Adherence to Conventional and Atypical Antipsychotics After Hospital Discharge

Esperanza Diaz, M.D.; Elizabeth Neuse, M.A.; Michelle C. Sullivan, R.N.; H. Rowland Pearsall, M.D.; and Scott W. Woods, M.D.

Background: This prospective study measured adherence to conventional and atypical antipsychotics after hospital discharge in patients with a diagnosis of schizophrenia and schizoaffective disorder. We examined the interaction of several predictors such as gender, severity of illness, attitudes toward medications, side effects, and dose frequency.

Method: The sample consisted of consecutive randomized and nonrandomized patients who were discharged from an inpatient unit with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder between December 1995 and July 1999. All patients were taking oral antipsychotics and consented to the use of an electronic adherence monitor at discharge. Medications were prescribed by usual care providers, and medication adherence was followed weekly for 3 months. The outcome measure was the medication adherence rate registered in the electronic monitors.

Results: We found no significant difference in adherence between the combined groups of atypical and conventional antipsychotics. Individual medication analysis found better medication adherence with olanzapine in comparison with risperidone and conventional antipsychotics, but the difference disappeared in the final model controlling for dose frequency. Dose frequency, gender, and akathisia predicted adherence.

Conclusions: Olanzapine initially appeared to be associated with an adherence advantage over risperidone and conventional antipsychotics, but the apparent advantage may have been due to a usual care dose frequency practice that associated olanzapine more often with once-daily dosing. This study suggests that dose frequency is an important predictor of medication adherence. An important caveat is that these results apply only to short-term adherence.

(J Clin Psychiatry 2004;65:354–360)

Received April 16, 2003; accepted July 21, 2003. From the Department of Psychiatry (Drs. Diaz, Pearsall, and Woods) and the Treatment Research Program (Mss. Neuse and Sullivan and Dr. Woods), Yale University, New Haven, Conn.

This study was supported by the National Alliance for Research on Schizophrenia and Depression and National Institute of Mental Health grants MH 57292 (Dr. Diaz) and MH 60743-01 (Dr. Woods).

Dr. Woods has received grant/research support from Eli Lilly and Janssen.

Corresponding author and reprints: Esperanza Diaz, M.D., Yale University CMHC, 34 Park Street, Room 273 A, New Haven, CT 06519 (e-mail: esperanza.diaz@yale.edu).

Medication adherence is a major factor influencing relapse in patients with schizophrenia and schizoaffective disorder.[1] Side effects with conventional neuroleptics have been described as an important reason for nonadherence to medications.[2,3] The introduction of atypical antipsychotics with fewer extrapyramidal side effects offered a strong theoretical rationale supporting the promise of better adherence with those medications than with conventional neuroleptics.[4,5]

Several methods have been used to evaluate treatment adherence: subjective report, questionnaires, pill counts, clinician reports, pharmacy records, and electronic monitoring. All of these methods have their limitations. During the pilot phase of the present study, we found that electronic monitoring devices could feasibly be used to estimate compliance with medication regimens in patients with severe schizophrenic disorders.[6]

The purpose of this study was to obtain prospectively, via an electronic monitor, the medication adherence rates of patients taking conventional and atypical antipsychotics after discharge from an inpatient hospitalization due to relapse. Relapse was presumably due to noncompliance with medications. We measured other potential baseline predictors of adherence: age, gender, ethnicity, level of symptoms, antipsychotic equivalent doses, dose frequency, support from family and friends, level of functioning, and side effects. We focused our attention on the first 3 months after hospital discharge because patients adjusting to the transition between inpatient and outpatient care are at highest risk for relapse and nonadherence to medications during that period.

