Cost of Relapse in Schizophrenia

by Peter J. Weiden and Mark Olfson

Abstract

To estimate the national annual cost of rehospitalization for multiple-episode schizophrenia outpatients, and to determine the relative cost burden from loss of medication efficacy and from medication noncompliance, the yearly number of neuroleptic-responsive multiple-episode schizophrenia inpatients in the United States who are discharged back to outpatient treatment was estimated. The cohort at risk for future relapse and rehospitalization was determined. The research literature on the expected rates of relapse for schizophrenia patients on maintenance antipsychotic medication was reviewed; in particular, monthly relapse rates under the optimal medication conditions of compliant patients taking optimal doses of a depot neuroleptic (optimal neuroleptic dose) and under the less optimal conditions of patients stopping medication (medication noncompliant) was estimated. Using established noncompliance rates from the literature, it became possible to estimate a "real world" rehospitalization rate for this cohort, as well as the relative burden accruing from loss of medication efficacy and from medication noncompliance. Finally, cost estimates for index hospitalizations and rehospitalizations were derived from data on national expenditures for inpatient mental health care. The monthly relapse rates are estimated to be 3.5 percent per month for patients on maintenance neuroleptics and 11.0 percent per month for patients who have discontinued their medication. Postdischarge noncompliance rates in community settings are estimated to be 7.6 percent per month. These estimates were entered into a survival analysis model to determine the real world relapse rate of this cohort. An estimated 257,446 multiple-episode (≥ two hospitalizations) schizophrenia patients were discharged from short-stay (≤ 90 days) inpatient units in the United States during 1986. The estimated aggregate baseline inpatient cost for the index hospitalizations of this cohort was $2.3 billion (1993 dollars). Within 2 years after discharge, the aggregate cost of readmission approached $2 billion. Loss of neuroleptic efficacy accounted for roughly 60 percent of the rehospitalization costs and neuroleptic noncompliance for roughly 40 percent. The economic burden due to loss of efficacy is relatively higher during the first postdischarge year, whereas the burden from noncompliance is higher in the second year. Because loss of medication efficacy and medication noncompliance act synergistically on relapse, substantial inpatient cost savings can be realized by linking better pharmacologic treatments of schizophrenia with more effective strategies to manage medication noncompliance.

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Schizophrenia inflicts incalculable suffering on patients and their families, and imposes a substantial

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economic burden on society (Wyatt and Clark 1987; McGuire 1991). Although cost estimates fail to capture the devastating human dimensions of the illness, they can help guide the allocation of treatment resources. Economists traditionally distinguish between direct and indirect costs. Direct costs are the actual dollar expenditures related to the treatment of an illness and typically include institutional care, professional services, and medications. Indirect costs include lost productivity and losses due to premature death. This article focuses on direct costs. Not surprisingly, the direct cost of schizophrenia is very large (Gunderson and Mosher 1975; Rice et al. 1990); a recent estimate of the total annual direct cost of schizophrenia is $19 billion (Wyatt et al., in press).

Many cost studies divide direct costs into component costs (e.g., inpatient treatment, outpatient treatment, jail, medication, etc.). A limitation of this approach, however, is that it is static and provides little information about specific costs that come from particular aspects of the disease, patient behavior, or treatment. For example, an obvious issue in the maintenance (outpatient) treatment of schizophrenia is the risk of relapse and its associated costs. Two major contributors to relapse during maintenance treatment are loss of medication efficacy and medication noncompliance. Clearly, it would be very useful to better understand the relationship between specific problems such as these and the ultimate cost of schizophrenia.

Method

Overview of Design. This analysis focuses on the neuroleptic-responsive, multiple-episode schizophrenia outpatient. First, we estimated the annual number of neuroleptic-responsive acute schizophrenia inpatients in the United States who are discharged back to outpatient treatment. This gave us a cohort at risk for future relapse and rehospitalization. Cost estimates for index hospitalizations and rehospitalizations were derived from data on national expenditures for inpatient mental health care during 1986, adjusted to 1993 dollars. Next, we reviewed the research on the expected rates of relapse for schizophrenia outpatients. In particular, we estimated the monthly relapse rates both under the best conditions, in which compliant patients are taking optimal neuroleptic doses, and under the higher risk condition of recent medication noncompliance. Finally, we used estimates of noncompliance rates to derive the "real world" rehospitalization rate as well as the relative cost burden from loss of medication efficacy and from medication noncompliance.

