ORIGINAL ARTICLE

# Predictors of Relapse Following Response From a First Episode of Schizophrenia or Schizoaffective Disorder

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**Background:** We examined relapse after response to a first episode of schizophrenia or schizoaffective disorder.

**Methods:** Patients with first-episode schizophrenia were assessed on measures of psychopathologic variables, cognition, social functioning, and biological variables and treated according to a standardized algorithm. The sample for the relapse analyses consisted of 104 patients who responded to treatment of their index episode and were at risk for relapse.

**Results:** Five years after initial recovery, the cumulative first relapse rate was 81.9% (95% confidence interval [CI], 70.6%-93.2%); the second relapse rate was 78.0% (95% CI, 46.5%-100.0%). By 4 years after recovery from a second relapse, the cumulative third relapse rate was 86.2% (95% CI, 61.5%-100.0%). Discontinuing antipsychotic drug therapy increased the risk of relapse by almost 5 times (hazard ratio for an initial relapse, 4.89 [99% CI, 2.49-9.60]; hazard ratio for a second relapse, 4.57 [99% CI, 1.49-14.02]). Subsequent analyses controlling for antipsychotic drug use showed that patients with poor premorbid adaptation to school and premorbid social withdrawal relapsed earlier. Sex, diagnosis, obstetric complications, duration of psychotic illness before treatment, baseline symptoms, neuroendocrine measures, methylphenidate hydrochloride challenge response, neuropsychologic and magnetic resonance imaging measures, time to response of the initial episode, adverse effects during treatment, and presence of residual symptoms after the initial episode were not significantly related to time to relapse.

**Conclusions:** There is a high rate of relapse within 5 years of recovery from a first episode of schizophrenia and schizoaffective disorder. This risk is diminished by maintenance antipsychotic drug treatment.

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PATIENTS WITH first-episode schizophrenia usually respond well to treatment,[1-5] but relapse is frequent during the first years of the illness and may be associated with clinical deterioration.[6] Previous studies have used different definitions of relapse, employed a variety of treatments and have reported a range of relapse rates. Despite this variability, some general trends are evident. In the first year, relapse rates in published studies[7-9] are relatively low. The largest rate was 41% in patients taking placebo (n = 17)[8]; only 17% of patients relapsed during 15 months in the study[9] with the largest sample size (n = 69). After the first year, relapse rates[8,10-15] rise substantially, with published rates of between 35% after 18 months[15] and 74% after 5 years of follow-up.[12]

Relapse prevention is a major challenge in the care of patients with schizophrenia. Our opportunity to study relapse and its predictors arose in the context of a long-term study of first-episode schizophrenia and schizoaffective disorder. Our patients had extensive clinical and biological assessments at baseline, were treated according to a specific medication algorithm, and were followed up prospectively with standardized assessments. This design allowed us to closely monitor symptom recurrences and to examine the association of clinical and biological variables and medication status with relapse.

## RESULTS

### PATIENTS

One hundred eighteen patients were treated in the study. The sample for the analyses presented consists of the 104 patients who were followed up for a minimum of 2 months after responding to treatment and thus were at risk for relapse. The sample included an equal number of men and women; their mean ± SD age at study

## PATIENTS, MATERIALS, AND METHODS

### STUDY DESIGN

The study design and methods have been described previously.[16,17] The study began in 1986; this report includes data collected until June 1, 1996. All patients were recruited from Hillside Hospital, Glen Oaks, NY; the study was conducted according to guidelines of the Long Island Jewish Medical Center, Glen Oaks, institutional review board. Written informed consent for the study was obtained from patients and, if available, from family members. Inclusion criteria were (1) a Research Diagnostic Criteria[18]–defined diagnosis of schizophrenia or schizoaffective disorder based on a Schedule for Affective Disorders and Schizophrenia[19] interview, (2) total lifetime exposure to antipsychotic medications of 12 weeks or less, (3) a rating of 4 (moderate) or more on at least 1 psychotic symptom item on the Schedule for Affective Disorders and Schizophrenia Change Version With Psychosis and Disorganization Items rating scale (SADS-C+PD),[20] (4) no medical contraindications to treatment with antipsychotic medications, and (5) no neurologic or endocrine disorder or neuromedical illness that could affect diagnosis or the biological variables in the study.

