative response to the medication. From the practical standpoint, this result suggests that clinicians should monitor patients' somatic complaints since these may herald an increased risk of nonadherence.

We found that hostility throughout the duration of the study was associated with nonadherence in subsequent time periods. Nonadherence to antipsychotic treatment is well known to significantly contribute to the development and severity of hostile and aggressive behavior of schizophrenia patients in the community.[25,27] It is widely believed that the patients first stop taking their medications and, as a result, become aggressive. Although this model is valid, our analyses suggest that hostility may precede nonadherence and, at least in some patients, perhaps contribute to its causation.

There has been considerable evidence in the literature linking treatment resistance in schizophrenia to violent and hostile behavior,[28–30] although the underlying mechanism of the link is not well understood. Our findings may suggest a novel mechanism of that link: hostile attitude leads to nonadherence, and nonadherence then gives the appearance of treatment resistance. Conversely, Alia-Klein et al.[27] found in a forensic sample of inpatients with various psychotic disorders a significant main effect of nonadherence on violence severity. Future studies are needed to better understand this relationship.

Similar to Dolder et al.,[20] we did not find that other characteristics reported in the literature, such as a higher number of past hospitalizations, greater degree of psychopathology, history of substance abuse, and lack of insight, were associated with nonadherence in our sample. One reason for this may be that our sample was specifically screened to participate in a medication trial requiring cooperative participation in various research procedures. In addition, our assessment of patients' insight was limited to the evaluation of the PANSS insight item. Better measures of insight might have yielded different results since other studies such as Perkins et al.[31] suggest insight may be important for medication adherence.

Perkins et al.[31] examined the likelihood of becoming medication nonadherent for 1 week or longer based on daily pill count in a 2-year study of patients recovering from first-episode schizophrenia spectrum disorders. In their analysis, patients with less belief in the need for treatment or who believed that medications were of low benefit were more likely to be nonadherent, as were patients with less improvement in positive and general psychopathology symptoms, whereas negative aspects of medication were not associated with likelihood of nonadherence. Our study did not have the same measures to capture patient beliefs regarding medication adherence as used in the Perkins et al. study,[31] but, in our study, nonadherent patients did have less positive and other symptom improvement compared with adherent patients, and similar to the Perkins et al.[31] study, negative aspects of medication did not appear to be associated with nonadherence.

In contrast to treatment response, we found that adherent and nonadherent patients had comparable outcomes in extrapyramidal symptoms as measured by the AIMS, Barnes Akathisia Rating Scale, and Simpson-Angus Scale. This finding is not surprising, as there was only a small change in extrapyramidal symptoms. As expected, adherent patients had significantly greater weight change, most likely due to the longer exposure to the study medication. However, change in weight did not predict future nonadherence to treatment.

Our data suggest that the higher rate of early study discontinuation in nonadherent patients was primarily due to patient decision and violation of protocol procedures, whereas poor efficacy did not appear to contribute to this difference. However, the patients' decision to discontinue their participation in the study may partially be influenced by their negative subjective perception of problems with the study medication.[22,23] Unfortunately, in this study, as in many others, it is difficult to interpret what underlying reasons result in discontinuation due to patient decision. In any event, nonadherence and discontinuation are, to some extent, overlapping in our study. At each visit, patients identified as nonadherent may have taken a portion of prescribed medication (partial nonadherence) or no medication at all (complete nonadherence). Persistent complete nonadherence, defined as missing 7 consecutive days of full medication dose, did lead to discontinuation per protocol requirement. It should be noted that when early discontinuation has been taken into consideration through a mixed-model repeated-measures analysis, adherent patients maintained a greater level of treatment response as measured by change in PANSS total score compared to nonadherent patients.