Population at Risk. To estimate the annual number and hospital distribution of chronic neuroleptic-responsive schizophrenia patients discharged to outpatient treatment in the community, we used the National Institute of Mental Health (NIMH) 1986 Client/Patient Sample Survey (C/PSS; Manderscheid and Sonnenschein 1990) and set a priori criteria to include those inpatients who (1) had at least one prior psychiatric hospitalization; (2) had a primary discharge diagnosis of schizophrenic, schizoaffective, or schizophreniform disorder; (3) had an index hospital stay of no more than 90 days; and (4) were neither admitted from nor discharged to another inpatient or residential care facility. Thus, the number we arrived at represents a conservative estimate of the total U.S. cohort of chronic, multiple-episode schizophrenia patients who are discharged annually to the community.

Defining Relapse Risk Categories. We reviewed prospective maintenance studies with at least 6 months of followup. Our goal was to determine relapse rates for patient groups under more narrowly defined treatment conditions than provided in other meta-analyses of maintenance neuroleptic studies (Davis 1976). We refer to these maintenance treatment conditions as "optimal neuroleptic dose," "medication noncompliant," and "medication withdrawal."

For the optimal neuroleptic dose relapse risk group, we wanted to identify patients who were on an optimal dose of maintenance antipsychotic (but who were not otherwise "protected" by intensive psychosocial therapies) under circumstances in which medication compliance was known. To develop the optimal neuroleptic dose analysis, we identified studies or study subgroups with subjects who (1) had recently relapsed and were restabilized (most often, the patients had been recently discharged) and (2) were receiving long-acting depot neuroleptic (e.g., fluphenazine or haloperidol decanoate) as their maintenance therapy. Excluded from the optimal neuroleptic dose group were study patients who (1) were initially recruited from a stable outpatient population, (2) dropped out of a study or showed signs of noncompliance before relapse, (3) were assigned to a less efficacious depot dose (e.g., a low-dose medi-

cation assignment), and (4) received high-intensity psychosocial therapy in addition to a depot neuroleptic and standard outpatient care. In effect, many of the patients in this category were identified subgroups from larger studies in which some, but not all, of the subjects met these four criteria.

The medication noncompliant relapse risk group was made up of stabilized patients who then became noncompliant to maintenance treatment. To be included in this group, subjects had to have been stabilized outpatients who, in the judgment of the investigator, stopped taking their medications while clinically stable. To see whether relapse rates in these patients differ from those in patients whose medications were discontinued by their physicians, we also analyzed monthly relapse rates of discharged patients whose antipsychotic medications were withdrawn by their clinicians. These patients made up the medication withdrawal risk group. Inclusion criteria for this group were that the patient had to have been recently stabilized from a relapse or recently discharged, and that the patient's medication withdrawal had to have occurred during outpatient treatment.

Owing to the variability of the study methods and the data presentation, we had to make several simplifying assumptions. First, because there is no consensus definition of relapse (Falloon et al. 1983), we stayed with each author's definition as long as it was a categorical outcome. Later on, however, during the cost analysis, we equated relapse with rehospitalization. At first glance, this would appear to exaggerate the subsequent rehospitalization cost estimates. However, there is a countervailing selection bias that underestimates the number of patients at risk for rehospitalization. Specifically, the index hospital cohort actually comes from a larger patient pool of relapsed schizophrenia outpatients, some of whom relapsed but were not rehospitalized during the 1986 calendar year.

Determining Noncompliance Rates. We identified prospective studies that reported noncompliance rates in schizophrenia. To be included, a study had to (1) identify an index cohort of schizophrenia patients discharged from the hospital with the recommendation of maintenance medication, and (2) report medication noncompliance rates (rather than dropouts from a research protocol).

Converting From Aggregate Followup Data to Monthly Rates. All of the above longitudinal relapse and noncompliance rates were then converted into monthly rates by using the following equation:

$$\text{Monthly rate} = \left(\frac{N \text{ survivors}}{N \text{ initial cohort}}\right)^{\frac{1}{N \text{ months followup}}} - 1$$

Depending on the variable of interest, the term "survivors" in the above equation represents the number of nonrelapsed or still-compliant patients remaining by the end of the study period. This calculation is not linear but reflects residual changes in the number of patients over time; this is analogous to monthly mortgage payments, in which interest payments change as the principal is slowly paid. This equation is an oversimplification because it assumes that rates of relapse and noncompliance stay constant over time. In reality, the monthly risk of relapse is slightly lower in the second postdischarge year than it was in the first year (Hogarty and Ulrich 1977). Similarly, noncompliance rates are highest in the first few months after discharge and then eventually level off to a much lower rate (Curson et al. 1985). However, as a practical matter, we had to make this simplifying assumption because many studies presented aggregate followup data. Also, with the exception of noncompliance right after discharge, the magnitude of the monthly differences in relapse and noncompliance rates is relatively small within the context of a 24-month postdischarge timeframe (Hogarty and Ulrich 1977; Davis et al. 1980; Weiden et al. 1991).