Initially, we did not limit the length of study participation. Later we established a maximum study time of 5 years and terminated the participation of patients who had been in the protocol longer (the longest duration of study participation was 475 weeks).

### ASSESSMENTS AND MEASURES

Assessments included the following. (1) Psychopathologic variables: SADS-C+PD[20] and the Clinical Global Impression (CGI) Scale[21] at baseline and every 2 weeks during acute treatment and every 4 weeks at other times and the Scale for the Assessment of Negative Symptoms[22] at baseline and every 4 weeks. (2) Adverse effects/motor symptoms: the Simpson-Angus Extrapyramidal Symptom (SAEPS) Scale[23] at baseline and every 2 weeks during short-term treatment and every 4 weeks at other times and the Modified Simpson Dyskinesia Scale[24] at baseline and every 8 weeks. (3) Premorbid social adjustment: the Premorbid Adjustment Scale (PAS)[25] was completed at baseline using information from patients and family members. "Premorbid" was defined as the period ending 6 months before the first psychiatric contact or hospitalization or 6 months before any evidence of florid psychotic symptoms. Individual PAS item ratings were averaged to provide mean scores for childhood, early adolescence, late adolescence, and adulthood. (4) Obstetric history: obtained from mothers by questionnaire and interview and from birth records when available, and scored using the McNeil-Sjöström scale.[26] (5) Neuropsychologic (NP) assessments: done when patients recovered from the initial episode or reached a stable plateau. The NP battery included 38 tests from which variables were selected to provide scores in 6 scales (language, memory, attention, executive, motor, and visuospatial function)[27] and a weighted global summary score for NP performance. For scale construction, raw scores were converted to standard scores ($z$ scores) relative to the performance of a healthy control group (n = 36). Patients also underwent an abbreviated NP battery assessing attention and motor function before starting antipsychotic drug therapy. For the purpose of analysis, raw scores were converted to factor scores on the basis of principal components analysis. (6) Magnetic resonance imaging brain scans were obtained during the index episode using a 1.0-T whole-body magnetic resonance imaging system (Magnetom; Siemens, Erlangen, Germany). Images acquired by a 3-dimensional gradient echo sequence (fast low angle shot) (coronal acquisition, 3.1-mm-thick contiguous slices, with a 256 × 256 matrix in a 24-cm field of view; number of excitations = 1; repeat time = 40 milliseconds; echo time = 15 milliseconds; and flip angle = 50°) were used for morphometric analysis.[28] A semiautomated mensuration system was used for assessing whole brain, ventricular, caudate, superior temporal gyrus, and hippocampal volumes (methods described previously[16,27,29,30]). Presence of a septum pellucidum abnormality was rated as absent, questionable, or present using previously reported methods.[31]

During the initial study years, patients were rated for psychotic symptom activation in response to intravenous methylphenidate hydrochloride before starting antipsychotic treatment.[16] Homovanillic acid[32] and baseline and apomorphine hydrochloride–stimulated growth hormone[16] levels were also obtained for a subgroup of patients by indwelling catheter serial sample collection.

### DEFINITIONS OF PREDICTOR VARIABLES

For analyses of relapse predictors, some variables required additional specification beyond that described above. Obstetric complications present equaled 1 or more complications rated 5 (potentially greatly harmful/relevant) on the McNeil-Sjöström scale; baseline hallucinations and delusions equaled the mean of the ratings for severity of delusions and severity of hallucinations on the SADS-C+PD; baseline disorganization equaled the mean of the SADS-C+PD ratings for bizarre behavior, inappropriate affect, and a composite measure of thought disorder consisting of the mean of the impaired understandability, derailment, and illogical thinking items; baseline negative symptoms equaled the mean of the global ratings for affective flattening, alogia, avolition-apathy, and anhedonia-asociality on the Scale for the Assessment of Negative Symptoms; baseline depressive symptoms equaled the Hamilton Depression scale total score extracted from the SADS-C+PD[33]; baseline

entry was 25.6 ± 6.3 years (range, 14-44 years); 40% were white, 37% were African American, 12% were Hispanic, 8% were Asian, and 3% were of mixed background. Fifty percent had some education beyond high school. Seventy-eight percent had never married. Patients had been ill for an extended period before study entry: the onset of the first behavioral changes related to the illness preceded study entry by a mean ± SD of 119 ± 181 weeks, and the first psychotic symptoms began 64 ± 146 weeks before study entry. Patients were severely ill at baseline. Their mean ± SD CGI Severity Scale score was 5.4 ± 0.94 and their mean ± SD Global Assessment Scale score was 27.6 ± 8.6. Research Diagnostic Criteria–defined diagnoses of the index episode were schizophrenia (n = 71;

