Effectiveness of Atypical Antipsychotic Medications in Reducing Violent Behavior Among Persons With Schizophrenia in Community-Based Treatment

by Jeffrey W. Swanson, Marvin S. Swartz, and Eric B. Elbogen

Abstract

This study prospectively compared the effectiveness of atypical antipsychotic medications to that of conventional neuroleptics in reducing violent behavior among patients with schizophrenia under "usual care" conditions in the community. Participants (n = 229) were adults with schizophrenia spectrum disorders receiving inpatient or outpatient services in public sector mental health systems in North Carolina. Subjects were followed for 2 years in an observational study using multiple methods of data collection at 6-month intervals to assess treatment, sociodemographic characteristics, clinical features, and violence outcomes. Treatment with atypical antipsychotic medications (clozapine, risperidone, or olanzapine) was found to significantly reduce the risk of violent behavior, whereas treatment with conventional neuroleptics did not have this same beneficial effect. A cumulative effect on reduced violence was attributable to consistent compliance with atypical antipsychotic medications over a 2-year period. Concurrent reductions in psychotic symptoms, substance abuse, and adverse medication side effects were found to mediate the association between adherence with atypicals and lower violence risk. Treatment with atypical antipsychotic medications should be considered as an important component of violence risk management for schizophrenia patients at risk for violent behavior.

Keywords: Schizophrenia, atypical antipsychotic medication, severe mental illness, violence.


While the great majority of persons with schizophrenia do not commit violent acts (Swanson 1994), clinicians recognize that some individuals with this disorder may pose a significant risk in the community—particularly those patients with co-occurring substance abuse problems who are noncompliant with prescribed psychiatric treatment, and those with a history of frequent relapses resulting in hospitalization or arrest (Geller 1992; Monahan 1992; Kent et al. 1995; Schalock et al. 1995; Swanson et al. 1996, 1997, 2000; Borum et al. 1997; Swartz et al. 1998a, 1998b). With clinicians increasingly held liable for the behavior of patients inadequately treated in the community, concerns about violence risk have increased (Borum et al. 1996; Cuffel 1997; Dixon et al. 1998; Simon 1998; Thienhaus and Piasecki 1998). The potential for violence in even a small proportion of persons with untreated psychotic disorders increases public fear, prevents acceptance and inclusion of persons with psychiatric disabilities in society, disrupts continuity of care, and limits the effectiveness of community-based mental health services (Link et al. 1987; Torrey 1994; Angermeyer and Matschinger 1996; Estroff et al. 1998; Penn and Martin 1998).

Because of the high human cost and legal liability associated with violent acts, and because the presumption of dangerousness is a key justification for involuntary treatment, the assessment of the risk of violence in psychiatric patients is among the most critical judgments clinicians make (Schopp 1996; Elbogen and Tomkins 2000). Consequently, much of the empirical research on violence and mental disorder in recent years has been driven by the need to develop more accurate methods of violence prediction and risk assessment (Monahan and Steadman 1994; Borum 1996; Douglas et al. 1999; Monahan et al. 2000, 2001). However, an equal emphasis is now needed on studies to evaluate and improve the effectiveness of community-based treatment in reducing violent behavior among persons with severe mental illness (Heilbrun 1997; Swanson et al. 2000).

Violence Reduction With New Pharmacotherapies for Schizophrenia

For some patients with schizophrenia, the new class of "atypical" antipsychotic medications—including cloza-
concentrate lessened aggressiveness, evidenced by lower scores on items measuring hostility in the Positive and Negative Syndrome Scale (PANSS). Similarly, Currier et al. (2000) found that risperidone treatment was associated with reduced violence risk among patients with schizophrenia (Hirose et al. 2001). One study found that risperidone did not reduce violence; however, this was a very small, selected sample—10 subjects on risperidone compared with 10 matched controls on a traditional neuroleptic, all patients in a maximum-security forensic hospital who had previously been violent (Beck et al. 1997). As with the body of literature on clozapine, these studies are limited in their generalizability to real-world conditions under which community-based treatment is delivered, and they cannot adequately address the question of whether risperidone may, over time, actually reduce the interpersonal violent behavior of persons with schizophrenia.

Much of the earlier research has focused on demonstrating the efficacy of clozapine in reducing aggression (Ratey et al. 1993; Buckley et al. 1995; Menditto et al. 1996; Rabinowitz et al. 1996; Spivak et al. 1997, 1999; Volavka 1999; Citrome et al. 2001). These studies generally corroborate anecdotal clinical reports that patients with schizophrenia who take clozapine are less likely to engage in physical and verbal aggression (Ratey et al. 1993; Rabinowitz et al. 1996) and are less likely to require restraints and seclusion in hospital settings (Chiles et al. 1994). Patients taking clozapine have been found to obtain lower hostility scores on the Brief Psychiatric Rating Scale (BPRS) (Volavka et al. 1993) and lower scores on the Overt Aggression Scale (Spivak et al. 1997). Research on patients with dual diagnoses of psychotic and borderline personality disorders has also shown that after starting clozapine treatment, these patients were significantly less likely to assault staff or peers on an inpatient ward (Chengappa et al. 1999). No studies to date have demonstrated clozapine’s effectiveness in reducing violent behavior in longitudinal community-based studies.

A few studies have examined the efficacy of risperidone in reducing violence risk in samples of schizophrenia patients (see Buckley et al. 1997). In a retrospective study of 139 subjects with schizophrenia, Czobor et al. (1995) found that risperidone treatment was associated with reduced scores on items measuring hostility in the Positive and Negative Syndrome Scale (PANSS). Similarly, Currier and Simpson (2001) demonstrated that risperidone liquid concentrate lessened aggressiveness, evidenced by lower PANSS hostility item scores, as well as lower scores on the Clinical Global Impressions scale. Marder et al. (1997) found similar decreases on the BPRS hostility scale for over 500 patients treated with risperidone. Most recently, electroconvulsive therapy combined with risperidone has been shown to reduce violent behavior among male inpatients with schizophrenia (Hirose et al. 2001). One study found that risperidone did not reduce violence; however, this was a very small, selected sample—10 subjects on risperidone compared with 10 matched controls on a traditional neuroleptic, all patients in a maximum-security forensic hospital who had previously been violent (Beck et al. 1997). As with the body of literature on clozapine, these studies are limited in their generalizability to real-world conditions under which community-based treatment is delivered, and they cannot adequately address the question of whether risperidone may, over time, actually reduce the interpersonal violent behavior of persons with schizophrenia.