Including Noncompliance in a Survival Curve Model. We incorporated the effects of neuroleptic noncompliance into the survival curve estimates as follows: let α represent the monthly odds that a recently discharged schizophrenia patient maintained on neuroleptics will relapse, and let β represent the monthly odds that a patient who recently stopped medication will relapse. The number of expected relapses for a population during that month can be expressed as

$$\text{Number of expected relapses for a month} = [\alpha \times (\text{number of compliant patients})] + [\beta \times (\text{number of noncompliant patients})].$$

For a population of medicated patients (N), a given proportion (γ) of new patients will become noncompliant each month. The num-

ber of patients surviving without relapse in the first month (m) can then be expressed as

$$N_{m+1} = N_m - [\alpha(N_m - \gamma N_m) + \beta(\gamma N_m)].$$

Because each subsequent month's group will have the survivors from the previous month, this equation can be repeated for the next month. Therefore, the equation for the next month's group that survived without relapse is

$$N_{m+2} = (N_{m+1}) - [\alpha(N_{m+1} - \gamma N_{m+1}) + \beta(\gamma N_{m+1})].$$

This equation was repeated for each of the 24-month intervals.

Estimating the Cohort at Risk for Rehospitalization. Mean length of stay, cohort at risk for rehospitalization, and distribution of admissions according to institution were obtained from the NIMH C/PSS, which was conducted via a complex, two-stage, stratified design. Mental health organizations were first sampled, and then discharged patients were selected at each sampled organization. The organizations included five types of specialized inpatient mental health settings: State and county mental hospitals (State mental hospitals), non-Federal general hospitals with separate psychiatric service(s) (general hospitals), private psychiatric hospitals, Veterans Affairs medical centers (VAMCs), and multiservice mental health organizations (MMHOs). These last organizations provide services that have two or more distinct program elements; therefore, MMHOs can include inpatient, outpatient, residential, or partial care services. Many community mental health centers were classified as MMHOs. To arrive at national estimates from survey data, NIMH weighted each survey patient and used these weights to extrapolate national estimates. Details of the survey design and weighting procedure are provided elsewhere (Sunshine et al. 1990).

Inpatient Costs From Relapse. Expenditure estimates were based on data from the 1986 Inventory of Mental Health Organizations and General Hospital Mental Health Services (IMHO/GHMHS) (Taube 1990). The IMHO/GHMHS was designed to collect information on all specialty mental health organizations in the United States. It includes questions on the types of services provided, staffing pattern, patient capacity, daily census, and expenditures from the various institutions. The IMHO/GHMHS provides estimates of the total psychiatric inpatient expenditures at State mental hospitals, general hospitals, private psychiatric hospitals, and VAMCs. However, it does not include many ancillary costs associated with the hospitalization of persons with schizophrenia, such as capital costs, insurance costs, and the costs of medications and doctors' services, which are billed separately. Because expenditures at MMHOs are not collected by program element (inpatient, outpatient, partial, and residential care), daily inpatient expenditures at State mental hospitals were used as a proxy for daily MMHO inpatient expenditures.

In the current report, information on total expenditures and average daily census was used to estimate total expenditures for a single inpatient day. These costs are just the basic costs and do not include the large number of ancillary costs associated with hospitalization. Daily inpatient expenditures were then multiplied by the number of relevant inpatient days to arrive at an estimate of annual inpatient treatment costs for each of the five inpatient treatment settings under study. The original data were in 1986 dollars. Since then, the costs of all medical services have markedly increased, so the final costs shown in the tables have been increased by 85 percent to reflect the increase in medical costs from 1986 to 1993 (U.S. Bureau of Labor Statistics 1994).

Cost Calculations. Costs of rehospitalization were estimated by multiplying the mean length of stay for index patients from that type of facility by the mean daily expenditures at that type of facility. The baseline inpatient cost is the average hospital cost of the baseline hospitalizations of the index cohort. The rehospitalization costs during maintenance treatment were estimated by applying the survival curve analyses to the index cohort to determine the expected number of rehospitalizations. Aggregate costs of these rehospitalizations were calculated by multiplying the number of expected readmissions by the average cost of the cohort's baseline admission using the following equation:

$$\text{Cost}_{\text{time}} = \frac{N \text{ relapse}_{\text{time}}}{N \text{ initial cohort}} \times \text{initial costs}_{1993 \text{ dollars}}$$

The real world survival curve was used to determine the expected total number of rehospitalizations, the optimal neuroleptic dose survival curve was used to calculate relapses owing to loss of medication efficacy, and the difference between the two yielded the number of relapses attributable

to medication noncompliance. For the cost-of-relapse estimate, the number of relapses was multiplied by the average cost of rehospitalization.