extrapyramidal signs present equaled a score of 1 (mild) or more on rigidity, cogwheel rigidity, akinesia, or bradykinesia on the SAEPS; parkinsonism present equaled a rating of 3 or more on rigidity or 2 or more on cogwheeling and rigidity on the SAEPS; and akathisia present equaled a rating of 2 or greater on akathisia on the SAEPS. To examine the effect of interepisode residual symptoms, patients were classified as having no residual symptoms, residual symptoms without prominent negative symptoms, and residual symptoms with prominent negative symptoms using the *DSM-IV*[34] schizophrenia course specifiers.

### TREATMENT PROTOCOL

Patients were treated openly according to a standard algorithm, progressing from one phase of the algorithm to the next until they met response criteria. The sequence was initial treatment with fluphenazine, up to 20 mg/d; after 6 weeks, the dose for nonresponders was increased to 40 mg/d for an additional 4 weeks. Patients nonresponsive to fluphenazine therapy were switched to haloperidol therapy, 20 mg/d, for 6 weeks, which was raised to 40 mg/d for 4 additional weeks if needed. Lithium was added for patients who were still unresponsive, and a trial of a neuroleptic agent from a different biochemical class—either molindone hydrochloride, up to 300 mg/d, or loxapine, up to 150 mg/d, was the next strategy (because of a protocol change during the study, lithium augmentation was not used for all eligible patients). Patients who were still treatment resistant were treated with clozapine, up to 900 mg/d. Benztropine mesylate, 2 to 6 mg/d, was given if extrapyramidal symptoms developed, and lorazepam, 1 to 3 mg/d, or propranolol, 10 to 60 mg/d, was prescribed for akathisia. Mood stabilizers were prescribed if needed. Patients who remained unresponsive were treated as clinically indicated by the research team.

### DEFINITION OF TREATMENT RESPONSE AND RELAPSE

Treatment response was operationally defined as a CGI global improvement scale rating of "much improved" or "very much improved" and a rating of 3 (mild) or less on all of the following SADS-C+PD psychosis items: severity of delusions, severity of hallucinations, impaired understandability, derailment, illogical thinking, and bizarre behavior. To be classified as responders, patients had to maintain this level of improvement for 8 consecutive weeks; treatment response was dated from the time response criteria were first met, ie, the beginning of this 8 weeks.

Responders continued taking the successful medication; if clinically appropriate, the dose was lowered by up to 50% in the maintenance phase of treatment. Patients who were clinically stable for 1 year were given the option of discontinuing use of the antipsychotic medication while continuing to be followed up by the study team. Patients who had symptom exacerbations after discontinuing medication use were given the antipsychotic drug that had been successful for them in the past. Continuous antipsychotic medication therapy was prescribed for the remainder of the study for all patients who developed signs of relapse. Whenever possible, we continued to follow up and assess patients who discontinued treatment against our advice; these patients were restarted on antipsychotic drug therapy if they later agreed to treatment.

The following rating scale criteria were used to define a relapse: at least "moderately ill" on the CGI Severity of Illness Scale, "much worse" or "very much worse" on the CGI Improvement Scale, and at least "moderate" on 1 or more of the SADS-C+PD psychosis items listed above; these criteria had to be sustained for a minimum of 1 week. Date of relapse was defined as the first day of this period. Patients who had nonpsychotic symptom exacerbations (eg, affective symptoms) were not classified as relapsed.

### DATA ANALYSIS

Because of the longitudinal nature of the study, length of follow-up (and the period at risk for relapse) varied among study patients. Survival analysis, which adjusts for differences in length of follow-up, was used to estimate the cumulative rate of relapse and to test the effects of potential predictors of relapse. Cumulative rates of relapse were estimated using life-table methods, with 95% confidence intervals (CIs) to indicate the precision of these relapse rate estimates.

Analyses that estimated the effects of single and multiple potential risk factors were done using Cox proportional hazards regression. To ensure that the proportional hazards assumption of Cox regression was met, we ran additional analyses incorporating the interaction terms of individual risk factors with time into the models. Because of the number of risk factors included in the Cox regression analysis, we defined statistical significance as $P<.01$. We thus used 99% CIs to indicate the precision of the hazard ratios from these analyses.