There have been no empirical studies examining the effects of olanzapine on violent behavior in patients with schizophrenia, although it is speculated that because olanzapine has pharmacological properties similar to the other atypical antipsychotic agents, it may also be effective in reducing aggression (Keck et al. 2000). Olanzapine has been found to reduce aggressive behavior in patients with Alzheimer’s disease (Clark et al. 2001) and in children, adolescents, and adults with developmental disabilities (Horrigan et al. 1997; Potenza et al. 1999). Case studies have also found anti-aggressive effects of olanzapine for patients with Huntington’s disease (Grove et al. 2000). One case report, however, suggests that olanzapine might have mitigating effects for some patients with schizophrenia (John et al. 1998).

In general, the promise of improved compliance and reduced violence risk among patients with schizophrenia would seem to recommend increased use of the atypical antipsychotic medications in treating these patients. However, widespread adoption of these new pharmacotherapies is tempered by their significantly higher cost. For this reason, it becomes important to establish the clinical effectiveness of these drugs under “usual care” conditions in the community—especially for patients with histories of violence who use disproportionate amounts of high-cost services—and thus to demonstrate that the benefits may translate into cost savings sufficient to justify their use as first-line therapies (Viale et al. 1997).

A recent randomized trial compared effects of treatment with various atypical antipsychotic medications with effects of treatment with haloperidol on self-reported hostility in a sample of inpatients with schizophrenia (Citrome et al. 2001). This study found that only clozapine treatment was associated with significantly lower hostility scores. Still, very little is known about the relationship between actual violent behavior in the community and treatment with atypical antipsychotic medications. It is possible, for
example, that clozapine reduces violence by means of a direct pharmacological effect on hostility and aggression, while the other atypical agents reduce violence more indirectly, by means of improved compliance and, consequently, diminished substance abuse.

Further research has been needed using improved methodologies of assessment, larger and more generalizable samples, and longer periods of observation under community-based treatment. Most of the extant research on the effects of atypical antipsychotic medications consists of case reports or controlled trials with relatively small sample sizes carried out in hospital inpatient settings (Citrome et al. 2001). Regarding the measurement of violence, most previous studies have employed scales of aggression and hostility as proxy measures of violence or have considered assaultive incidents in inpatient settings. Community violence is difficult to assess accurately because it requires gathering data from multiple sources to corroborate subjects’ self-report of violent incidents (Mulvey and Lidz 1993; Swanson et al. 1999). No investigations have prospectively examined the long-term impact of treatment with atypical antipsychotic medications on violent behavior measured directly in the community.

Another limitation of previous research is that, with few exceptions (Citrome et al. 2001), studies to date have examined treatment with only one or another of the atypical medications; however, it may be theoretically and methodologically preferable to consider the effects of these new medications as a group with respect to violence risk reduction (Keck et al. 2000). First, studying treatment with only one medication limits sample size, whereas examining the effects of the atypicals as a class provides increased statistical power. Second, as psychiatrists attempt to optimize medication benefits, it is likely that patients will have their medication regimens changed often from one atypical agent to another. Therefore, in observational effectiveness studies, it may be increasingly difficult to find patients who are “pure types” with respect to a single medication regimen. Third, although each atypical agent is unique in its receptor binding and clinical profile, the atypical antipsychotics share some psychopharmacological features, including putative action on similar neurotransmitter systems (e.g., serotonin) implicated in violent behavior (Lieberman et al. 1998; Duncan et al. 1999; Elbogen and Huss 2000), and are generally characterized by few extrapyramidal symptoms (i.e., greater tolerability) compared to traditional neuroleptics.

While it appears likely from earlier studies that the atypicals may exert some direct pharmacological effects that inhibit aggressive and violent behavior, it is also plausible that the atypicals may lower violence risk by indirect means, for instance, by improving treatment adherence and reducing substance abuse, which are risk factors for violence as well as for exacerbated psychotic symptoms. Better control of psychotic symptoms per se may reduce violence, insofar as violent behavior, in some schizophrenia patients, is linked to paranoid delusions, auditory hallucinations, and negative affect (Cheung et al. 1997).

Treatment with atypicals may lead to improved compliance due to reduced adverse side effects as well as reduced substance abuse. Adverse side effects are only one of many reasons why patients with schizophrenia stop taking prescribed medication (and thus increase their risk for violence). Substance abuse may reinforce a pattern of non-adherence, insofar as persons dependent upon alcohol and illicit drugs become either unwilling or unable to comply with a prescribed regimen of antipsychotic medications.

Olson and colleagues (2000) found that substance abuse was the strongest predictor of medication noncompliance in 213 patients with schizophrenia or schizoaffective disorder. Other studies have found that persons with dual diagnoses have significantly greater psychotic symptomatology than their counterparts without substance abuse, and yet are far more likely to skip doses or stop taking prescribed psychotropic medication (Dixon et al. 1999). Continued poor compliance with recommended medications can lead, in turn, to exacerbated psychiatric symptoms and overall psychiatric instability, suicidality, and aggression (Chengappa et al. 2002). The study by Olson and colleagues (2000) also reported that patients who stopped taking antipsychotic medication were more likely to avoid outpatient treatment, and to experience symptom relapse, homelessness, emergency room visits, and rehospitalization. In short, heightened risk of violent behavior is often intertwined with a complex cluster of poor outcomes—and there are good reasons to expect that the new generation of antipsychotic medications may reduce violence risk by multiple causal pathways. If this new category of drugs is shown to be more effective than conventional neuroleptics in reducing violent behavior in usual care settings, then closer comparisons of these individual medications can be made with respect to their variant pharmacologic properties and hypothesized direct and indirect effects in violence risk reduction.