Results

Population at Risk and Baseline Hospitalization Costs. During 1986, there were an estimated 257,446 discharges from specialized U.S. inpatient mental health settings that met our study criteria. These discharges were unevenly distributed among the various types of inpatient facilities (table 1). More than two-thirds came from either general hospitals (42.9%) or State mental hospitals (28.8%), and the remainder came from VAMCs (14.1%), MMHOs (7.7%), and private psychiatric hospitals (6.5%). The average length of stay and average cost per hospitalization are also shown in table 1. The total inpatient cost for the index hospitalizations of the 1986 cohort was $2.3 billion (1993 dollars).

Relapse Rates After Discharge. Tables 2 and 3 show the studies for the optimal neuroleptic dose and medication noncompliant groups. The numbers of patients shown in the tables represent the subgroups for the particular analyses. The monthly optimal neuroleptic dose relapse rate (α) is 3.5 percent per month and the medication noncompliant rate (β) is 11.0 percent. Of note is that the relapse rates when the medications were discontinued by the patient appear considerably higher than those when the medications were withdrawn by the patient's clinician (8.4% per month; see table 4).

Medication Noncompliance Rates After Discharge. Table 5 shows the rates at which recently discharged relapsed schizophrenia patients stopped taking medication. The average of 7.6 percent per month (γ) was used to obtain the real world survival curve shown as the bottom curve in figure 1. As a comparison, the top curve in the figure represents the survival estimate for the "Best Case" relapse condition of 3.5 percent per month.

Rehospitalization Costs Attributable to Relapse. The real world survival curve shows that approximately 50 percent of the initial cohort were rehospitalized during their first postdischarge year (estimated relapse n = 126,792; 49.2% of initial cohort). By 2 years after discharge, just over 80 percent of the initial cohort will be rehospitalized (n = 208,274; 80.9%). Because the nonrelapsed cohort is smaller since the first year relapsers are no longer included, the absolute number of relapsers declines for the second postdischarge year. However, the relative odds of relapse increases from 49.2 percent during the first-year period to 65.3 percent during the second year, because many patients start the second year in the higher risk noncompliance group.

The optimal neuroleptic dose and real world curves show the estimated contributions of loss of efficacy and noncompliance to relapse. At the 1-year point, approximately 68 percent is owing to loss of neuroleptic efficacy and approximately 32 percent is owing to neuroleptic noncompliance. This ratio is not static because a significant proportion of the nonrelapsed cohort at the end of the first year are in the higher risk medication noncompliant group. During the

Table 1. Baseline hospital costs of the index sample, including type of inpatient facility and length of stay for 1986 hospitalization (1993 dollars)

Type of inpatient facility	Percentage of index cases	Mean length of stay (days)	Average hospital cost per patient ($)	Total cost ($ millions)
General	42.9	15.0	7,086	782.5
State	28.8	35.0	11,678	864.6
Veterans	14.1	24.4	8,785	318.3
MMHOs (CMHCs)[1]	7.7	18.9	6,347	125.3
Private	6.5	19.5	12,366	207.4
All facilities	100.0	22.6	9,252	2,298.1

Note.—MMHOs = multiservice mental health organizations; CMHCs = community mental health centers

[1]There is no separate category for CMHCs; however, most CMHCs are in this category.

Table 2. Monthly relapse rates for recently stabilized patients maintained on optimal doses of depot therapy

Author	Year	*n*	Followup (months)	Relapse rates (% per month)
Crawford and Forrest	1974	66	9.5	3.6
Del Guidice et al.	1975	30	16.0	4.9
Falloon et al.	1978	21	12.0	4.2
Hogarty et al.	1979	54	24.0	1.8
Knights et al.	1979	40	6.0	6.9
Schooler et al.	1980	75	12.0	3.5
Scottish Group	1988	11	12.0	0.8
Hogarty et al.	1991	21[1]	24.0	2.7
Average			15.1	3.5

[1]Includes a few patients on oral neuroleptic regimens, but most patients were on depot fluphenazine.

