Relationship Between Relapse and Hospitalization in First-Episode Psychosis

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Objective: **Relapse is a frequently used outcome measure in schizophrenia research. However, difficulties in reliably measuring relapse diminish its usefulness. Hospitalization is a potential alternative, but its relationship to relapse has not been assessed.** _Methods:_ **This study used data from a two-year, prospective study to examine associations between relapse and hospitalization in a cohort of 200 Canadian patients with first-episode psychosis. First, the relationship between relapse and hospitalization was assessed by cross-tabulating relapse and hospitalization. Next, survival curves of time to first relapse or hospitalization were compared. Finally, to examine the convergent validity of relapse and hospitalization, the predictive capacity of three predictors were examined: a substance use disorder diagnosis, prior hospitalization, and medication adherence.** _Results:_ **Rates of both relapse and hospitalization were similar. During the two-year follow-up, 37% of the patients experienced a relapse, and 26% were hospitalized. As an indicator of relapse, hospitalization had a low sensitivity (47%) and high specificity (87%). A higher risk of hospitalization and relapse was associated with prior hospitalization, a substance use disorder diagnosis, and medication nonadherence.** _Conclusions:_ **Results indicated that relapse and hospitalization are separate but related outcome measures. They had similar frequencies and were found to have similar relationships with some predictors. Relapse is a more useful outcome measure in smaller clinical studies in which routine standardized clinical measures can be used. Hospitalization is more relevant in larger studies or as a quality indicator for studies using administrative databases, and it serves as a good measure for quality management in health systems. (_Psychiatric Services_ 64:796–799, 2013; doi: 10.1176/appi.ps.201200440)**

I n clinical trials of interventions for first-episode psychosis, both the relapse rate and the hospitalization rate have been used as outcome measures. Relapse has been defined as "a recurrence of positive psychotic symptoms which are of clinical significance, which persist for a sustained period of time and which follow a period of partial or full remission" (1).

Two studies that differed significantly in their purpose and design illustrate the use of relapse and hospitalization rates as outcome measures (2,3). The first study used relapse as the primary outcome and had a predefined definition of relapse; patients were assessed at monthly intervals (2). In addition, all study patients had to be in remission, which made the assessment of relapse less complex. The second study, which examined representative cohorts drawn from geographic catchment areas, used both relapse and hospitalization as outcome measures (3). However, not all patients achieved remission, the assessments of relapse were conducted by chart review, and the definitions of relapse were reported as "available on request."

In a recent review of the problems and challenges of assessing relapse in first-episode psychosis, it was reported that many studies have not used standardized or validated observer measures for assessing relapse and that significant aspects of the definition of relapse have often not been specified (1). Only three of 16 studies reviewed satisfied the authors' six criteria for the operationalization of relapse. In fact, hospitalization was the most common definition of relapse, suggesting confusion between the concepts of relapse and hospitalization. Many of the studies that addressed the cost and consequences of relapse used hospital costs as the primary driver of the cost of relapse, which further muddles these two concepts (4).

The use of hospitalization as an outcome measure in schizophrenia has also been reviewed (5). The author of the review concluded that hospitalization has face validity but suggested that it may be difficult to compare its significance across differing health care contexts because access to, and use of, beds may differ across systems. This limitation does not occur when randomization is used in a study conducted in a single health

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care system or when a clinical trial randomly assigns a sufficient number of patients to the treatment conditions. In multicenter trials, hospitalization may also be an acceptable outcome measure if the center is treated as a stratification variable in the analysis. A test of this theory can be seen in a secondary analysis of hospitalization data from the multicenter CATIE study (Clinical Antipsychotic Trials of Intervention Effectiveness). The analysis showed that the same pharmacological interventions that predicted the primary outcome in the original study (6)—time to all-cause discontinuation of medication—also predicted time to hospitalization, even though the patients were treated in different health care systems (7). The validity of hospitalization as an outcome measure was demonstrated in a first-episode psychosis study, which found a positive relationship between hospitalization and both quality of life and global psychopathology, two important clinical outcomes for patients with first-episode psychosis (8).