The primary goal of the current study was to prospectively examine the effectiveness of atypical antipsychotic medications, as compared to treatment with typical neuroleptics, in reducing community violence among persons with schizophrenia over a 2-year period, using multiple sources of information to measure actual violent incidents. The secondary goal was to test key interaction effects and potential mediating variables, in order to better specify the indirect pathways by which the atypicals may reduce violent behavior in this population. These interacting variables include medication adherence, adverse side effects, psychotic symptomatology, and co-occurring substance abuse.
Methods

Study Design and Sample. The data used for this analysis are from the North Carolina site of the Schizophrenia Care and Assessment Program (SCAP), a multicenter, prospective, observational study focused on assessing the clinical, functional, and service utilization outcomes associated with routine care, both pharmacological and non-pharmacological, for persons diagnosed with schizophrenia in five U.S. geographic regions. In North Carolina, 403 persons with schizophrenia-related disorders were recruited from several treatment facilities in an “open” system of care across a nine-county, mixed urban and rural area in the north-central region of the state. These individuals were enrolled using two recruitment strategies simultaneously, with screening for inclusion diagnoses: (1) sequential inpatient admissions at a regional public psychiatric hospital, an acute psychiatric unit of a private university hospital, and a veterans affairs hospital; and (2) random selection of outpatients from four area mental health programs’ case rosters and one veterans affairs medical center outpatient clinic. Enrollment began in 1997 and was completed in 1999. Subjects were followed for 2 years, with clinical data collection at 6-month intervals. Methods included (1) structured interviews conducted in person; (2) review and abstraction of medical records; (3) electronic retrieval of data from health care management information systems on service utilization and costs; and (4) retrieval of arrest records from the North Carolina Department of Justice archival data base. The SCAP research design was purely observational, with the purpose of understanding routine clinical care practices and treatment outcomes, and therefore no intervention or interference with usual patterns of treatment was done.

Diagnoses were based on review of clinical records. Because the SCAP was designed as an observational study of the treatment of persons diagnosed with schizophrenia under “usual care” conditions, all adult patients in treatment with recently documented DSM-IV diagnoses of schizophrenia, schizoaffective disorder, or schizotypal disorder were eligible for the study. Because the aim of the study was to examine the treatment of patients who were thought to have or who were diagnosed as having schizophrenia, chart diagnoses assigned in the past year were thus accepted prima facie and not verified by additional research diagnostic assessments upon enrollment. Participants also had to be able and willing to provide informed consent, had to be 18 years of age or older, and could not have participated in a clinical drug trial within 30 days prior to enrollment. Institutional review board approval was obtained at participating study sites prior to the initiation of the study, and informed consent was received for all participants. At the time the analyses were conducted for this report, data were available for 229 individual patients, with a total of 438 person-period observations (i.e., the sum of the number of individual subjects times the number of 6-month observational periods for each subject) over 2 years.

Instruments. Violent behavior was measured with a composite index that combined three sources of data: (1) subject self-report using the MacArthur Community Violence Interview (MCSI) (Monahan et al. 2001); (2) systematic review of outpatient and inpatient medical records, including civil commitment documents and other legal information, using a chart-abstraction instrument for coding evidence of violence that was developed in the Duke Mental Health Study (Swanson et al. 1999); and (3) review of records of arrests for violent offenses documented in the North Carolina Department of Justice data base. Violent behavior was defined operationally as any assault or battery committed against another person specifically involving physical contact intended to harm (e.g., hitting, shoving, kicking, biting) or threatening another person with a lethal weapon in hand. Assaultive behavior meeting this definition reported from any one of the three sources was considered a positive indicator of violence.

Type of pharmacological treatment was coded into three hierarchical, mutually exclusive categories for each 6-month period of observation, using data collected from medical record abstractions: (1) atypical antipsychotic—any prescription for clozapine, risperidone, or olanzapine in effect for more than half the given period; (2) conventional neuroleptic—a prescription for any other antipsychotic medication (but none of the three listed above) in effect for more than half the period; and (3) none—no antipsychotic medication prescription in effect for more than half the period. At the time of the study, other atypical agents such as quetiapine and ziprasidone were not in common use. We did not have sufficient statistical power available to examine the effects of specific atypical agents, for instance, to compare violence outcomes among patients prescribed olanzapine versus risperidone versus clozapine. We also did not have sufficient data available to allow an informative analysis of the causes or effects of medication switching within periods, dosing differences, polypharmacy and the potential contribution of adjunct medications (e.g., beta-blockers, anticonvulsants, benzodiazepines), and any potential differences by route of administration of conventional neuroleptics (i.e., depot vs. oral medications).

For the purpose of causal attribution in longitudinal time-series analysis, treatment effects were lagged, with models estimating associations between treatment type in
a given 6-month period and violent behavior in the subsequent 6-month period. If we had not lagged the treatment period in our analysis, it would have been impossible to tell the direction of causality in any association between medication and violence—that is, whether the medication had caused a reduction in violence or, instead, whether violence had precipitated a change to a new type of medication.

Medication compliance was measured at each 6-month assessment using a self-report item with a 5-point fixed response scale, coded 1 ("I never missed taking my medicine") to 5 ("I stopped taking the medicine altogether").

Mental health services utilization intensity was coded as a simple count of the number of outpatient service encounters during the 6-month period. This included visits for outpatient therapy, case management, and medication checks, and any other billable encounters with mental health service providers.

Demographic covariates included age, gender, and race (African-American vs. white/other).

Baseline clinical predictors that were examined included recent psychiatric hospitalization history (0 vs. 1 or more admissions in the past year), Global Assessment of Functioning (GAF) score (Endicott et al. 1976), and co-occurring substance use, assessed using clinician ratings on the Alcohol Use Scale and the Drug Use Scale (Drake et al. 1996). These independent variables were chosen for analysis based on prior clinical and epidemiological studies of risk factors related to violence, and to control variability in violence risk that may be associated with severity of psychopathology, substance abuse comorbidity, prior hospital recidivism, and sociodemographic characteristics. Because this was an observational study without random assignment to treatment regimen, and because treatment selection may covary naturally with clinical as well as demographic risk factors for violence, it was necessary to control for putative predictors of both violence and treatment in order to properly interpret longitudinal treatment effects on reduced violence risk.