Table 3. Monthly relapse rates for stabilized schizophrenia patients who become noncompliant

Author	Year	*n*	Followup (months)	Relapse rates (% per month)
Hogarty and Goldberg	1973	49	6.0	14.6
Johnson[1]	1979	56	6.0	13.2
Serban[2]	1980	222	24.0	6.9
Gaebel and Pietzker	1985	18	12.0	10.1
Hogarty et al.[3]	1991	28	24.0	10.4
Average			12.0	11.0

[1]Noncompliance is implied but may have been with the assent of the psychiatrist
[2]The study did not clearly delineate compliance-associated relapse, but such relapse is implied by the authors.
[3]The initial sample were patients assigned to the control group.

second postdischarge year, the relative contribution of noncompliance to rehospitalization is about equal to that of loss of medication efficacy.

Table 6 shows the corresponding costs of rehospitalization. The cost related to neuroleptic nonresponse is approximately $1.2 billion, with $800 million for the first year and $400 million for the second year. The cost attributable to neuroleptic noncompliance is approximately $705 million, with $370 million for the first year and $335 million for the second year.

Discussion

Cost of Relapse. The United States spends roughly $2.3 billion each year on short-term inpatient services for multiple-episode schizophrenia patients. Using the real world survival analysis, we estimate that within 2 years after discharge, the first rehospitalization episodes for these patients will cost almost $2 billion in direct hospital expenditures. Approximately 63 percent of these expenditures will be from loss of medication response ($1.2 billion) and 37 percent from medication noncompliance ($705 million) (table 6). The relative contribution of loss of medication efficacy is greater in the first postdischarge year and that of noncompliance is greatest during the second year.

Use of Survival Curve Modeling. Previous research on costs of mental illness has employed static models. Cost estimates are generally derived from the summation of service expenses provided during a fixed time period. In practice, however, a patient population's risk of rehospitalization changes over time. We tried to measure the dynamic character of relapse and inpatient costs during maintenance-phase treatment by applying survival curve analysis to the prediction of rehospitalization. To our knowledge, this report represents the first time that survival analysis has been used in the field of mental health care finance. While clinically disturbing, it was reassuring to us that this model's estimate of a 1-year real world rehospitalization rate of 50 percent is in line with results from epidemiological studies (Caton 1982; Eaton et al. 1992*a*, 1992*b*). We believe that survival analysis has the potential to help mental health administrators and service planners estimate expenditures and allocate clinical resources in a more cost-efficient manner. An example of the potential usefulness is presented below.

Effects of Improving Drug Efficacy or Compliance. While it is obvious that improving either compliance rates or drug efficacy would help control the cost of relapse, the survival technique can be used to model how changes in these parameters can affect the

Table 4. Monthly relapse rates for recently relapsed or recently discharged but stabilized schizophrenia outpatients withdrawn from maintenance neuroleptics

Author	Year	*n*	Followup (months)	Relapse rates (% per month)
Gross and Reeves	1961	70	6.0	12.0
Troshinsky et al.	1962	19	12.0	8.0
Engelhardt et al.	1967	56	6.0	5.5
Hirsch et al.	1973	38	12.0	3.1
Hogarty and Goldberg	1973	173	10.0	11.9
Johnson	1979	71	24.0	4.9
Capstick	1980	59	23.7	6.5
Wistedt et al.	1983	16	6.0	15.1
Average			12.5	8.4

Table 5. Monthly noncompliance rates after discharge

Author	Year	*n*	Followup (months)	Noncompliance rates (% per month)
Parkes et al.	1962	53	12.0	5.5
Renton et al.	1963	124	12.0	5.0
Raskin and Dyson	1968	45	6.0	17.7
Serban and Thomas[1]	1974	516 (chronic)	24.0	6.5
Serban and Thomas[1]	1974	70 (acute)	24.0	5.3
Caton[2]	1982	119	12.0	13.8
Gaebel and Pietzker[3]	1985	64	12.0	5.4
Frank and Gunderson[4]	1990	72	18.0	5.4
Weiden et al.[5]	1991	72	24.0	5.4
Thomas et al.[6]	1992	384	6.0	8.5
Zygmunt and Weiden[7]	1992	115	12.0	6.3
Average			15.8	7.6

[1]Sample was divided into acute (e.g., first-episode) and chronic schizophrenia patients, with noncompliance rates reported separately. No specific criteria for noncompliance were used, but this was the focus of the study.

[2]Aftercare adherence was used as a proxy measure for medication compliance.

[3]Report is on patients discharged to a specialty schizophrenia clinic. No specific criteria for noncompliance were used; the authors assumed that all cases of medication cessation represented noncompliance.

[4]Patients were assigned to two types of psychotherapy; medication treatment was the clinician's choice. Results are reported as number of patients with at least one episode of "poor" compliance on a trichotomous (good/fair/poor) outcome measure. Time of start of followup ranges from 0 to 3 months after discharge.

