Dosing Frequency and Adherence to Antipsychotic Medications

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Objectives: **This study investigated whether dosing frequency affects antipsychotic medication adherence among patients with schizophrenia.** ***Methods:*** **Databases from the Department of Veterans Affairs were used to assess adherence among patients with a diagnosis of schizophrenia. Adherence was measured by using antipsychotic medication possession ratios (MPRs). Adherence was compared among patients who experienced an increase or decrease in dosing frequency and among patients on stable regimens of once-daily or more than once-daily dosing.** ***Results:*** **Among patients with a dose increase (N=1,639), those with increases in dosing frequency (N=258) had a mean change in MPRs of –.105, compared with –.002 for those without a dosing frequency change (N=1,381) (p<.001). Patients with decreases in dosing frequency (N=1,370) had a small but significant increase in mean MPRs (MPR change=.045) when compared with 2,740 patients without a dosing frequency change (MPR change=–.018) (p<.001). Among patients on stable regimens (N=32,612), there were no significant differences in MPRs between those receiving once-daily dosing (MPR=.80) and those receiving more than once-daily dosing (MPR=.80).** ***Conclusions:*** **Among patients on less stable dosing regimens, increases in dosing frequency may result in modest decreases in adherence. (*Psychiatric Services* 59:1207–1210, 2008)**

Partial adherence to antipsychotic medications remains both common and problematic in the treatment of schizophrenia. Despite anticipated improvements in adherence with the wider use of second-generation antipsychotics, recent studies show that more than 40% of patients continue to have difficulty maintaining full adherence (1–4). Patients with prolonged gaps in medication adherence are nearly four times more likely than those who are fully adherent to be hospitalized for psychiatric reasons. Even small gaps of one to ten days appear to be associated with increased rates of admission (4).

There are multiple contributing factors to partial adherence (5,6). Dosing frequency is one factor that may be readily amenable to intervention by clinicians or health systems.

Prior studies investigating the relationship between dosing frequency and adherence in schizophrenia have delivered mixed results (7–10). Some studies have found a significantly negative correlation between increases in dosing frequency and medication adherence (8,10), whereas others have found no relationship (7,9). Most of these studies used medication electronic monitoring systems (MEMS) to measure adherence, which limits the size and composition of the population that can be studied (7,9,10).

For this study we utilized pharmacy records from Department of Veterans Affairs (VA) databases to evaluate the relationship between dosing frequency and medication adherence in a large sample of patients with schizophrenia. We compared changes in adherence among patients who underwent an increase or decrease in dosing frequency with those of patients whose dosing frequency did not change. We also compared adherence between patients on a stable regimen of once-daily or more than once-daily dosing. We hypothesized that stable regimens of more than once-daily dosing and increases in dosing frequency would be associated with poorer adherence.

Methods

The study was conducted in concordance with institutional review board approval for use of the National Psychosis Registry by the VA Ann Arbor Health system. Patients with a diagnosis of schizophrenia or schizoaffective disorder were identified by using the registry, which is maintained by the Serious Mental Illness Treatment Research and Evaluation Center in Ann Arbor, Michigan. We included patients filling at least one outpatient pharmacy prescription for risperidone, quetiapine, ziprasidone, olanzapine, aripiprazole, or haloperidol during fiscal year (FY) 2005 (October 1, 2004, through September 30, 2005).

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Patients were excluded if they were on more than one antipsychotic during the year, their only medication fill was at hospital discharge, or they had more than one medication fill during an inpatient stay.

Adherence was measured for each patient by using a medication possession ratio (MPR). The numerator for the MPR was calculated by adding the number of days' supply of antipsychotic medication available to a patient from each outpatient prescription that was filled during the year. The denominator was calculated as the number of noninstitutionalized days between a patient's first prescription fill and the end of the year. An MPR of 1.0 indicates full adherence, whereas an MPR of .5 indicates that a patient received only half the medication needed to ensure continuous use. The MPR has been shown to have a low false-positive rate for classifying patients with serious mental illness as poorly adherent (11), and MPRs correlate well with clinically meaningful outcomes, such as hospitalization rates (3).

Prescriptions were classified as either once daily or more than once daily by referencing the text of their prescriptions to a list of standard terms used to indicate dosing frequency.

Demographic variables used as covariates in our analyses included each patient's age (as a continuous variable), sex, race (white, African American, American Indian, Asian or Pacific Islander, multiracial, or unknown), ethnicity (Hispanic or non-Hispanic), and marital status (married, unmarried, or unknown). Clinical variables included psychiatric admission in the prior year (FY 2004), the number of psychotropic medication classes (for example, antipsychotic, antidepressant, and anxiolytic) prescribed during the year, and the presence of co-occurring substance use diagnoses.

To determine whether dosing frequency affects adherence among patients with schizophrenia, we conducted analyses in three distinct subpopulations: patients with increases in their total dose during the year who either did or did not also have increases in dosing frequency, patients initially prescribed more than once-daily dosing who either remained on this regimen or decreased to once-daily dosing, and patients with no change in dosing frequency throughout the year. We designed these analyses to better illuminate the relationship between dosing and adherence after important clinical decision points.