METHOD

The study sample consisted of consecutive patients who were discharged from an inpatient unit with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder between December 1995 and July 1999 and who consented to the use of an electronic adherence monitor. The first patients enrolled in the study participated in an initial randomized pilot phase from December 1995 to September 1996 when risperidone was the only marketed atypical antipsychotic other than clozapine. Data from these patients on feasibility of using an electronic adher-

ence monitor in this population were reported previously.[6] The subsequent randomized phase enrolled patients between November 1997 and July 1999. If patients did not consent to randomization, we permitted them to participate in the adherence study after the pilot phase, provided they consented to monitoring. The study was approved by the Institutional Review Board. All participating subjects provided informed consent.

The inclusion criteria were DSM-IV diagnosis of schizophrenia or schizoaffective disorder, hospitalization in a community mental health center for psychotic relapse, voluntary consent, and currently taking oral antipsychotic medication. Patients were excluded if they were supervised to take medications, were taking more than one antipsychotic, were taking a long-acting depot injectable antipsychotic, or were taking clozapine. Patients taking clozapine were excluded because of the possible effects on compliance of the required weekly visits and blood draws. The usual care physicians chose the medication doses and frequency. The dose equivalents selected in these analyses for risperidone and olanzapine were 1 and 4 mg per 100 mg/chlorpromazine, respectively.[4]

Data Collection

After consent was obtained, a baseline battery of tests was completed shortly before patients were discharged from the inpatient unit. Baseline instruments assessed demographics, diagnosis, severity of illness, side effects, and attitude toward medications. The instruments used included the Structured Clinical Interview for DSM-III-R,[7] the Global Assessment Scale (GAS),[8] the Positive and Negative Syndrome Scale (PANSS),[9] the Rating of Medication Influences (ROMI),[10] the Yale Extrapyramidal Symptom Scale (YESS),[11] the Yale Extrapyramidal Symptom Scale Atypical (YESSA) (C. Mazure, Ph.D., oral and written communication, Jan. 1996), the Barnes Akathisia Scale (BAS),[12] the Simpson-Angus Scale (Simpson-Angus),[13] and the Abnormal Involuntary Movement Scale (AIMS).[14]

At discharge, patients were given antipsychotic medication in a bottle with an electronic monitor cap, the Medication Event Monitoring System (MEMS) (Aprex Corp., Freemont, Calif.). This cap is capable of registering the number of pill bottle openings with date and time of each opening. Patients were asked to return for weekly study visits for the next 3 months. At each visit, data were downloaded from the MEMS cap. A small fee was offered to the patients for each follow-up visit.

Data Analysis

The dependent variable was MEMS percent adherence. The medication adherence rate was calculated as the number of bottle openings over the number of prescribed openings in the 3-month time period. To obtain a more accurate count, we looked at the printout calendar of bottle openings with the subjects at each follow-up visit. We used a questionnaire to check for extra openings, e.g., by mistake or pharmacy, or lack of openings for valid reasons, e.g., took pills away for the weekend. These openings were added or subtracted to the final number of openings for the final calculation of adherence.

We conducted 2 parallel analyses. For our primary analysis, we assumed that adherence was zero if MEMS data were missing for any reason. We chose this assumption for our primary analysis because it made the most conservative assumption about missing data. For our secondary analysis, we assumed that mean adherence during a period of missing data was the same as during the time of measurement. In the secondary analysis, patients with completely missing data were omitted.

Preliminary univariate analyses were used to test the association between the type of antipsychotic medication and percentage adherence. We also used univariate analyses to determine correlations between medication adherence and other variables such as gender, attitudes toward medication, severity of psychosis, random versus nonrandom design, and dose frequency. We planned to include correlations that were trend significant to a multiple regression model testing the predictive value of type of medication on medication adherence to identify mediating or proxy effects.[15]

RESULTS

Description of the Sample and Baseline Measures

Table 1 shows the distribution of the sample by phase and medication type. The sample consisted of 50 subjects: 68% were randomized and 32% were not randomized. Subjects were 44% white, 48% African American, and 8% other. Diagnoses included 43% with schizophrenia and 57% with schizoaffective disorder. Sixty-six percent of patients were taking atypical medications and 34% were taking conventional medications. Table 2 shows baseline measures by medication group. The mean ± SD chlorpromazine equivalent dose for the antipsychotics prescribed was 603 ± 323 mg. There were no significant differences between the conventional and atypical groups on any of the baseline measures.