[5]Quasi-prospective analysis of a depot specialty clinic cohort. Definition of noncompliance = ≥ 1 week of complete medication cessation. Some subjects were enrolled in a maintenance depot dosage protocol.

[6]Initially compliant sample followed by telephone interview.

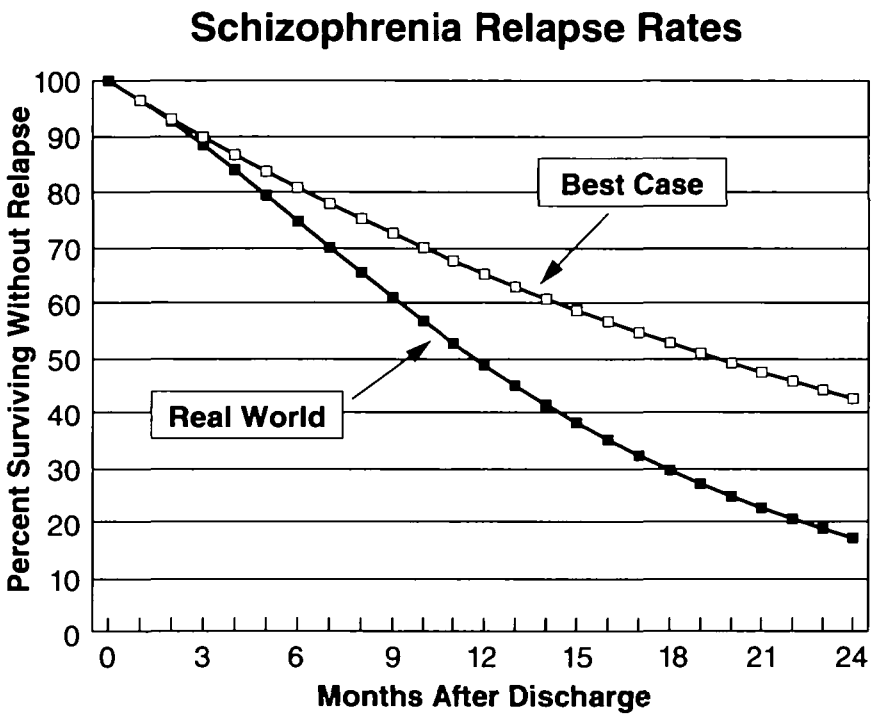
[7]Prospective noncompliance study of a separate sample from three hospital/treatment sites. Criteria for noncompliance = ≥ 1 week of complete medication cessation.

course and costs of relapse over time. For example, one might wish to compare the cost savings of hypothetical improvements in drug efficacy or compliance. According to this model, a hypothetical new medication that is 50 percent more efficacious would decrease the first-year postdischarge rehospitalization rates by 18 percent; conversely, improving compliance by 50 percent would decrease 1-year rehospitalization rates by 12 percent. A hypothetical 50 percent improvement in *both* medication efficacy and medication compliance would decrease rehospitalization rates by 37 percent.

The actual numbers from these hypothetical scenarios are less important than the general point that comes out of this modeling. The bad news is that the recent development of more effective drugs to replace currently available neuroleptics cannot be the sole answer to the problem of relapse and rehospitalization in schizophrenia unless these drugs can also be linked with better outpatient compliance. The good news is that there should be synergistic benefits from simultaneously improving both medication compliance and medication efficacy.

Limitations. It is important to bear in mind several important qualifications. The analysis is restricted to direct hospital costs and does not address other direct costs associated with schizophrenia. Also, we limited the cohort selection criteria to reflect neuroleptic-responsive chronic schizophrenia patients discharged back to the community; we did not analyze either first-episode hospitalizations or neuroleptic-unresponsive long-term inpatients. Schizophreniform or first-break patients might have

Figure 1. Survival analysis of optimal neuroleptic dose and real world rehospitalization risk for multiepisode neuroleptic-responsive schizophrenia patients



This survival analysis assumes a constant optimal neuroleptic dose relapse rate of 3.5 percent per month, a constant medication noncompliance rate of 7.6 percent per month, and a constant medication noncompliant relapse rate of 11 percent per month See text for further discussion of modeling assumptions.

very different relapse or compliance profiles from the estimates used here, which were derived predominantly from multiple-episode patient samples. Also, we excluded from relapse rate analysis the potential benefits that comprehensive outpatient programs such as the assertive community treatment model (Stein and Test 1980) have on reducing relapse rates. This omission will underestimate the efficacy of neuroleptics when combined with intensive rehabilitation. However, an equalizing force may be that the assumptions for the optimal neuroleptic dose group do not represent actual psychopharmacologic practice (Kissling 1994). Finally, this study did not consider the possible impact on compliance or relapse rates that might occur from maintenance treatment with atypical antipsychotics (clozapine or risperidone).