Analysis. The incidence of violence over four 6-month periods (2 years total) was modeled using generalized estimating equations regression analysis for repeated measures (Diggle et al. 1994; Stokes et al. 1995), with the probability of violent incidents estimated prospectively as a function of medication type in the previous periods, controlling for time, baseline violence, intensity of mental health services utilization, medication compliance, baseline clinical risk factors, and demographic characteristics. These models are designed to incorporate all available longitudinal data for each subject, and to estimate the net association of multiple fixed as well as time-varying predictors of violence, which may covary with, and condition the effects of, the key independent variable (medication type). The models also adjust for lack of independence between observations for each subject over time. Our analysis used a specific procedure designed for an autoregressive covariance structure, that is, a matrix in which the correlation gradually declines between baseline and successive followup measures of the dependent variable (violence).

Results

Sample Description. At the time these analyses were conducted, a sample of 229 SCAP subjects in North Carolina was available with followup data sufficient to estimate 2-year trends in violence as a function of treatment. As described above, these subjects were enrolled using two recruitment strategies simultaneously: sequential inpatient admissions and random selection from community mental health center case rosters. The study was designed with a recruitment goal of obtaining 50 percent of the sample with a record of hospitalization in the prior year. Of the 229 individuals included in the present analysis, 37 percent were from the recently hospitalized cohort, while 63 percent were outpatients who had not been hospitalized within the preceding year.

Regarding gender distribution, 58 percent of the subjects were male and 42 percent were female. Age ranged from 18 to 71 years, with a mean of 42.5, a median of 41.5, and a standard deviation of 10.4 years. With respect to racial background, 77 percent of the subjects were of African-American descent and 23 percent were self-identified as white or other. This demographic distribution fairly reflects the population of consumers with severe mental illness receiving services in the public mental health care system in the north-central region of North Carolina (Swanson et al. 1999).

Considering clinical status, baseline GAF scores ranged from 15 to 70, with a mean of 36.7, a median of 35, and a standard deviation of 9.8. This distribution indicates that, on average upon enrollment, these subjects were clinically rated as having major impairment in several functional areas (e.g., work, social relations, judgment, thinking). Twenty-one percent of the subjects were identified as having co-occurring substance abuse during the 6 months preceding enrollment.

Refusal and Retention Rates. The baseline refusal rate was 22 percent and sample retention was approximately 80 percent over 2 years of followup. Specifically, retention of subjects declined from 83.7 percent at 6 months to 73.3 percent at 24 months. There was no significant association between attrition and baseline violence; hence, whereas 15.3 percent of subjects were assessed as violent...
at baseline, the percentage with a baseline history of violence was only slightly lower—13.7 percent—among subjects retained at 18 months.

It must be noted that the data presented here were from an ongoing study in which only a portion of subjects had reached the due date for each followup wave; thus, only a small proportion had been enrolled for 2 years. The subset of data that were available for this study included 229 individuals with a combined total of 438 person-period observations distributed as follows: 6 months, \( n = 216 \); 12 months, \( n = 129 \); 18 months, \( n = 68 \); 24 months, \( n = 25 \).

Baseline Association Between Subject Characteristics and Type of Medication Prescribed. Because our design was observational in nature and did not involve random assignment to medication, it was important to examine any preexisting associations between the type of antipsychotic medication prescribed at baseline and the subjects' demographic and clinical characteristics. To prevent potential selection biases from distorting results, it was also crucial to statistically control for these baseline characteristics in our multivariable time-series analyses estimating the effects of medication type on violence.

Table 1 presents the frequency distributions resulting from a cross-tabulation of subject characteristics with the predominant type of medication prescribed when subjects were enrolled in the study. Of the 229 subjects included in this analysis, 35 had not had any prescription in effect for an antipsychotic medication during more than half the 6-month period preceding enrollment.

<table>
<thead>
<tr>
<th>Predominant Type of Antipsychotic Medication at Baseline</th>
<th>Statistical Significance</th>
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<tbody>
<tr>
<td>0: None</td>
<td>1: Conventional</td>
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</table>

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td>Below median (18–41 yrs)</td>
</tr>
<tr>
<td>Median or above (≥42 yrs)</td>
</tr>
</tbody>
</table>

| **Gender** |
| Female | 9 (9.28) | 56 (57.73) | 32 (32.99) | 97 | * |
| Male | 26 (19.70) | 59 (44.70) | 47 (35.61) | 132 |

| **Race** |
| African-American | 28 (15.82) | 98 (55.37) | 51 (28.81) | 177 | *** |
| White/other | 7 (13.46) | 17 (32.69) | 28 (53.85) | 52 |

<table>
<thead>
<tr>
<th>Baseline clinical characteristics</th>
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<tbody>
<tr>
<td><strong>Initial treatment setting</strong></td>
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<tr>
<td>Inpatient</td>
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<tr>
<td>Outpatient</td>
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| **Global Assessment of Functioning** |
| Below median (<32) | 22 (18.18) | 52 (42.98) | 47 (38.84) | 121 |
| Median or above (≥32 or higher) | 13 (12.04) | 63 (58.33) | 32 (29.63) | 108 |

| **History of substance abuse** |
| No | 21 (11.60) | 90 (49.72) | 70 (38.67) | 181 | * | *** |
| Yes | 14 (29.17) | 25 (52.08) | 9 (18.75) | 48 |

| **History of violent behavior** |
| No | 26 (13.40) | 98 (50.52) | 70 (36.08) | 194 |
| Yes | 9 (25.71) | 17 (48.57) | 9 (25.71) | 35 |

* \( p < 0.05 \); ** \( p < 0.01 \); *** \( p < 0.001 \)
gone untreated with medication were significantly younger, more likely to be male, and more likely to have a co-occurring substance use disorder. These respondents were also more likely to have been recruited into the study during a hospital admission, that is, following an illness relapse that may have resulted from not taking medication.

As summarized in the far right column of Table 1, with the exception of race, none of the potential "selection" variables examined was significantly associated with receiving a prescription for an atypical versus a conventional antipsychotic medication. The finding that African-American patients were significantly less likely than white patients to have been prescribed an atypical (28.9% vs. 53.9%; \( p < 0.001 \)) deserves further study but is beyond the scope of the present article.

It is notable that baseline history of violent behavior was not significantly associated with medication type. Nevertheless, baseline violence—and each of the variables specified in Table 1—was included as a statistical control to guard against selection bias in the multivariable analyses to be presented below.