Dose frequency for the different antipsychotics, determined by the usual care doctors, is shown in Table 3. Table 3 also shows mean ± SD MEMS percent adherence broken down by medication and prescribed dose frequency. Once-daily dosing was prescribed less frequently for risperidone (14%) and conventional antipsychotics (6%) than for olanzapine (78%, $\chi^2 = 17.9$, $p < .001$). Adherence was significantly higher for once-daily dosing ($p = .001$). Only 2 risperidone patients and 1 conventional patient received dosing once daily. Mean compliance was quite low (17%) in the 4 olanzapine patients dosed twice daily. Also, adherence was higher in a single patient pre-

Table 1. Description of Sample and Distribution by Medication Assignment

Study Phase	Enrollment Dates	Conventional (N = 17)	Atypical (N = 33)			Total (N = 50)
			Risperidone	Olanzapine	Quetiapine	
Randomized pilot	12/95–9/96	6	7	NA	…	13
Randomized	11/97–6/99	8	5	7	1	21
Nonrandomized	11/97–6/99	3	2	11	…	16

Table 2. Univariate Analysis of Baseline Patient Measures by Medication Type[a]

Variables	Conventional N = 17	Atypical N = 33	Total N = 50
Gender, women, N (%)	5 (26.3)	8 (27.6)	13 (27.1)
Age, y	33.3 ± 10	34.5 ± 8.9	34.1 ± 9.2
PANSS score	89.5 ± 15.6	87.3 ± 17.1	88.1 ± 16.5
GAS score	31.3 ± 6.5	28.8 ± 8.7	29.6 ± 8.0
ROMI side effects score	2.3 ± 0.9	1.8 ± 1.2	1.9 ± 1.1
YESS score	3.9 ± 3.5	4.4 ± 2.8	4.2 ± 3.0
YESSA score	23.6 ± 8.2	24.5 ± 5.2	24.2 ± 6.3
Simpson-Angus score	2.4 ± 2.8	2.8 ± 2.6	2.7 ± 2.7
AIMS score	0.9 ± 2.3	0.9 ± 1.4	0.9 ± 1.7
BAS score	0.8 ± 1.1	0.8 ± 1.1	0.8 ± 1.1

[a]There were no significant differences between the groups. All values except gender are mean ± SD.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, GAS = Global Assessment Scale, PANSS = Positive and Negative Syndrome Scale, ROMI = Rating of Medication Influences, Simpson-Angus = Simpson-Angus Scale, YESS = Yale Extrapyramidal Symptom Scale, YESSA = Yale Extrapyramidal Symptom Scale Atypical.

scribed a conventional antipsychotic once a day, and patients prescribed risperidone twice a day were somewhat adherent.

Primary Analysis: Medication Adherence

We were able to obtain MEMS percent adherence data on 55% of patient days after hospital discharge. The primary analysis assumed a compliance of zero for missing data. The overall MEMS percent adherence averaged 37.5% ± 36.0% over the 3 months after discharge. The mean adherence to conventional antipsychotics was 29.6% ± 29.0% and to atypicals was 41.6% ± 38.9%. This difference was not significant. To investigate possible differences among atypical antipsychotics, the medication type variable was redefined as conventional versus risperidone versus olanzapine with types coded as 0, 1, and 2, respectively. These analyses required that the 1 quetiapine patient be excluded.

Univariate analysis. The omnibus comparison of the 3 groups was statistically significant ($F = 5.1$, $p = .01$). Pairwise comparisons revealed that compliance with olanzapine (58.0% ± 40.2%, N = 18) was significantly higher than with conventionals (29.6% ± 29.0%, N = 17, $p = .039$). Compliance with risperidone (23.5% ± 27.5%, N = 14) in comparison with olanzapine was significant ($p = .015$) but versus conventionals was not significant.