Cox proportional hazards regression was run with neuroleptic medication status (taking drugs vs not taking drugs) entered as a time-dependent covariate. A lag of 7 days was incorporated into the medication status time-dependent variable so that a patient was considered to be taking medication until a week after stopping medication use and considered to be not taking medication until a week after restarting medication use. These lags were instituted to model the time needed for medications to wear off after discontinuation or build up when resumed and to account for the possibility that stopping medication use constituted part of the relapse process. Additional Cox regression models examining other potential predictors of relapse controlled for medication status as a time-dependent covariate.

82% paranoid, 11% undifferentiated, 6% disorganized, and 1% catatonic subtypes) and schizoaffective disorder (n = 33).

Patients were followed up for a mean ± SD of 207 ± 101 weeks. The mean ± SD antipsychotic drug dose in fluphenazine equivalents during acute treatment was 24 ± 15 mg/d. Twenty-eight patients received some treatment that did not conform to the standard medication algorithm. Nine patients were in initial pilot protocols and began treatment with conventional antipsychotic medications other than fluphenazine. Nineteen patients began treatment with fluphenazine but subsequently received medications not specified in the algorithm for a variety of clinical reasons.

**Table 1. Cumulative Relapse Rates by Episode of Illness**

| Year* | Relapse Rate (95% Confidence Interval) | Patients Remaining at Risk at End of Year, No. |
|---|---|---|
| | **First Relapse—104 Patients at Risk** | |
| 1 | 16.2 (8.9-23.4) | 80 |
| 2 | 53.7 (43.4-64.0) | 39 |
| 3 | 63.1 (52.7-73.4) | 22 |
| 4 | 74.7 (64.2-85.2) | 9 |
| 5 | 81.9 (70.6-93.2) | 4 |
| | **Second Relapse—63 Patients at Risk** | |
| 1 | 19.1 (8.4-29.9) | 36 |
| 2 | 48.7 (33.6-63.9) | 17 |
| 3 | 56.0 (43.2-80.2) | 10 |
| 4 | 56.0 (43.2-80.2) | 3 |
| 5 | 78.0 (46.5-100.0) | 1 |
| | **Third Relapse—20 Patients at Risk** | |
| 1 | 12.5 (0-28.7) | 10 |
| 2 | 31.1 (4.8-57.4) | 7 |
| 3 | 72.4 (41.0-100.0) | 2 |
| 4 | 86.2 (61.5-100.0) | 1 |

**Refers to year(s) after recovery from the previous episode.*

Magnetic resonance imaging, NP, and obstetric measures were not obtained on all patients because of clinical condition or patient or family member refusal.

## RELAPSE RATES

Relapse rates are presented in **Table 1**. The cumulative rate for first relapse for the 104 patients was 81.9% (95% CI, 70.6%-93.2%) by the end of the 5-year follow-up. For the 63 patients who recovered after the first relapse, the cumulative rate for a second relapse was 78.0% (95% CI, 46.5%-100%) after 5 years. Similarly, the cumulative rate for a third relapse was 86.2% (95% CI, 61.5%-100%) by the end of 4 years among 20 patients who were at risk after recovery from the second relapse.

A survival analysis of relapse using medication status as a time-dependent covariate indicated that the risk for a first and second relapse was almost 5 times greater when not taking than when taking medication (hazard ratio for the first relapse, 4.89 [99% CI, 2.49-9.60]; hazard ratio for the second relapse, 4.57 [99% CI, 1.49-14.02]). Survival analyses for the third relapse produced high but unstable estimates because of the small number of patients at risk.

Thirteen stable patients who had discontinued antipsychotic drug therapy dropped out of the study (5 patients had been followed up for ≥2 years after recovery from the initial episode, 4 patients were at risk for relapse for 1-2 years, and 4 patients were at risk for relapse for <1 year). These were categorized as censored observations at the time they dropped out. This raised the possibility that our hazard ratios were biased upward because they would not reflect the possibility that these patients might have remained stable without taking medication after they dropped out. To assess this possibility, we reran our analyses assuming that these 13 patients continued not taking antipsychotic drugs and did not relapse from the time they dropped out of the study until either the June 1, 1996, cutoff date for our analyses or the date that would have marked their completion of 5 years in the study. For the first relapse, the hazard ratio estimating the effect of not taking antipsychotic medications was 3.31 (99% CI, 1.66-6.61) in these analyses. Thus, even given these extreme assumptions, stopping antipsychotic drug therapy had a large effect on relapse.