Our estimates of the cohort at risk are subject to several errors; these include the inaccuracy of discharge diagnoses, the overcounting of patients who were rehospitalized more than once in the 1986 calendar year, and the failure to include in the cohort schizophrenia outpatients who relapsed but were not rehospitalized during 1986. The relapse rate estimates went only as far as the first relapse; costs of multiple rehospitalizations were not calculated. Our biggest concern is that our results underestimate the impact of treatment dropout occurring right after discharge. We have already discussed problems in fitting the time data into a uniform monthly rate model; indeed, there is a tendency for the shorter followup studies to show higher relapse or noncompliance rates.

The proportion of relapsing outpatients who are subsequently hospitalized may vary with treatment setting, resource availability, and a range of other factors related to health care seeking and access that may have changed between 1986 and today. Because acute, short-stay patients are more expensive per diem, using average inpatient costs for settings that also serve chronic long-stay inpatients (e.g., the State hospitals) probably underestimates the true readmission cost. Finally, our model assumes

Table 6. Estimated hospital costs from maintenance phase relapse in the United States: Effects of loss of medication efficacy and medication noncompliance (millions 1993 dollars)

	Year 1 (%)	Year 2 (%)	Combined (%)
Loss of efficacy costs	$ 799.7 (68.4)	$399.9 (54.4)	$1,199.6 (62.9)
Noncompliance costs	370.0 (31.6)	335.1 (45.6)	705.1 (37.1)
Total cost	1,169.7	735.0	1,904.7

that the length of inpatient stay has not changed in the years between 1986 and 1993. In fact, length of stay is decreasing in some types of facilities while increasing in others (Salit and Marcos 1991). Another assumption is that discharged patients are compliant with their initial referrals with outpatient care. However, high rates of dropout even before the initial outpatient visit have been reported from a variety of treatment settings (Nicholson 1994).

Conclusion

We estimate that the total annual cost of short-term hospital admissions for relapsing schizophrenia patients approaches $2.3 billion. Then, within 2 years of discharge, the aggregate cost of readmission for such a cohort is approximately $2 billion. Loss of neuroleptic efficacy accounts for about 63 percent of rehospitalization costs and neuroleptic noncompliance for about 37 percent. The economic burden caused by loss of efficacy is higher during the first postdischarge year, whereas the burden from noncompliance is higher during the second year. Further modeling shows that a hypothetical improvement in either medication efficacy or medication compliance is limited by the continued presence of the other problem. Improving *both* medication efficacy and medication compliance, however, would be synergistic. Our findings underscore the economic significance of loss of efficacy to neuroleptic treatment and the impact noncompliance as a further confounding factor limiting the "real world" effectiveness of maintenance treatment. Cost savings during maintenance treatment can be realized from the development of *either* more effective pharmacologic treatments *or* more effective clinical strategies to manage neuroleptic noncompliance. Improving both will have synergistic effects on relapse rates and their ensuing hospital costs.

References

Capstick, N. Long-term fluphenazine decanoate maintenance dosage requirements of chronic schizophrenic patients. *Acta Psychiatrica Scandinavica*, 61:256–262, 1980.

Caton, C.L.M. Effect of length of inpatient treatment for chronic schizophrenia. *American Journal of Psychiatry*, 139:856–861, 1982.

Crawford, R., and Forrest, A. Controlled trial of depot fluphenazine in out-patient schizophrenics. *British Journal of Psychiatry*, 124:385–391, 1974.

Curson, D.A.; Barnes, T.R.; Bamber, R.W.; Platt, S.D.; Hirsch, S.R.; and Duffy, J.C. Long-term depot maintenance of chronic schizophrenic outpatients: The 7-year follow-up of the Medical Research Council fluphenazine placebo trial: III. Relapse postponement or relapse prevention? The implications for long-term outcome. *British Journal of Psychiatry*, 146:474–480, 1985.

Davis, J.M. Comparative doses and costs of antipsychotic medication. *Archives of General Psychiatry*, 33:858–861, 1976.

Davis, J.M.; Dysken, M.W.; Haberman, S.J.; Javaid, J.I.; Chang, S.S.; and Killian, G.A. Use of survival curves in analysis of antipsychotic relapse. *Advanced Biochemical Psychopharmacology*, 24:471–481, 1980.