A limitation of the current study concerns the measure of medication adherence. Even though the adherence status in the current study based on pill counts provided a more accurate and reliable measure of the true adherence level than subjective report by the subject or subjective assessment by the investigator, there is still room for error, as it cannot be determined for certain if the pills have indeed been taken by the patients. For example, pills may be discarded, and the patient may thus be covertly noncompliant. A previous study found that pill count may underestimate the rate of nonadherence compared to more sophisticated methods such as electronic monitoring.[32] The validity of the pill counts as a measure of medication nonadherence in this study is supported by its significant association with plasma concentration levels. Adherent patients had greater concentration levels compared to nonadherent patients at each of the 2 testing occasions (4 and 8 weeks), with statistically significant differences at 4 weeks. The groups did not significantly differ at study end, possibly due to selective and greater study attrition of nonadherent patients.

Additional limitations are the relatively short duration of the study of 8 weeks and the non-naturalistic sample

characteristics. A longer follow-up period may have provided additional information on the long-term effect of medication nonadherence on treatment outcome, including functional outcome. The particular sample characteristics may limit our findings to patients who volunteer for a research study requiring frequent visits and who receive significant support from research staff during these visits.

CONCLUSION

Medication nonadherence, as measured by pill counts, was present in approximately one third of the subject population during this 8-week prospective study. Our study corroborates previous reports on the negative effect of nonadherence on a wide spectrum of clinical outcomes and the cumulative negative impact of increased duration of nonadherence to a prescribed medication regimen, and it shows that depressive symptoms at baseline, somatic concern, and hostility during treatment constitute significant risk factors for nonadherence to medication. These findings may help clinicians to identify patients at risk for nonadherence and utilize appropriate interventions to enhance medication adherence and ultimately improve treatment outcome.

Drug name: olanzapine (Zyprexa).

Financial disclosure: **Dr. Lindenmayer** has served as a consultant to Eli Lilly and Johnson & Johnson and has received grant/research support from Johnson & Johnson, Eli Lilly, AstraZeneca, Bristol-Myers Squibb, Pfizer, and Roche. **Drs. Liu-Seifert**, **Kulkarni**, **Kinon**, **Stauffer**, **Edwards**, **Adams**, and **Ascher-Svanum** and **Ms. Chen** are employees of and stock shareholders in Eli Lilly. **Dr. Buckley** has served as a consultant to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, Lundbeck, Pfizer, Solvay, and Wyeth; has received grant/research support from AstraZeneca, the National Institute of Mental Health, Pfizer, Solvay, and Wyeth; and has received honoraria from Bristol-Myers Squibb, Janssen, Lundbeck, and Pfizer. **Dr. Citrome** has served as a consultant to Avanir, Azur, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Jazz, Pfizer, Vanda, and Forest; has received grant/research support from AstraZeneca, Barr, Bristol-Myers Squibb, Eli Lilly, Forest, Janssen, and Pfizer; has received honoraria from Avanir, Azur, Eli Lilly, GlaxoSmithKline, Janssen, Jazz, Pfizer, Vanda, and Forest; has served on the speakers or advisory boards of Azur, Abbott, AstraZeneca, Eli Lilly, and Pfizer; and is a stock shareholder in Bristol-Myers Squibb, Eli Lilly, Pfizer, Merck, and Johnson & Johnson. **Dr. Volavka** has received honoraria from Eli Lilly and served on the speakers or advisory boards of Eli Lilly and AstraZeneca.