Given the strong association between medication discontinuation and relapse, we next examined the possibility that antipsychotic drug therapy discontinuation was an early phase of the relapse process rather than a precipitant, ie, patients who are becoming psychotic might lose insight and stop taking medication. If this were the case, relapse onset and antipsychotic discontinuation should be temporally close; a long period between stopping antipsychotic drug use and relapse onset would not be consistent with this hypothesis. One way to examine this issue was to lengthen the lag period in our analyses during which patients were classified as taking medication after administration of their last actual medication dose. If stopping antipsychotic drug therapy occurred at or just before the time of relapse, lengthening these lag periods would cause patients in our analyses to be considered as taking medication at the time of relapse and thereby decrease the relapse risk associated with not taking antipsychotic drugs. In subsequent analyses using longer lag periods, antipsychotic drug therapy discontinuation continued to be associated with a substantial relapse risk; this suggests that stopping antipsychotic drug use was not just an early manifestation of relapse. For example, the hazard ratios associated with not taking medication for the first relapse were 4.49 (99% CI, 2.31-8.75) using a 14-day lag, 4.16 (99% CI, 2.15-8.06) using a 28-day lag, and 4.41 (99% CI, 2.27-8.57) using a 56-day lag.

## PREDICTORS

Because antipsychotic medication status was such a strong predictor of relapse, the time-dependent covariate measuring medication status (using a 7-day lag period) was controlled for in analyses of other predictor variables. Analyses of predictors of the first relapse are presented in **Table 2**. Early adolescent premorbid adjustment was the only variable significantly related to first relapse; late adolescent premorbid adjustment and hippocampal volume were trend level predictors ($P<.05$). Results of subsequent analysis of individual PAS items indicated that shorter time to first relapse was significantly associated with social withdrawal in late adolescence (hazard ratio, 1.29; 99% CI, 1.09-1.61) and poor adaptation to school in early adolescence (hazard ratio, 1.38; 99% CI, 1.06-1.81); relapse was also associated at a trend level ($P<.05$) with poor school adaptation in childhood (hazard ratio, 1.41; 99% CI, 0.96-2.05) and late adolescence (hazard ratio, 1.17; 99% CI, 0.96-1.44).

To demonstrate the clinical relevance of our premorbid adjustment findings, the **Figure** presents the predicted cumulative relapse rates for patients in the 25th and 75th percentiles of early adolescent global PAS scores (PAS scores = 0.8 and 1.7, respectively). Predicted rates

**Table 2. Predictors of First Relapse***

| Characteristic | HR (99% CI) |
|---|---|
| Female | 1.02 (0.53-1.98) |
| Diagnosis of initial episode (schizoaffective vs schizophrenia) | 0.68 (0.33-1.40) |
| Obstetric complications (n = 53)† | 0.73 (0.22-2.40) |
| Childhood PAS score | 1.37 (0.89-2.11) |
| Early adolescence PAS score | 1.57‡ (1.02-2.40) |
| Late adolescence PAS score | 1.34§ (0.99-1.83) |
| Adulthood PAS score | 1.12 (0.86-1.47) |
| Duration of psychotic symptoms before study entry of >1 y† | 1.28 (0.56-2.90) |
| Baseline hallucinations and delusions | 1.15 (0.82-1.61) |
| Baseline disorganization | 1.22 (0.88-1.69) |
| Baseline negative symptoms | 0.90 (0.57-1.42) |
| Baseline depressive symptoms | 0.97 (0.92-1.02) |
| Baseline extrapyramidal symptoms† | 1.16 (0.34-3.98) |
| Parkinsonism during the first 16 wk of treatment† | 1.64 (0.77-3.50) |
| Akathisia during the first 16 wk of treatment† | 1.12 (0.52-2.39) |
| Dystonia during the first 16 wk of treatment† | 0.94 (0.48-1.87) |
| Baseline homovanillic acid level, ng/mL (n = 56) | 1.02 (0.93-1.12) |
| Growth hormone | |
| Baseline, ng/mL (n = 55) | 0.98 (0.85-1.13) |
| Mean response to apomorphine therapy, ng/mL (n = 43) | 0.98 (0.90-1.06) |
| Psychotic symptom activation to methylphenidate (n = 61)† | 0.72 (0.29-1.84) |
| Magnetic resonance imaging measures (n = 95) | |
| Whole-brain volume, $cm^3$ | 1.00 (1.00-1.00) |
| Lateral ventricular volume, $cm^3$ | 0.99 (0.94-1.05) |
| Caudate volume, $cm^3$ | 1.23 (0.81-1.87) |
| Superior temporal gyrus volume, $cm^3$ | 0.98 (0.92-1.05) |
| Hippocampal volume, $cm^3$ | 1.23§ (0.95-1.60) |
| Presence of cavum septum‖ | 1.56 (0.48-5.09) |
| Neuropsychologic measures | |
| Baseline attention (n = 45) | 1.20 (0.64-2.23) |
| Baseline motor (n = 45) | 1.24 (0.65-2.35) |
| Global neuropsychologic functioning after response to initial episode (n = 74) | 1.22 (0.75-1.99) |
| Time to treatment response of initial episode, wk | 1.00 (0.99-1.02) |
| Interepisode residual symptoms | 1.25 (0.58-2.68) |