In the primary analysis, other significant univariate predictors of adherence were random versus nonrandom assignment ($r = –.349$, $p = .013$), dose frequency ($r = –.482$, $p = .000$), female gender ($r = .411$, $p = .003$), YESS scores ($r = –.286$, $p = .049$), and BAS scores ($r = –.319$, $p = .027$). Age and PANSS, GAS, ROMI side effects, YESSA, AIMS, and Simpson-Angus scores were not significantly associated with adherence.

Multivariate analysis. Multivariate analyses are shown in Table 4. The effect of olanzapine versus risperidone versus conventional was not independent from other significant univariate predictors. Gender and dose frequency remained significant but random versus nonrandom and the BAS did not.

The main reason that olanzapine versus risperidone versus conventional lost significance in the multivariate model was that the multivariate model corrected for the confounding correlation between dose frequency and medication type shown in Table 3. Exploratory analyses revealed that olanzapine versus risperidone versus conventional medication type was always significantly associated with adherence when dose frequency was removed from the model ($p = .017$); conversely, olanzapine versus risperidone versus conventional medication type was never significantly associated with adherence when dose frequency was included in the model. A second reason that olanzapine versus risperidone versus conventional lost significance in the multivariate model was that nonrandomized patients were more often prescribed olanzapine (Table 1) and the univariate advantage of olanzapine was stronger in the nonrandomized olanzapine patients (Figure 1).

The BAS lost significance in the multivariate analysis because random versus nonrandom assignment was significantly correlated with the BAS. When we ran exploratory models excluding random versus nonrandom, the BAS was significant ($p = .027$).

Secondary Analysis: Medication Adherence

The secondary analysis assumed that mean adherence during a period of missing data was the same as during the time of measurement. The overall MEMS percent adherence averaged 47.0% ± 38.3% over the 3 months after discharge. The mean adherence to conventional antipsychotics was 35.8% ± 32.0% and to atypicals was 52.7% ± 40.4%. Again, to investigate possible differences among atypicals, the medication type variable was redefined as conventional versus risperidone versus olanzapine with types coded as 0, 1, and 2, respectively. The 1 quetiapine patient was excluded.

Table 3. Mean ± SD MEMS Percent Adherence of Patients (N) by Medication Type and Dose Frequency

	q.d.		b.i.d.		t.i.d.		Total	
Medication	MEMS %	N	MEMS %	N	MEMS %	N	MEMS %	N
Risperidone	0 ± 0	2	27 ± 28	12	…	…	24 ± 28	14
Olanzapine	70 ± 34	14	17 ± 33	4	…	…	58 ± 40	18
Conventional	78	1	27 ± 28	14	22 ± 30	2	30 ± 29	17
Total	62 ± 39	17	26 ± 28	30	22 ± 30	2	38 ± 36	49

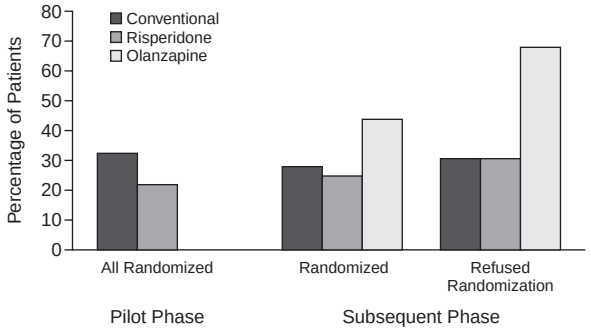
Abbreviation: MEMS = Medication Event Monitoring System.

Table 4. Primary Multivariate Regression Analysis on Prediction of Adherence[a]

Predictors	B	t	p (2-tailed)
Conventional/risperidone/olanzapine	–0.504	–0.077	.939
Randomized vs. nonrandomized	–7.34	–0.732	.469
Gender	–30.15	–3.37	.002
Dose frequency	–29.60	–3.1	.004
Barnes Akathisia Scale	–5.96	–1.48	.147

[a]Dependent variable = mean MEMS % adherence.
Abbreviation: MEMS = Medication Event Monitoring System.