When increasing a patient's antipsychotic dose, clinicians are often faced with a decision about whether to prescribe the additional medication as a separate dose or to maintain a patient on once-daily dosing. We evaluated the potential impact of this decision by selecting patients who were initially on once-daily dosing and had a 50% or greater increase in total dose during the year. We then compared mean MPRs of those who had an increase in dosing frequency with those remaining on once-daily dosing.

To evaluate the impact of decreases in dosing frequency, we identified patients who had a change from more than once-daily to once-daily dosing during the year. For each of these patients we matched two patients as controls; they were prescribed to take their medication more than once daily and filled their medications in the same week that the index patients had the decrease in dosing frequency. However, the patients serving as controls did not have a change in dosing frequency. By matching on the date of the index medication fill we controlled for trends in adherence patterns over time. Mean MPRs were then compared between the two groups.

Finally, we compared mean MPRs for the year for patients remaining on stable dosing regimens (once-daily or more than once-daily dosing) throughout the year.

For both the increase and decrease in dosing frequency analyses, we fit multivariate linear regression models. The MPR after the change in dosing frequency (or matched date for control patients) was the continuous dependent variable, and change in dosing frequency was the major independent variable of interest. Covariates included in the models were the MPR before the dose change and the demographic and clinical covariates described previously. For patients on stable dosing frequencies, the MPR was the dependent variable and dosing frequency was the major independent variable of interest in our multivariate analyses. Comparisons of mean MPRs were performed by using a two-sided Wilcoxon ranked-sum test.

Results

Among the 32,612 patients who were on a stable regimen, 95% were male (N=30,856), 60% were Caucasian (N=19,482), 31% were African American (N=10,031), 8% were Hispanic (N=2,499), 25% were married (N=8,236), and the mean±SD age of the sample was 56±11. There were only minor differences in demographic variables based on dosing frequency. [A table showing demographic characteristics by antipsychotic dosing frequency is available as an online supplement at ps.psychiatryonline.org.]

A total of 1,639 patients were identified who initially had once-daily dosing of an antipsychotic medication and a 50% or greater increase in their total medication dose during the year. Patients who changed to more than once-daily dosing (N=258) subsequent to the increase in dose had a decrease in mean MPR of –.105, compared with an MPR of –.002 for those who remained on once-daily dosing after the dose increase (N=1,381) ($p<.001$) (Table 1). In multivariate analyses, an increase in dosing frequency remained significantly associated with decreased adherence. The only covariate significantly associated with poorer adherence in this analysis was African-American race.

We identified 1,370 patients who had a decrease in antipsychotic dosing frequency from more than once daily to once daily during the year. These patients were matched to a control group of 2,740 patients who did not have a decrease in dosing frequency during the year. The mean change in MPR after the dosing frequency change (or matched date for the control group) was .045 for patients with a decrease in dosing frequency and –.018 for patients with no change ($p<.001$). In multivariate analyses, a decrease in dosing frequency was significantly associated with improved adherence. A comorbid substance use diagnosis and African-American race were associated with poorer adherence, whereas older age and being prescribed a larger number of psychotropic medica-

tion classes were associated with better adherence.

The largest sample of patients consisted of 32,612 VA patients who remained on a single antipsychotic medication and a consistent dosing frequency during FY 2005. There was no significant difference in mean MPRs between those prescribed once-daily dosing (N=23,169) and those prescribed more than once-daily dosing (N=9,443). Both groups had a mean MPR of .80.

In multivariate analysis, more than once-daily dosing frequency was weakly associated with poorer adherence among patients on a stable regimen (parameter estimate=–.014, p<.001). Demographic variables associated with poorer adherence were younger age, African-American race, Hispanic ethnicity, and being married. Hospitalization in the prior year, a substance use diagnosis, and being prescribed fewer psychotropic medication classes were also associated with poorer adherence (Table 2). The overall variance in adherence explained by these factors was small, with the R^2 for the regression model being .076.

Discussion

Although previous studies of antipsychotic medication adherence have sometimes included dosing frequency as part of their analysis, no prior studies have used a large national database to evaluate dosing frequency and adherence among patients with schizophrenia who have experienced either an increase or decrease in dosing frequency or have remained on stable dosing during the year.

Previous studies have also not specifically evaluated the relationship between changes in dosing frequency and adherence. Our study found that among patients who underwent a 50% or greater total dose increase, those who had increases in dosing frequency subsequently had modest decreases in adherence when compared with those who remained on once-daily dosing. There are several possible explanations for this finding. Patients who received an increase in antipsychotic dose are likely to have had increased levels of psychiatric symptoms that prompted this change, and these high symptom levels may make adjusting to more than once-daily dosing more difficult. Patients who were switched to more than once-daily dosing after the dose increase may also have had more difficulty with side effects, and these side effects may partially be responsible for poorer levels of adherence after the dosing change.