**All analyses included neuroleptic medication status (taking vs not taking) as a time-varying covariate. Analyses involving ventricular, caudate, superior temporal gyrus, and hippocampal volume controlled for whole-brain volumes. HR indicates hazard ratio; CI, confidence interval; and PAS, Premorbid Adjustment Scale.*

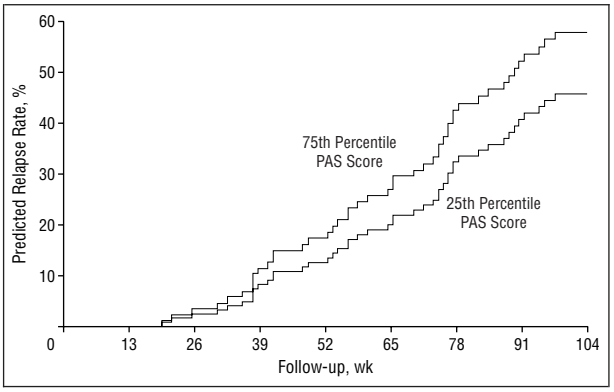
*†Present vs absent.*

*‡P<.01.*

*§P<.05.*

*‖0 indicates absent; ½, questionable; and 1, present.*

were based on Cox proportional hazards regression; antipsychotic drug status was set at 0.5 (midway between taking and not taking drugs), the approximate mean for this variable. At 1 year, the relapse rate for patients in the 75th percentile was 43% larger than that for patients in the 25th percentile, but there was little absolute difference because both had low relapse rates (17.3% [99% CI, 6.2%-27.1%] and 12.9% [99% CI, 3.1%-20.2%] for patients in the 75th and 25th percentiles , respectively). With the substantial increase in overall relapse rate at 2 years of follow-up, the difference in relapse between patients in the 75th and 25th percentiles was potentially large enough (57.8% [99% CI, 39.6%-70.5%] vs 44.3% [99% CI, 26.0%-58.1%], respectively) to be clinically important.




*Predicted cumulative relapse rates for patients in the 25th and 75th percentiles for early adolescent global Premorbid Adjustment Scale (PAS) scores (PAS scores = 0.8 and 1.7, respectively) based on Cox proportional hazards regression. The drug status time-varying covariate was set at 0.5 (midway between taking and not taking drugs).*

## COMMENT

We found that most patients who recover from a first episode of schizophrenia or schizoaffective disorder experience psychotic relapse within 5 years. Furthermore, patients who recover from a first relapse have high rates of second and third relapses despite careful monitoring by a dedicated research treatment team.

Our study offered stable patients the option of discontinuing antipsychotic medication after 1 year of treatment. Those who did so were carefully monitored and treated at the first sign of symptom exacerbation. This conformed to clinical practice at our center when the study began and is consistent with the recently published "American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia,"[35] which recommends at least 1 year of maintenance antipsychotic medication treatment for remitted first-episode patients. Our data show that medication discontinuation substantially increases relapse risk. This is consistent with earlier findings[8,10] and argues strongly for maintenance medication therapy for first-episode patients with schizophrenia and schizoaffective disorder.