Figure 1. Adherence by Medication Type and Study Phase



Univariate analysis. The omnibus comparison of the 3 groups was statistically significant ($F = 2.7$, $p = .07$). Pairwise comparisons revealed that compliance with olanzapine (80.3% ± 18.7%, $N = 13$) was significantly higher than with conventionals (33.5% ± 28.6%, $N = 15$, $p < .001$). Compliance with risperidone (30.0% ± 27.8%, $N = 11$) in comparison with olanzapine was significant ($p = .021$) and versus conventionals was not significant.

In the secondary analysis, other significant univariate predictors of adherence included dose frequency ($r = –.396$, $p < .004$) and female gender ($r = –.377$, $p = .007$). Age and PANSS, GAS, ROMI side effects, YESS, YESSA, AIMS, Simpson-Angus, and BAS scores were not significantly associated with adherence.

Multivariate analysis. Again, as in the primary analysis, the effect of olanzapine versus risperidone versus conventional was not independent from other significant univariate predictors. In the final model, only gender (female) remained significant.

DISCUSSION

The principal finding of this study was that less frequent daily dosing at hospital discharge was associated with better subsequent outpatient medication adherence over the short-term. Olanzapine initially appeared to be associated with higher adherence compared with risperidone and conventional antipsychotics, but multivariate analysis revealed that better adherence with olanzapine was not an independent effect; rather, better adherence appeared to be mediated by the frequent once-daily prescription of olanzapine. Another important finding was that female gender was independently associated with better adherence. Consent versus nonconsent to randomization had no effect on medication adherence. The duration of the study was too brief to determine whether longer-term adverse events such as weight gain[16] affected adherence.

Strengths

This study had several strengths. Some methodological strengths were related to the method of measuring adherence and methods of analyzing it. The MEMS cap provided an objective and quantitative method of measurement. We analyzed medication adherence 2 ways in order to determine whether missing data had an important influence on our results. The fact that we obtained similar results in both analyses increases confidence in the validity of the findings.

There are other strengths of the study as well. We studied adherence in a severely ill group of patients in whom adherence is an important clinical issue. The study reflects outcomes obtained by usual care prescribers, and, therefore, the results may be applicable to clinical practice. Another strength of the study is that most patients were chosen at random to receive atypical versus conventional antipsychotics, thus minimizing any assignment bias that could have affected adherence.

Limitations

The small sample size, the highly selected sample, the length of the study period, the usual care dose frequency practices, the choice of method to measure adherence, the fact that some data were missing, and the antipsychotic dose equivalents affected the results of this study.

Sample. The sample size was ultimately small. In particular, sample sizes were very low for some medication subsamples broken down by prescribed dose frequency. Several factors affected the sample size. Some patients were discharged before they could give informed consent for a research study. This loss of potential subjects was a consequence of the increasingly short-term length of stay in an inpatient unit. Some patients were discharged to supervised medication administration arrangements, precluding them from participating in the study. If subjects were supervised, we could not measure their adherence. Some patients were prescribed depot medications and thus were lost to a study of adherence to oral medications. Other patients were reluctant to participate in random assignment. All of these factors taken together led to a highly selected sample.

To maximize sample size, we allowed patients to enroll in the study who had not been randomized to medication assignment. This nonrandomized group seems to have captured subjects who were interested in a particular newer atypical medication. Permitting nonrandomized patients to participate did not seem to alter the findings. Randomized versus nonrandomized participation was not a significant predictor of adherence (Table 4).

Length of study period and usual care dosing practices. There were 2 important consequences of the study extending over a period of $3^1/_2$ years. First, 2 new atypical antipsychotics were introduced: olanzapine and quetiapine, although we were not able to include quetiapine subjects in the analysis, as this medication was introduced toward the end of our recruitment period and only 1 subject was prescribed the drug at that time. A consequence of the introduction of a new medication was that many patients and prescribers were infused with a great deal of hope, and some patients then refused to be randomized because they did not want to miss the chance to try the newly introduced medicine. Our results are consistent with this interpretation. The group of patients who refused randomization mostly chose to take olanzapine (11 of 16, Table 1).