REFERENCES

1. Cramer JA, Rosenheck R. Compliance with medication regimens for mental and physical disorders. Psychiatr Serv 1998;49:196–201
2. Perkins DO. Predictors of noncompliance in patients with schizophrenia. J Clin Psychiatry 2002;63(12):1121–1128
3. Ayuso-Gutierrez JL, del Rio Vega JM. Factors influencing relapse in the long-term course of schizophrenia. Schizophr Res 1997;28:199–206
4. Olfson M, Mechanic D, Hansell S, et al. Predicting medication noncompliance after hospital discharge among patients with schizophrenia. Psychiatr Serv 2000;51:216–222
5. Perkins DO. Adherence to antipsychotic medications. J Clin Psychiatry 1999;60(suppl 21):25–30
6. Gilbert PL, Harris MJ, McAdams LA, et al. Neuroleptic withdrawal in schizophrenic patients: a review of the literature. Arch Gen Psychiatry 1995;52:173–188
7. DeQuardo JR, Tandon R. Do atypical antipsychotic medications favorably alter the long-term course of schizophrenia? J Psychiatr Res 1998;32:229–242
8. Kinon BJ, Volavka J, Stauffer V, et al. Standard and higher dose of olanzapine in patients with schizophrenia or schizoaffective disorder: a randomized, double-blind, fixed-dose study. J Clin Psychopharmacol 2008;28(4):392–400
9. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
10. Kay SR, Opler LA, Fiszbein A. Positive and Negative Syndrome Scale (PANSS) Manual. North Tonawanda, NY: Multi-Health Systems, Inc; 1992
11. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
12. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
13. Heinrich DW, Hanlon TE, Carpenter WT. The Quality of Life Scale: an instrument for rating the schizophrenic deficit-syndrome. Schizophr Bull 1984;10:388–398
14. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;212:11–19
15. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
16. Psychopharmacology Research Branch, National Institute of Mental Health. Abnormal Involuntary Movement Scale (AIMS). In: Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:534–537
17. Kinon BJ, Volavka J, Bergstrom RF, et al. Steady state concentrations after standard and higher doses of oral olanzapine in patients with schizophrenia or schizoaffective disorder with suboptimal prior response. Neuropsychopharmacol 31(suppl 1):S115
18. Davis JM, Chen N. The effects of olanzapine on the 5 dimensions of schizophrenia derived by factor analysis: combined results of the North American and international trials. J Clin Psychiatry 2001;62(10):757–771
19. Mahmoud RA, Engelhart LM, Janagap CC, et al. Risperidone versus conventional antipsychotics for schizophrenia and schizoaffective disorder: symptoms, quality of life and resource use under customary clinical care. Clin Drug Investig 2004;24:275–286
20. Dolder CR, Lacro J, Dunn L, et al. Antipsychotic medication adherence: is there a difference between typical and atypical agents? Am J Psychiatry 2002;159:103–108
21. Csernansky JG, Mahmoud R, Brenner R; Risperidone-USA-79 Study Group. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. N Engl J Med 2002;346:16–22
22. Amador XF, Gorman JM. Psychopathologic domains and insight in schizophrenia. Psychiatr Clin North Am 1998;21:27–42
23. van Putten T, May PR, Marder SR. Response to antipsychotic medication: the doctor's and the consumer's view. Am J Psychiatry 1984;141:16–19
24. Simpson SH, Eurich DT, Majumdar SR, et al. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ 2006; 333:15
25. Ascher-Svanum H, Faries DE, Zhu B, et al. Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. J Clin Psychiatry 2006;67(3):453–460
26. Ascher-Svanum H, Zhu B, Faries D, et al. A prospective study of risk factors for nonadherence with antipsychotic medication in the treatment of schizophrenia. J Clin Psychiatry 2006;67(7):1114–1123
27. Alia-Klein N, O'Rourke TM, Goldstein RZ, et al. Insight into illness and adherence to psychotropic medications are separately associated with violence severity in a forensic sample. Aggress Behav 2007;33:86–96
28. Conley RR, Buchanan RW. Evaluation of treatment-resistant schizophrenia. Schizophr Bull 1997;23:663–674
29. Krakowski MI, Kunz M, Czobor P, et al. Long-term high-dose neuroleptic treatment: who gets it and why? Hosp Community Psychiatry 1993;44:640–644
30. Volavka J. Neurobiology of Violence. 2nd ed. Washington, DC: American Psychiatric Publishing, Inc; 2002
31. Perkins DO, Johnson JL, Hamer RM, et al. Predictors of antipsychotic medication adherence in patients recovering from a first psychotic episode. Schizophr Res 2006;83:53–63
32. Remington G, Kwon J, Collins A, et al. The use of electronic monitoring (MEMS) to evaluate antipsychotic compliance in outpatients with schizophrenia. Schizophr Res 2007;90:229–237