Decreases in dosing frequency were associated with a small but statistically significant increase in adherence among patients initially on more than once-daily dosing, compared with patients with no change in dosing frequency. This finding suggests that decreasing patients' dosing frequencies is likely to result in only modest gains in adherence. However, it also suggests that changes in dosing frequency per se are not necessarily associated with poorer adherence.

Finally, in unadjusted analyses, dosing frequency was not associated with differences in adherence among a large majority of patients with schizophrenia on stable dosing regimens. This finding needs to be interpreted cautiously, because patients on stable regimens are likely to be clinically stable and may have already been switched to the most acceptable dosing strategy. This finding therefore provides only limited guidance for initial treatment recommendations, although it does suggest that initiatives to simplify dosing regimens for clinically stable patients may not result in marked benefit.

Our results also illuminate potential reasons for the mixed findings in the literature on the impact of dosing on adherence among patients with schizophrenia, because the association between dosing frequency and adherence appears to be dependent on the treatment population selected.

Our findings of no adherence differ-

Table 1

Antipsychotic medication adherence among 1,639 veterans with a ≥50% total dose increase during fiscal year 2005, by dosing frequency

Variable[a]	Patients continued on once-daily dosing (N=1,381) M	SD	Patients increased to multiple daily doses (N=258) M	SD	p
MPR before total dose increase	.92	.32	.89	.40	.22
MPR after total dose increase	.92	.38	.79	.31	<.001
Change in MPR	–.002	.37	–.105	.40	<.001

[a] MPR, medication possession ratio, or the ratio between the amount of medication a patient fills from the pharmacy and the amount needed for continuous use during a specified period. A value of 1.0 represents complete adherence, and a value of .0 represents complete nonadherence.

Table 2

Multiple regression model of the effects of patient-level variables on antipsychotic medication adherence among 32,612 veterans with schizophrenia on stable dosing regimens in fiscal year 2005[a]

Variable	Parameter estimate	p
African-American race	–.119	<.001
Hispanic ethnicity	–.080	<.001
Substance use diagnosis	–.075	<.001
Psychiatric admission in 2004	–.050	<.001
More than once-daily dosing	–.014	<.001
Age	.002	<.001
Male gender	.001	.94
Unmarried	.031	<.001
Number of psychotropic medication classes	.035	<.001
Intercept	.676	<.001

[a] Dependent variable: medication possession ratio

ences among patients on stable dosing regimens is consistent with another recently published study that found no relation between dosing frequency and adherence among outpatients with schizophrenia when MEMS was used to measure adherence over a six-month observation period (9). Our findings also agree with a prospective study that found no relation between dosing frequency and adherence among 61 patients with schizophrenia followed for two years after hospital discharge (7), although these patients may have been less stable.

Two other recent studies using MEMS to measure adherence have reported increased dosing frequency to be associated with poorer adherence (8,10). These studies had shorter observation periods, ranging from four weeks to three months, and the study by Diaz and colleagues (8) followed patients only after hospital discharge, a group that may have been likely to have had increases in their total antipsychotic dose and may be more analogous to our analysis of patients experiencing an increase in total antipsychotic dose.

Most of our findings regarding the effects of demographic variables on adherence are in line with prior studies (5,12). One counterintuitive finding is that unmarried patients had better adherence than married patients among patients with stable dosing regimens. This finding suggests either that a spousal relationship may diminish adherence or, alternatively, the spousal relationship may buffer patients and allow poorer adherence with less risk of instability.

Use of existing databases limits which patient-level characteristics are available for analysis. Factors that may be important in adherence, such as degree of side effects, are not available in our current databases. However, we were able to include demographic variables and some variables relevant to illness severity in multivariate analysis. Our population also consisted of veterans and was predominantly male, potentially limiting generalizability to a broader population of patients with schizophrenia. Although the percentage of women in the study was small, the absolute numbers of women were higher than in prior studies, and sex was not associated with differences in dosing frequency or adherence.

We examined changes in dosing frequency and adherence across a variety of antipsychotic medications. However, individual medications may have different recommendations for dosing frequency and also be more or less likely to be taken regularly by patients for reasons unrelated to dosing, potentially confounding observed relationships between dosing frequency and adherence (13).

We used the MPR as our measure of adherence and could not actually determine whether patients ingested medication that they had refilled. Patients also may have obtained medications from other sources, resulting in falsely low MPRs. However, use of non-VA health systems is generally low among VA mental health users (14,15), and in this study we examined adherence among patients who remained engaged in VA treatment over time. Previous work has demonstrated a strong relationship between patients' MPRs and psychiatric hospitalization, giving evidence of the validity and usefulness of this measure (2–4). We note that unfortunately all current methods of adherence measurement have limitations.

Conclusions

Among patients who received an increase in their overall dose of antipsychotic medication, increases in dosing frequency were associated with modest reductions in adherence. Among patients who were on more than once-daily dosing, decreases in dosing frequency were associated with improvements in adherence. However, among patients with stable dosing regimens, there were no differences in adherence between those receiving once-daily dosing and those receiving more than once-daily dosing. Clinicians increasing dosing frequency might consider the possibility of decreased adherence after this change. However, health systems may not need to push for broad mandates for simplified dosing among patients with stable regimens.

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