How long should maintenance treatment last? A definitive answer requires systematic medication discontinuation studies, but our data provide some suggestions. The almost 5-fold increase in relapse risk associated with stopping antipsychotic drug use in our analyses was based on the entire follow-up for each patient; our ability to make inferences about a particular period depends on the number of patients who relapsed during that period. We had enough patients who relapsed within 2 years (n = 50) to be confident that medication use should be continued at least this long. Is maintenance medication therapy needed for first-episode patients who have been stable for longer than 2 years? We had only 15 patients who relapsed for the first time after 2 years of stability; 8 of these patients had discontinued medication use when they relapsed, suggesting the continued importance of maintenance medication treatment.

Aside from medication status, premorbid social adjustment was the only predictor of relapse in our study. Kane et al[8] found a significant association between so-

cial isolation in childhood and adolescence as measured by the Premorbid Asocial Adjustment Scale[36] and relapse in first-episode patients taking placebo but not in patients taking antipsychotic drugs for maintenance. Our results, based on a larger sample, indicate that premorbid social isolation predicts initial relapse independent of medication status and that poor adaptation to school also predicts relapse in first-episode patients. Thus, specific behaviors that are present long before the expression of overt psychotic symptoms predict some aspects of the course of psychotic symptoms once they develop. This raises the possibility of a subtype of patients with schizophrenia and schizoaffective disorder characterized by poor early adjustment and a severe, relapsing course.

Few of our predictor variables have been examined in other first-episode samples. Our failure to find an association between sex and relapse is consistent with previous studies.[8,10] Crow et al[10] found that relapse was more common in patients who had an illness onset of 1 year or longer before starting antipsychotic drug use; we did not confirm this, although this variable was associated with initial treatment response in our sample. Study differences in the treatments given and in the definitions of relapse used may have contributed to these divergent findings. Furthermore, illness duration before medication use averaged 2.8 months in the study by Crow et al vs 16.0 months in our study, suggesting differences between the studies in patient clinical characteristics, illness definition, or both. Additional studies are required to clarify the effects of illness duration before treatment on relapse.

In the 5-year follow-up of a subsample of the Northwick Park cohort, Geddes et al[11] found that depressive delusions at baseline were associated with lower risk of readmission. Neither the severity of baseline depressive symptoms nor the presence of affective symptoms sufficient to warrant a schizoaffective diagnosis was related to relapse in our sample. We did, however, find a possible relationship between affective symptoms and relapse. Review of clinical profiles of the 8 patients in our sample who survived 1 year or longer without taking antipsychotic drugs and without relapse revealed that affective symptoms were prominent in this small subgroup who were relatively "invulnerable" to discontinuation of antipsychotic drug therapy.

The failure of most of our candidate variables to predict relapse is interesting given that many of them predicted treatment response to the initial episode in our sample.[1,32,37-40] This suggests either that the pathologic mechanisms of relapse differ from those of acute treatment response or—if common mechanisms initially underlie treatment response and relapse—that the pathologic process changes over time because of a deteriorative component, the effects of prolonged antipsychotic medication exposure, or both.

Our findings have some potential limitations. Our study used a standardized treatment algorithm; this allowed patients to be taking different antipsychotic drugs and different doses depending on their response to treatment. This may have introduced confounds between treatment variables and outcome that would not have been present if we had provided treatment with a set dose of only 1 antipsychotic medication. On the other hand, the treatment algorithm strategy more closely follows optimal clinical practice and thus our findings may be more generalizable to "real world" settings than would a single antipsychotic drug design. Our study preceded the widespread availability of the new generation of antipsychotic medications. Whether use of these agents as first-line treatments will produce different results is an open, and important, question.

Although many studies have addressed maintenance treatment in schizophrenia and schizoaffective disorder, relatively few studies have examined relapse in the early years of illness. The high rate of relapse we found and the salience of its relationship to medication discontinuation strongly argues for an increased attention to maintenance treatment issues in the initial stages of schizophrenia and schizoaffective disorder from a clinical and scientific perspective. The fact that so many of our patients refused maintenance antipsychotic drug therapy—even after experiencing 1 or more relapses and despite vigorous patient and family educational efforts—highlights the need for developing strategies to enhance compliance at this early illness stage.

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