A second consequence of the study duration was the change in risperidone prescribing guidelines. The naturalistic design did not permit controlling prescribers' behavior or their conformity to dosing frequency guidelines. Risperidone was labeled for b.i.d. dosing until October 17, 1997, approximately midway during our study. After the labeling change, most of the patients taking risperidone, except for 2, continued to take twice-daily doses. Despite the possibilities, measured adherence was fairly low. Usual care prescribers generally continued to use the old labeling for reasons that are unknown. A further consequence of not controlling practice was that dosing frequency practices differed across medications, complicating the determination of medication effects on adherence. There was no cause/effect between dose and later date of enrollment, nor was there a cause/effect between dose frequency and later date of enrollment.

Adherence method. We must take into consideration the limitations of medication adherence studies in seriously ill subjects. There is no perfect way to measure adherence. Although the MEMS method provides a quantitative and objective measurement of adherence, it is possible that using the MEMS could artificially inflate adherence. In general, when subjects know their adherence is being monitored they often either improve their actual adherence or employ deceptive strategies to appear more adherent.[17] In this study, we may have further inflated adherence by offering all participants a small fee to encourage cap return. Similarly, to enhance data capture, we asked that all participants return for weekly visits, and this practice also could have inflated adherence. Taking into consideration all of the limitations of the adherence measure, we emphasize that all participating subjects were followed by weekly MEMS and were paid.

Adherence rates. An initial look at the adherence rates gave an advantage to olanzapine, but when we controlled for dose frequency, the rates were no different between the medications. We cannot conclude that olanzapine had better adherence than the other medication groups. Another factor that might have affected risperidone adherence was the risperidone dose used by the usual care prescribers. During the study period, risperidone was prescribed at higher doses than is used currently, perhaps producing more side effects than with lower, still effective, doses.

Missing data. We were unable to record 45% of the planned MEMS adherence data. Previously, we described difficulties obtaining complete data on medication adherence in these severely ill patients.[6] The 45% missing data occurred despite the fee to encourage cap return and the weekly visits.

Antipsychotic dose equivalents. The equivalent doses chosen in these analyses for risperidone and olanzapine were 1 and 4 mg per 100 mg/chlorpromazine. There is controversy around equivalent doses for atypicals, with estimates for risperidone ranging from 1 to 1.5 mg/100 mg chlorpromazine and estimates for olanzapine ranging from 4 to 5 mg/100 mg chlorpromazine.[4] It may be possible that the risperidone doses at the time of the study were too high, and that if the patients had received lower doses, adherence might have been better.

Comparisons With Previous Studies

Medication type. Our finding that medication type was not associated with adherence is consistent with 2 of 3 previous reports comparing adherence between atypicals and conventionals.[18–20] A retrospective study of outpatient Veteran's Affairs pharmacy records showed a significantly better rate of adherence for atypicals in comparison with conventionals.[18] The atypicals studied with

this method were risperidone (N = 80), olanzapine (N = 63), and quetiapine (N = 28, nonrandomized). At 6 months, patients receiving atypical antipsychotics appeared to miss 12.2% of prescribed doses compared with 22.9% for patients receiving conventionals. There were no significant differences among patients receiving atypicals. Unlike the present study, the possible effect of dose frequency was not controlled.

The second study compared adherence between clozapine (N = 205) and haloperidol (N = 210) during a randomized double-blind clinical trial.[19] Dosing frequency was not described; however, since the trial was double-blind, it may be presumed not to vary across medications. Adherence was measured using the pill-count method. Adherence was not significantly different between clozapine and haloperidol.