**Prevalence of Violence.** At baseline, it was determined that 15.3 percent of the subjects had committed violent acts in the 6 months prior to enrollment (as identified by MCVI self-report interview, medical record review, civil commitment documents, or arrest records). The 1-year prevalence of violence from all sources of data was 21.8 percent; however, only 9 percent of the sample had official records of being arrested for violent offenses during the year. Of those who were violent, about 41 percent had committed serious violent acts involving weapon use or causing injury to another person, while the remaining 59 percent were involved in only less serious incidents of battery (e.g., physical fights involving shoving or slapping but without causing injury or using weapons).

**Cross- sectional Analysis of Medication Type and Violence.** Prior to conducting longitudinal analysis of violence risk trends with lagged treatment effects, we examined the cross-sectional association between violence and predominant medication type for the first year \((n = 229)\). The prevalence of violence was found to be highest in the group of patients without any prescribed antipsychotic during more than half the year \((n = 44; 36.4\% \text{ violent})\); lower among those prescribed conventional neuroleptics \((n = 116; 21.6\% \text{ violent})\); and lowest among those prescribed an atypical antipsychotic \((n = 69; 13.0\% \text{ violent})\). Table 2 presents a test of the statistical significance of these rates using logistic regression. The analysis shows that the odds of any violence were significantly lower only in the group prescribed atypical antipsychotic medications compared to those who were untreated with antipsychotics during more than half the year \((\text{odds ratio [OR]} = 0.26; \text{ } p < 0.01)\). In this model, about 4 percent of the variance in the rate of violence was accounted for by differences in medication type.

When patients prescribed atypicals were compared directly with those prescribed conventional antipsychotics, this cross-sectional analysis showed that the rate of violence was lower, but not significantly so, among those in the atypical group. However, a more appropriate and powerful test of this comparison—using all available longitudinal data and controlling for medication compliance and potential selection effects—is described below.

**Longitudinal Analysis of Medication Type and Violence.** As mentioned above, a total of 438 person-period observations were available for analysis covering 2 years of followup assessments. Table 3 presents the results of a time-series analysis using generalized estimating equations. These models estimate the longitudinal effects of medication on reduced violent behavior in the subsequent period, controlling for time and key covariates, as well as adjusting for the nonindependence of repeated measures for individuals (autoregressive covariance structure). To capture the long-term effects of consistent treatment over time, the medication variables were recoded as the cumulative number of 6-month periods during which the medication type (atypical vs. conventional antipsychotic) was prescribed for over half a given period. Medication compliance and mental health service intensity were included as separate time-varying covariates, while baseline violence, demographic characteristics, and clinical risk factors were included as controls.

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**Table 2. Cross-sectional association between predominant medication type and violent behavior in 1 year: Logistic regression analysis \((n = 229)\)**

<table>
<thead>
<tr>
<th>Predominant medication type during year</th>
<th>Violence odds ratio</th>
<th>95% confidence Interval</th>
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<tbody>
<tr>
<td>No antipsychotic ≥90 days (comparison)</td>
<td>1.00</td>
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<tr>
<td>Conventional antipsychotic</td>
<td>0.48</td>
<td>(0.23–1.03)*</td>
</tr>
<tr>
<td>Atypical antipsychotic</td>
<td>0.26</td>
<td>(0.10–0.67)**</td>
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*Note.* Chi-square = 8.57 with 2 df \((p = 0.01)\); –2 log likelihood = 232.03. Variance explained by model: Pseudo \(R^2 = 0.04\). Rank correlation predicted to observed: \(C = 0.62\).

*\( p < 0.10; \) **\( p < 0.01\)
Table 3. Longitudinal effects of medication type and covariates on reduced violent behavior in persons with schizophrenia: Time-series analysis (n = 438)

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Model 1</th>
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<th>Model 2</th>
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<tbody>
<tr>
<td></td>
<td>Violence odds ratio</td>
<td>95% confidence interval</td>
<td>p</td>
<td>Violence odds ratio</td>
</tr>
<tr>
<td>Time</td>
<td>Time 6-mo assessment period: 1.20 (0.81–1.78)</td>
<td>0.96 (0.62–1.50)</td>
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<tr>
<td>Baseline violence</td>
<td>Any violence in 6 mos prior to enrollment: 5.65 (2.85–11.21)</td>
<td>4.54 (2.64–11.62)</td>
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<tr>
<td>Treatment variables</td>
<td>Lagged, time-varying effects</td>
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<td></td>
<td>Mental health service intensity: 1.03 (1.01–1.05)</td>
<td>1.03 (1.01–1.05)</td>
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<td></td>
<td>Medication compliance: 0.30 (0.16–0.57)</td>
<td>0.35 (0.15–0.80)</td>
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<td></td>
<td>Conventional antipsychotic (current + n previous periods): 0.96 (0.73–1.27)</td>
<td>1.01 (0.67–1.52)</td>
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<tr>
<td></td>
<td>Atypical antipsychotic (current + n previous periods): 0.64 (0.46–0.91)</td>
<td>1.05 (0.69–1.60)</td>
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<td>Interaction effects of prescribed medication by compliance</td>
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<tr>
<td></td>
<td>Conventional antipsychotic periods × compliance: 1.35 (0.79–2.30)</td>
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<tr>
<td></td>
<td>Atypical antipsychotic periods × compliance: 0.40 (0.17–0.96)</td>
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<td>Demographic covariates</td>
<td>Younger age: 0.97 (0.93–1.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male gender: 1.50 (0.74–3.04)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>African-American race: 1.76 (0.64–4.91)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline clinical predictors</td>
<td>Hospitalization history: 1.24 (0.58–2.65)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Global Assessment of Functioning score: 0.95 (0.91–0.99)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Substance abuse history: 3.04 (1.49–6.22)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note.—Rank correlation of predicted probabilities to observed rates: C = 0.813 (model 1); C = 0.862 (model 2). Variance explained by model: Pseudo $R^2 = 0.18$ (model 1); Pseudo $R^2 = 0.28$ (model 2). Chi-square for improvement of model fit: model 1 compared to base model with intercept and wave only: 52.86 with 5 df; $p < 0.001$; model 1 compared to model 2: 31.06 with 8 df; $p < 0.001$.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Model 1 shows a significant main effect for the cumulative number of 6-month periods of prescribed atypical antipsychotic medication on reduced incidence of violence in the subsequent period (OR = 0.64; $p < 0.05$), controlling for time, baseline violence (OR = 5.54; $p < 0.001$), mental health service intensity, medication compliance, and treatment with conventional antipsychotics. We also found a strong and significant negative association between medication compliance and violence (OR = 0.30; $p < 0.001$) but a positive association between violence and mental health service intensity (number of billed service encounters per period) (OR = 1.03; $p < 0.01$).