In our review of this topic, we identified no studies that explicitly examined the relationship between relapse and hospitalization in schizophrenia. To examine this relationship, we compared frequencies, sensitivity and specificity, time course, and risk factors for both relapse and hospitalization. The risk factors that we examined included two variables that have a demonstrated association with relapse and hospitalization: prior hospitalization and poor medication adherence (9). We also examined gender, which is not consistently associated with hospitalization or relapse.

Methods

We examined both relapse and hospitalization in a longitudinal cohort study of patients with a first episode of psychosis. The longitudinal cohort study (1998–2002) of a population-based incident cohort was conducted in Calgary, Alberta, Canada. Details of the design and results of the original study are reported elsewhere (10). Clinical and demographic variables were assessed at baseline, one year, and two years from study enrollment. The study was approved by

the University of Calgary Conjoint Research Health Ethics Board. Individual informed consent was required from each patient before study enrollment. The primary outcome of the original study was relapse, and the sample size was based on a power analysis designed to compare current relapse rates with historical relapse rates, the latter estimated from a systematic review of relapse rates among patients with schizophrenia or schizoaffective disorder (11). Patients were given a diagnosis on the basis of all sources of information, including structured clinical interviews at study enrollment and at one year in the clinical service. The one-year diagnosis was used to define the study sample (10).

Direct clinical assessments of relapse were made by using explicit criteria recommended by Linszen and colleagues (12). The reliability of the assessment of relapse was checked against an independent clinical chart review and against hospitalization records. Results showed agreement of 84% between the researcher's assessment of relapse and the chart review. Relapse was assessed and recorded in this way for a cohort of 200 patients who were experiencing a first episode of psychosis and who met diagnostic criteria for schizophrenia or schizoaffective disorder. Hospitalization was assessed in the same cohort. Hospitalization data were obtained from a regional health system database, which is used for legislatively mandated reporting of all hospitalizations at the local and national levels. In the original study, hospitalization was not reported. Medication adherence was assessed using a 3-point scale that categorized patients as demonstrating total nonadherence, inadequate adherence, and good adherence (13).

For the study reported here, we divided the sample into an adherent group and a combined group that included nonadherent and inadequately adherent patients. Substance use disorder was defined as any diagnosis of substance abuse or dependence made with the Structured Clinical Interview for DSM-IV. The Case Manager Rating Scale for Substance Use (14) was used to determine the patient's level

Table 1

Demographic characteristics of 200 patients with first-episode psychosis

Characteristic	N	%
Sex		
Male	132	66
Female	68	34
Age (mean±SD)	24.8±8.5	
Marital status	176	88
Single		
Married[a]	13	7
Divorced or widowed	10	5
Education	84	42
Less than high school		
High school graduate	36	18
More than high school	79	40
Employment	28	14
Full-time		
Part-time	21	11
Student	51	26
Unemployed	59	30
Other[b]	41	21

[a] Includes common-law marriages. Data were missing on marital status and education for one patient.
[b] Includes homemakers and persons not in the labor force because of disability and retirement, as well as seven patients who reported self-employment

of use of alcohol, cannabis, cocaine, stimulants, narcotics, hallucinogens, sedatives, and other substances. Level of use was ranked as none, mild, moderate, severe, or extremely severe.

Results

Characteristics of the 200 patients are summarized in Table 1.

During the first year of follow-up, 46 of the 200 patients relapsed (23%, 95% confidence interval [CI]=17.4–29.4). In the second year of follow-up, an additional 44 patients relapsed (27%, CI=20.5–34.7) among 162 participants who had relapse data recorded during that year. Relapses were recorded during both the first and the second follow-up year for 16 of the 162 patients. Among the 200 respondents, one or more relapses were recorded for 74 participants, yielding a two-year relapse rate of 37% (CI=30.0–44.1). A total of 162 participants were successfully followed for the entire two years; in this group, 64 relapses were recorded, yielding a relapse rate of 40% (CI=31.9–47.1).

During the first year, 31 of the 200 patients were hospitalized (16%,

CI=10.8–21.3). In the second year, 27 patients had hospital admissions (14%, CI=9.1–19.0). The two-year rate for the entire cohort was 26% (CI=19.6–32.1). [Because all hospital admissions could be identified in the electronic data, these calculations were not affected by attrition.]