A third report,[20] a cross-sectional study of patients with schizophrenia, asked retrospectively about treatment prior to hospital admission in order to measure the subjective response to antipsychotics using the self-report Drug Attitude Inventory (DAI). The DAI measure categorizes compliance as adequate, irregular, or discontinuation. The investigators found that a positive subjective response was related to drug compliance but found no significant differences in adherence between atypicals (clozapine N = 10 and risperidone N = 16) and conventional antipsychotics (N = 34). There was no correlation with the drug dose used. Dosing frequency was not described.[20]

In the 1 study reporting a difference,[18] patients receiving atypicals had been selected on the basis of previous failure with conventional antipsychotics. It is possible that this procedure could select a more adherent group. This same study reporting a difference and 1 of the other negative studies[19] included patients randomized to treatment. Each of the studies used different methods of adherence measurement. Only 1 of the 3 studies presumably controlled for any effects of dose frequency by its double-blind design comparing clozapine versus haloperidol.[19] The present study controlled for dose frequency by using it as a covariate.

Dose frequency. Our finding that prescribed dose frequency is an important predictor of adherence with antipsychotic medications is consistent with several studies in other patient populations.[22–24] The MEMS method has been used to evaluate patients with epilepsy.[24] In this study, compliance rates were 87% with q.d. dosing, 81% with b.i.d. dosing, 77% with t.i.d. dosing, and 39% with q.i.d. dosing. Another MEMS study[21] conducted with hypertensive patients found that compliance improved dramatically as prescribed dose frequency decreased. A systematic review of studies of medication compliance using the MEMS method across general medical and psychiatric conditions has been conducted.[22] This review concluded that the number of prescribed doses per day was inversely correlated with compliance. A recent meta-analysis of comparative antihypertensive trials concluded that q.d. dosing regimens were associated with higher rates of adherence than multiple daily dosing regimens.[23]

Our results showing better compliance with decreased dose frequency are not fully consistent because of the extremely poor compliance in the risperidone patients taking the medicine once daily. The sample (N = 2), however, was extremely small.

Gender. In our study, 27% of the subjects were female. Female gender was a positive predictor of medication adherence. In agreement with our findings, male gender was a significant predictor of extreme noncompliance in Afro-Caribbeans with a diagnosis of schizophrenia.[25] Also in agreement with our findings, adolescent and young adult women taking human immunodeficiency virus medicines showed better adherence than men.[26] We could find no other previous studies of gender influence on medication adherence in schizophrenia. We found a report[27] from general medicine of predictors of medication adherence in which gender was not associated with higher compliance, which disagrees with our results. The study included patients receiving treatment for asthma, as well as renal, cardiac, or oncology reasons.[27]

Further studies are needed to confirm these results and then to explore why female patients might take a higher proportion of their prescribed medication than males. Such investigations could potentially suggest methods to enhance adherence among male patients as well.

Implications

Medication type. Medication adherence was not significantly different between atypical and conventional antipsychotics in this small sample. There was an initial suggestion that medication adherence was better for olanzapine, but this possibility disappeared when we controlled for dose frequency. These findings must be considered in the context of the study limitations: sample size, changes in prescribing during study period, and lack of control of prescribing practices. As discussed earlier, 2 of the previous studies, none using an electronic monitor, also found no difference in adherence between patients taking atypicals and conventionals.[19,20] The bulk of the evidence so far does not substantiate claims that atypicals improve adherence.

Dose frequency. Taken together with other studies, our results support a clinical practice of prescribing antipsychotics once daily when feasible. The present study confirms that dose frequency is an important predictor of medication adherence. Future studies comparing medication adherence with different antipsychotics should control for dose frequency. Since adherence is strongly enhanced by once-daily dosing, it would be important to investigate whether commonly prescribed antipsychotics may be effectively prescribed once daily. When multiple daily doses are used in inpatient treatment, particular

efforts should be made to simplify treatment regimens at discharge.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