In model 2, the effects of medication on violence risk were expressed as interactions between the type of medication prescribed and the degree of compliance with that medication. Also, controls were added to hold constant the effects of baseline demographic and clinical risk factors—some of which covary with medication type (table 1) and thus might bias the results if not statistically controlled. This model shows a statistically significant net effect of treatment with atypicals on reduced violence. Specifically, the product of the number of 6-month periods that a subject was prescribed an atypical antipsychotic medication, and the degree of compliance with that medication during each period, was negatively associated with violence risk in the subsequent period (OR = 0.40; $p < 0.05$). However, the comparable variable for treatment with a conventional neuroleptic had no longitudinal effect on reduced violence risk (OR = 1.35; nonsignificant), despite the fact that a greater number of subjects received treatment with conventional medications, thus providing adequate statistical power to test the effect. The model also continued to show a significant main effect for medication compliance, that is, reducing violence (OR = 0.35; $p < 0.05$). Increased violence risk was predicted by greater functional impairment (lower GAF score) (OR = 0.95; $p < 0.05$) and the presence...
of substance abuse comorbidity (OR = 3.04; \( p < 0.001 \)) as assessed at baseline.

Given the observational design of this study and the absence of random assignment to treatment conditions, it is possible that selection bias could affect these results, for example, if "less problematic" patients with lower violence risk were differentially selected for treatment with atypical antipsychotic medications. To ascertain whether such a bias existed, we conducted a multivariable time-series analysis estimating effects on receipt of prescription for atypical antipsychotic medication (model not shown). The results showed no significant longitudinal effect of violent behavior, substance abuse, or compliance on the likelihood of receiving atypical antipsychotic medications in the subsequent period, when controlling for medication prescribed in the previous period. Rather, the only significant predictor of receiving a prescription for an atypical antipsychotic during any given period was having a previous prescription for an atypical antipsychotic. Also, to ascertain whether there might be a confounding effect of time by medication prescribed, we ran an additional version of the final model with interaction effects specified for wave \( \times \) medication type; these interaction effects were not statistically significant, while the effects that were shown to be significant in model 2 remained so—
even with these additional variables in the model.

Finally, figures 1 and 2 illustrate the predicted probabilities of violent behavior over 6-month intervals as a function of the cumulative number of periods during which each of the two types of medication was prescribed, controlling for the variables included in model 2 of table 3. Figure 1 shows that patients prescribed conventional antipsychotic medications did not show a significant decline in violence probability from the first to the

**Figure 1. Probability of violent behavior by antipsychotic medication type and duration: North Carolina Schizophrenia Care and Assessment Program subjects (n = 438 person-period observations with complete data)**

![Graph showing predicted probabilities of violent behavior](https://example.com/graph1.png)

*Note.*—Estimates of lagged treatment effects on violence in subsequent wave, using generalized estimating equation time-series regression models controlling for wave, baseline violence, mental health services utilization, demographics (age, sex, race), and baseline clinical predictors (Global Assessment of Functioning, substance abuse, hospitalization). Subjects were coded for predominant medication type if prescription covered more than half a given 6-month period (≥90 days).
Figure 2. Probability of violent behavior by antipsychotic medication type and duration: North Carolina Schizophrenia Care and Assessment Program subjects (n = 259 person-period observations with complete data and reported medication compliance)

Note.—Estimates of lagged treatment effects on violence in subsequent wave, using generalized estimating equation time-series regression models controlling for wave, baseline violence, mental health services utilization, demographics (age, sex, race), and baseline clinical predictors (Global Assessment of Functioning, substance abuse, hospitalization). Subjects were coded for predominant medication type if prescription covered more than half a given 6-month period (≥90 days).

Fourth periods of observation (0.1203 to 0.1027). However, patients consistently taking atypical antipsychotic medications did show reduced probability of violence over time (0.0924 to 0.0109).

Figure 2 presents the same analysis, but for only subjects who reported being compliant “most of the time” with their prescribed medication. Patients who were administered and took conventional antipsychotic medications did not show a decline in violence risk. However, patients who were compliant with atypical antipsychotic medications showed reduced rates of violent behavior starting in the first period of observation. Based on these models, the predicted probability of violence after four periods of compliance with prescribed atypical antipsychotic medications was negligible (0.0006).
Conversely, self-reported compliant patients taking typical neuroleptic medications actually showed an increase in the predicted probability of violence after four treatment periods, although the increase was not statistically significant.

**Individual subject analysis.** It may also be informative to consider these results in terms of individual subjects, in addition to person-period observations. Overall, there were 60 individual patients who were prescribed mostly atypical antipsychotic medications and reported being compliant with their medications “most of the time” during each period. There were 88 patients who were prescribed mostly conventional antipsychotics and reported being compliant “most of the time.” The rate of any violence over all followup waves was significantly lower in the atypical/compliant group than in the conventional/compliant group (5.0% vs. 15.9%; chi-square = 4.16 with 1 df, p < 0.05). However, the remaining 73 subjects who were noncompliant with their medications or spent most of the study period with no prescription for any antipsychotic medication in effect were the most likely to be violent: 23 (31.5%) of these (untreated or noncompliant) individuals were assessed by one or more sources to have committed at least one violent act during the study’s followup period.