Sensitivity of hospitalization as a measure of relapse was 47% (CI=35.6–59.3), and specificity was 87% (CI=80.1–92.6). Relapse was recorded in each of eight quarters of the two-year follow-up period, whereas the dates of hospital admission were recorded in days from study entry. To produce survival curves having the same scales on the x-axis, time was recorded in days for both analyses (for example, the first follow-up visit at three months was recorded as 91 days). As would be expected, on the basis of the frequency estimates reported above, the survival curves diminished more rapidly for relapse than for hospitalization. In these analyses, gender predicted relapse (log-rank test, χ^2=3.62, df=1, p=.05) but not hospitalization.

Prior hospitalization was associated with hospitalization (log-rank test, χ^2=4.10, df=1, p=.04). The hazard ratio (HR) for this association was 1.8 (CI=1.0–3.1) However, prior hospitalization was not significantly associated with relapse. A diagnosis of a substance use disorder was not significantly associated with hospitalization or with relapse. Adherence, however, was associated with both hospitalization (log-rank test, χ^2=4.07, df=1, p=.04) and relapse (log-rank test, χ^2=5.52, df=1, p=.02). The HRs for these associations were 2.0 (CI=1.0–4.0) and 1.9 (CI=1.1–3.7), respectively.

Discussion

In this study we quantified the relationship between relapse and hospitalization. The results showed that the hospitalization rate is a highly specific but insensitive measure of relapse. Less than half of those who relapsed were hospitalized, but nearly all of those who were admitted to the hospital had a relapse. This could be interpreted to mean that hospitalization is a more sensitive measure of quality of care than relapse in that some individuals who experienced a relapse were not hospitalized because

their relapse was successfully managed by community services. For example, in settings where access to mobile crisis teams, outreach services, or alternatives to hospitalizations is available, hospitalization rates may be reduced although relapse rates might stay the same.

Both similarities and differences were found in the associations between potential predictors of relapse and hospitalization. For example, medication adherence was associated with both relapse and rehospitalization. Prior hospitalization and medication nonadherence were both associated with hospitalization. Although prior hospitalization and a diagnosis of a substance use disorder were not significantly associated with relapse, the HRs were all elevated, suggesting that the negative impact of these variables was detected by both indicators. It is possible that the study sample was not large enough to provide enough power to confirm the relationships with hospitalization.

Although the focus of this study was first-episode psychosis, most participants had schizophrenia, and the challenges of measuring and preventing relapse and hospitalization are similar in first-episode and in multi-episode schizophrenia. The likelihood of relapse and hospitalization is higher early in the course of the disorder (15), which makes the first episode a good time to study this issue.

A number of limitations may limit the generalizability of the findings. First, the results are based on data from a single, mainly urban health system serving approximately one million people. In different health systems with other combinations of services, the relationship may differ, but few systematic data are available. Second, although we used a rigorous definition of relapse, there is still no agreed-upon standardized method for the assessment of relapse, and it is possible that different methods might result in different hospitalization rates. For example, a recent medication discontinuation study that separately reported rates of relapse and hospitalization found a 92% "exacerbation" rate and a 13% hospitalization rate (16). Comparison with our results is difficult because the other study

was a small clinical trial that assessed patients every two weeks for six months and then monthly and that used an intentionally low threshold of reemergence of defining symptoms to restart pharmacotherapy (17).

Conclusions

Our data suggest that relapse and hospitalization are related but different measures. They both reflect outcomes, such as medication adherence, of important processes of care. At the same time, although they are not identical, they are both useful outcome measures and should be examined independently. Relapse assessed with consensus-based criteria and with methods that meet the six criteria recommended by Gleeson and colleagues (1) is an appropriate outcome for prospective studies in which individual patients can be routinely assessed with reliable and valid rating scales.

Hospitalization, on the other hand, can be used in addition to relapse in patient groups at higher risk of hospitalization and in studies of larger populations in which administrative databases are used. Hospitalization occurs less frequently than relapse, but it is an important, reliable, and valid outcome measure in its own right. It has a higher severity threshold than relapse but carries a greater clinical significance for patients and families and greater financial significance for health systems. Hospitalization also has greater potential as a useful outcome measure in routine assessments of health systems.

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