REFERENCES

1. Weiden PJ, Olfson M. Cost of relapse in schizophrenia. Schizophr Bull 1995;21:419–429
2. Adams S Jr, Howe JT. Predicting medication compliance in a psychotic population. J Nerv Ment Dis 1993;181:558–560
3. Van Putten T. Why do schizophrenic patients refuse to take their medications? Arch Gen Psychiatry 1974;31:67–72
4. Jibson MD, Tandon R. New atypical antipsychotic medications. J Psychiatr Res 1998;32:215–228
5. Rosenheck R, Cramer J, Jurgis G, et al. Clinical and psychopharmacologic factors influencing family burden in refractory schizophrenia. J Clin Psychiatry 2000;61:671–676
6. Diaz E, Levine HB, Sullivan MC, et al. Use of the Medication Event Monitoring System to estimate medication compliance in patients with schizophrenia. J Psychiatry Neurosci 2001;26:325–329
7. Spitzer RL, Williams JB, Gibbon M, et al. The Structured Clinical Interview for DSM-III-R (SCID), 1: history, rationale, and description. Arch Gen Psychiatry 1992;49:624–629
8. Endicott J, Spitzer RL, Fleiss JL, et al. The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 1976;33:766–771
9. Kay SR, Opler LA, Lindenmayer JP. The Positive and Negative Syndrome Scale (PANSS): rationale and standardization. Br J Psychiatry Suppl 1989;7:59–67
10. Weiden P, Rapkin B, Mott T, et al. Rating of Medication Influences (ROMI) scale in schizophrenia. Schizophr Bull 1994;20:297–310
11. Mazure CM, Cellar JS, Bowers M, et al. Assessment of extrapyramidal symptoms during acute neuroleptic treatment. J Clin Psychiatry 1995;56:94–100
12. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
13. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;46:11–19
14. Psychopharmacology Research Branch, National Institute of Mental Health. Abnormal Involuntary Movement Scale (AIMS). In: Guy W, ed. ECDEU Assessment Manual for Psychopharmacology, Revised. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:534–537
15. Kraemer H, Stice E, Kazdin A, et al. How do risk factors work together? mediators, moderators, and independent, overlapping and proxy risk factors. Am J Psychiatry 2001;158:848–856
16. Allison DB, Mentore JL, Moonseong H, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156:1686–1696
17. Levine RJ. Monitoring for adherence: ethical considerations. Am J Respir Crit Care Med 1994;149:287–288
18. Dolder CR, Lacro JP, Dunn LB, et al. Antipsychotic medication adherence: is there a difference between typical and atypical agents? Am J Psychiatry 2002;159:103–108
19. Rosenheck R, Chang S, Choe Y, et al. Medication continuation and compliance: a comparison of patients treated with clozapine and haloperidol. J Clin Psychiatry 2000;61:382–386
20. Garcia Cabeza I, Sanz Amador M, Arango Lopez C, et al. Subjective response to antipsychotics in schizophrenic patients: clinical implications and related factors. Schizophr Res 2000;41:349–355
21. Eisen SA, Miller DK, Woodward RS, et al. The effect of prescribed daily dose frequency on patient medication compliance. Arch Intern Med 1990;150:1881–1884
22. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther 2001;23:1296–1310
23. Iskedjian M, Einarson TR, MacKeigan LD, et al. Relationship between daily dose frequency to antihypertensive pharmacotherapy: evidence from a meta-analysis. Clin Ther 2002;24:302–316
24. Cramer JA, Mattson RH, Prevey ML, et al. How often is medication taken as prescribed? a novel assessment technique. J Am Med Assoc 1989;261:3273–3277
25. Sellwood W, Tarrier N. Demographic factors associated with extreme noncompliance in schizophrenia. Soc Psychiatry Psychiatr Epidemiol 1994;29:172–177
26. Martinez J, Bell D, Camacho R, et al. Adherence to antiviral drug regimens in HIV-infected adolescent patients engaged in care in a comprehensive adolescent and young adult clinic. J Natl Med Assoc 2000;92:55–61
27. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psychosom Res 1999;47:555–567