**Mediating variables.** The analysis presented in table 4 tests key mediating variables, which may partly account for the effect of the atypicals on reduced violence. Change scores from baseline to current 6-month period were examined for three potential mediators—psychotic symptomatology, co-occurring substance abuse, and adverse side effects of medication. We found a significant bivariate association between each of these change scores and reduced risk of violent behavior. Specifically, the odds of any violence were reduced with fewer psychotic symptoms (OR = 0.86; p < 0.05), reduced substance abuse (OR 0.56; p < 0.01), and reduced adverse side effects of medication (OR = 0.83; p < 0.05). However, there was intercorrelation between these three change scores, and when they were entered simultaneously into a multivariable model, only psychotic symptom change remained statistically significant, as shown in Model 2 of table 4. A final model was specified (Model 3 in table 4) in which the interaction effects between each of these change scores were found to significantly decrease violence risk. In this final model, the direct effect on violence reduction attributable to atypical antipsychotic treatment (atypical periods by compliance) was rendered statistically nonsignifi-

| Table 4. Longitudinal effects of antipsychotic medication and mediating variables on violent behavior in persons with schizophrenia (n = 438 person-person observations) |
|----------------------------------|-----------------|-----------------|-----------------|
|                                  | Model 1         | Model 2         | Model 3         |
|                                  | Odds ratio      | 95% confidence interval | Odds ratio      | 95% confidence interval | Odds ratio      | 95% confidence interval |
| Medication treatment variables  |                 |                 |                 |
| (lagged, time-varying effects)  |                 |                 |                 |
| Typical antipsychotic periods   | 1.35            | 0.79–2.31       | 1.25            | 0.74–2.10             | 1.25            | 0.74–2.09             |
| × compliance                    |                 |                 |                 |
| Atypical antipsychotic periods  | 0.39            | 0.16–0.96*      | 0.42            | 0.18–1.00             | 0.48            | 0.21–1.09             |
| × compliance                    |                 |                 |                 |
| Mediating variables             |                 |                 |                 |
| A. Improvement in psychotic symptoms | 0.77          | 0.65–0.92**    |                 |                 |
| B. Improvement in substance abuse | 0.73            | 0.50–1.05      |                 |                 |
| C. Improvement in adverse side effects | 0.87            | 0.72–1.04      |                 |                 |
| Interaction of mediating variables | 0.50             | 0.28–0.88*    | 0.55            | 0.37–0.83**          | 0.40            | 0.22–0.74**          |
| A × B                           |                 |                 |                 |
| A × C                           |                 |                 |                 |
| B × C                           |                 |                 |                 |

*Note.—Rank correlation of predicted probabilities to observed rates: C = 0.86 (model 1); C = 0.89 (model 2); C = 0.90 (model 3). Variance explained by model: Pseudo $R^2 = 0.28$ (model 1); Pseudo $R^2 = 0.33$ (model 2); Pseudo $R^2 = 0.35$ (model 3). Chi-square for improvement of model fit: model 1 compared to base model with intercept and wave only: 372.71 with 15 df, p < 0.001; model 1 compared to model 2: 61.88 with 3 df, p < 0.001; Model 2 compared to Model 3: 1.10 with 4 df, p < 0.001. All models are adjusted for effects of time, inter-subject correlation, outpatient treatment intensity, baseline violence, demographic variables (age, sex, race), baseline clinical variables (hospitalization history, substance abuse, psychotic symptoms, functional impairment), baseline adverse medication side effects, the main effects of specified interactions, and three-way interaction of mediators in final model.

* p < 0.05; ** p < 0.01
significant, and the fit of the model improved significantly over the model without the interaction effects of mediators.

The analysis shown in Table 4 provides some evidence that the superior effect of treatment with atypical antipsychotic medications in reducing violence is due in part to a set of indirect effects, i.e., reductions in key risk factors for violence. Moreover, these risk factors operate jointly and exert reciprocal effects. In particular, co-occurring substance abuse is the most powerful risk factor predicting violent behavior in this sample (OR = 3.04; \( p < 0.001 \)) and treatment with atypicals significantly reduced substance abuse (OR = 0.40; \( p < 0.05 \)), controlling for medication nonadherence (OR = 3.37; \( p < 0.0001 \)) and adverse side effects (OR = 1.47; \( p < 0.05 \)) (model not shown). In turn, substance abuse was significantly associated with elevated psychotic symptomatology (\( t = 1.99 \) with 2 df; \( p < 0.05 \)).

Figure 3 displays graphically the predicted probabilities of violence for subjects treated with typical vs. atypical antipsychotic medications, stratified by adherence level and the number of mediating variables on which subjects showed concurrent clinical improvement above average for the sample. The graph shows generally that diminished violence risk was associated with treatment with atypicals vs. typicals, but the effect was conditioned by adherence among subjects who showed concurrent improvement at least two of three clinical domains (psychotic symptoms, substance abuse, and adverse side effects). Specifically, among those subjects who showed broad clinical improvement without regular adherence to medication, the type of medication prescribed did not appear to affect violence risk.

Figure 3. Probability of any violent behavior in 6 months by medication type, compliance, and clinical improvement mediators

<table>
<thead>
<tr>
<th>Area of improvement: psychotic symptoms, substance abuse, adverse side effects of medication.</th>
<th>Improvement in less than 2 areas</th>
<th>Improvement in 2 or more areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotic: Conventional</td>
<td>Not adherent most of the time</td>
<td>(n) (18) (66)</td>
</tr>
<tr>
<td>Atypical</td>
<td>Adherent most of the time</td>
<td>(n) (34) (111)</td>
</tr>
</tbody>
</table>
Discussion

This is the first prospective observational study to examine the long-term effectiveness of treatment for schizophrenia with atypical antipsychotic medications under "usual care" conditions, which specifically assessed the reduced risk of violence in the community as an outcome of treatment. The key finding of this study is that schizophrenia patients who were prescribed atypical antipsychotic medications (including clozapine, risperidone, or olanzapine) and who complied with these medications over time had a significantly lower risk of violent behavior compared to patients treated with conventional neuroleptics or no antipsychotic medications. By comparison, even long-term treatment with conventional antipsychotic medications did not significantly reduce violence risk. These results were found using a multivariable repeated-measures time-series analysis with lagged treatment effects, controlling for salient demographic and clinical risk factors. Consistent with previous research, increased violence risk was also significantly associated with substance abuse, greater functional impairment (severity of psychiatric disturbance as measured by the GAF), poor medication compliance, and previous history of violence. Furthermore, the findings showed both a cumulative effect of treatment over the four periods of observation, and an interaction effect with compliance: the longer patients were prescribed atypical antipsychotic medications, and the more consistently they adhered to the prescribed regimen, the lower the patients’ probability of violent behavior. Finally, an analysis of mediating variables suggested that the superior effectiveness of atypicals in reducing violence involves a complex set of indirect and intercorrelated effects: decrease in adverse side effects of medication, decrease in substance abuse, and better control of psychotic symptoms.

The current study corroborates previous reports suggesting that atypical antipsychotic medications may reduce aggression and violence in patients with schizophrenia (Taylor et al. 1996; Glazer and Dickson 1998; Volavka 1999). The results of this study have important clinical implications for both inpatient and outpatient mental health providers regarding violence risk management of patients with a diagnosis of schizophrenia and related disorders.

Over the past few decades, an extensive body of research has developed on violence risk assessment in psychiatric settings (Griggs and Tomkins 1996). The purpose of this research has largely been to establish empirically validated risk factors (Monahan and Steadman 1994; McNiel 1998) and to develop actuarial risk assessment tools (Borum 1996; Monahan et al. 2000; Monahan et al. 2001). However, despite improved violence risk assessment methods, researchers have had more difficulty consistently demonstrating the effects of treatment and risk management strategies in reducing violence. Harris and Rice (1997) conclude that very few effective techniques exist for reducing aggressive behavior in persons with psychiatric disorders, although some behavioral therapies have shown promise (Shloss et al. 1989; Beck et al. 1991; see generally Paul and Lentz 1977). Given the strength of the findings in the present study, the administration of atypical antipsychotic medication appears to be an important ingredient in effective clinical treatment—and violence risk management in particular—for schizophrenia patients residing in the community.

The findings may have especially significant implications for reducing the long-term cost of treatment for schizophrenia. Among all those who suffer from this disease and other serious psychiatric disorders, a small proportion who become dangerous or engage in violent behavior account for a disproportionately large share of the cost of providing the most expensive services in the most restrictive settings (Borum et al. 1996). The study found a significant positive association between violence and mental health service intensity, which suggests that patients who were likely to be violent over time tended to have greater severity and complexity of need for mental health services.

In North Carolina, where this study was conducted, the large majority of state mental hospital admissions are involuntary commitments, which often are precipitated by threatening or assaultive behavior in patients with psychoses who experience exacerbation or relapse of their illness following a period of nonadherence with medication (Swanson et al. 1999). Partly as a result, the North Carolina Division of Mental Health, Developmental Disabilities, and Substance Abuse Services spent $285 million in fiscal year 2000—71 percent of its adult mental health care budget—on institutional (hospital) care (Stein 2001). Moreover, during the same year, the North Carolina Department of Corrections spent an estimated $117 million for the incarceration of about 5,000 individuals with primary psychiatric disorders (excluding substance abuse)—on average, more than $23,000 per inmate with mental illness. It is estimated that only about 9 percent of these persons with mental illness received psychotropic medication while incarcerated. Given timely treatment with appropriate medications and other mental health interventions, it seems likely that many of these offenders would never have committed the crimes that landed them behind bars (Swanson 2001).

This study may be somewhat limited in its generalizability, insofar as the demographic distribution of our sample (patients in the public mental health care system in North Carolina) differs from the population of all persons with this disorder (Keith et al. 1991; Kendler et al.
resent an attempt to self-medicate psychotic symptoms and by persons with severe mental illness may sometimes rep-

2001; Miles et al. 2003). Use of alcohol and illicit drugs (Dixon 1999; RachBeisel et al. 1999; Monahan et al. 

highly associated with violent and aggressive behaviors, including assaultiveness, suicide, hostility, and criminality (Dixon 1999; RuchBeisel et al. 1999; Monahan et al. 2001; Miles et al. 2003). Use of alcohol and illicit drugs by persons with severe mental illness may sometimes represent an attempt to self-medicate psychotic symptoms and distress. Substance abuse may, in turn, lead to violent behavior in several ways: by stimulating or disinhibiting aggressive impulses; by exacerbating delusions of threat as well as real conflict in domestic and other social relationships; by exposing the user to criminogenic environments in which violence is commonplace; and by increasing economic stress and survival demands (which are already con-
siderable for persons with severe psychiatric disorders). In theory, then, the improved side effect profile of the atypical antipsychotic medications could indirectly reduce the risk of violent behavior among SMI individuals—principally by means of better compliance and reduced substance abuse comorbidity (Owen et al. 1996).

However, we also found evidence that medication noncompliance is an important independent risk factor for violence, i.e., even controlling for substance abuse. This finding has important implications for clinical management of violence risk. If patients are compliant with atypical antipsychotics, violence risk is dramatically reduced. Insofar as compliance is determined by drug tolerability and the atypicals are associated with fewer side effects, it is possible that the atypicals may reduce violence indirectly via better compliance. Clearly, however, medication compliance in schizophrenia treatment is a complex phenomenon, and is affected by multiple independent variables, including insight, severity of psychotic symptoms, substance abuse, adverse social environments, availability of supportive caregivers, and the quality of the collaborative bond between the patient and clinician—in addition to the well-documented effects of unpleasant side effects (Valenstein et al. 1998; Olsson et al. 2000; Menzin et al. 2003). Moreover, while patients taking atypicals may experience fewer adverse side effects, some side effects may persist. Thus, for a number of reasons, noncompliance may continue to be a problem for many patients even if they are prescribed atypical antipsychotic medications; in such cases, other strategies should be considered.

Several scientific reviews have concluded that depot antipsychotics modestly improve medication compliance and other clinical outcomes (Kane 1983; Fenton et al. 1997; Adams and Eisenbruch 2000). At present, risperidone is the only atypical antipsychotic medication with an approved long-acting injectable form of administration. Hence, clinicians may need to consider use of depot conventional neuroleptics or other community-based interventions designed to improve treatment adherence, such as Assertive Community Treatment programs (Burns and Santos 1995). Similarly, where substance abuse persists during a course of atypical antipsychotic therapy, additional treatment targeting substance abuse directly is still needed.

Given that violence among individuals with serious psychiatric disorders may result from multiple etiologies—with complex interactions between developmental, cognitive, clinical, and social-environmental risk factors (Swanson et
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