Del Guidice, J.; Clark, W.G.; and Gocka, E.F. Prevention of recidivism of schizophrenics treated with fluphenazine enanthate. *Psychosomatics*, 16:32–36, 1975.

Eaton, W.W.; Bilker, W.; Haro, J.M.; Herrman, H.; Mortensen, P.B.; Freeman, H.; and Burgess, P. Long-term course of hospitalization for schizophrenia: Part II. Change with passage of time. *Schizophrenia Bulletin*, 18(2):229–241, 1992*a*.

Eaton, W.W.; Mortensen, P.B.; Herrman, H.; Freeman, H.; Bilker, W.; Burgess, P.; and Wooff, K. Long-term course of hospitalization for schizophrenia: Part I. Risk for rehospitalization. *Schizophrenia Bulletin*, 18(2):217–228, 1992*b*.

Engelhardt, D.M.; Rosen, B.; Freedman, N.; and Margolis, R. Phenothiazines in the prevention of psychiatric hospitalization. *Archives of General Psychiatry*, 16:98–101, 1967.

Falloon, I.R.; Marshall, G.N.; Boyd, J.L.; Razani, J.; and Wood-Siverio, C. Relapse in schizophrenia: A review of the concept and its definitions. *Psychological Medicine*, 13:469–477, 1983.

Falloon, I.R.; Watt, D.C.; and Shepherd, M. A comparative control trial of pimozide and fluphenazine decanoate in the continuation therapy of schizophrenia. *Psychological Medicine*, 8:59–70, 1978.

Frank, A.F., and Gunderson, J.G. The role of the therapeutic alliance in the treatment of schizophrenia. *Archives of General Psychiatry*, 47:228–235, 1990.

Gaebel, W., and Pietzker, A. Multidimensional study of the outcome of schizophrenic patients 1 year after discharge: Predictors and influence of neuroleptic treatment. *European Archives of Psychiatry and Neurological Sciences*, 235:45–52, 1985.

Gross, M., and Reeves, W.P. Relapse after withdrawal of ataractic drugs. In: Greenblatt, D., ed. *Mental Patients in Transition*. Spring-

field, IL: Charles C Thomas, 1961. pp. 313–321.

Gunderson, J.G., and Mosher, L.R. The cost of schizophrenia. *American Journal of Psychiatry,* 132:901–906, 1975.

Hirsch, S.; Giand, R.; Rohde, P.D.; Stevens, B.C.; and Wing, J.K. Outpatient maintenance of chronic schizophrenic patients with long-acting fluphenazine: Double-blind placebo trial. *British Medical Journal,* I:633–637, 1973.

Hogarty, G.E.; Anderson, C.; Reiss, D.; Kornblith, S.J.; Greenwald, D.P.; Ulrich, R.F.; and Carter, M. Family psychoeducation, social skills training, and maintenance chemotherapy in the aftercare treatment of schizophrenia: II. Two-year effects of a controlled study on relapse and adjustment. *Archives of General Psychiatry,* 48:340–347, 1991.

Hogarty, G.E., and Goldberg, S. Drug and sociotherapy in the aftercare of schizophrenic patients. *Archives of General Psychiatry,* 28:54–64, 1973.

Hogarty, G.E.; Schooler, N.R.; Ulrich, R.F.; Mussare, F.; Ferro, P.; and Herron, E. Fluphenazine and social therapy in the aftercare of schizophrenic patients: Relapse analysis of a two-year controlled study of fluphenazine decanoate and fluphenazine hydrochloride. *Archives of General Psychiatry,* 36:1283–1294, 1979.

Hogarty, G.E., and Ulrich, R.F. Temporal effects of drug and placebo in delaying relapse in schizophrenic outpatients. *Archives of General Psychiatry,* 34:297–301, 1977.

Johnson, D.A.W. Further observations on the duration of depot neuroleptic maintenance therapy in schizophrenia. *British Journal of Psychiatry,* 135:524–530, 1979.

Kissling, W. Compliance, quality assurance, and standards for relapse prevention in schizophrenia. *Acta Psychiatrica Scandinavica,* 89(Suppl. 382):16–24, 1994.

Knights, A.; Okasha, M.S.; Salih, M.A.; and Hirsch, S.R. Depressive and extrapyramidal symptoms and clinical effects: A trial of fluphenazine versus flupenthixol in maintenance of schizophrenic outpatients. *British Journal of Psychiatry,* 135:515–523, 1979.

Manderscheid, R.W., and Sonnenschein, M.A., eds. *Mental Health, United States, 1990.* Rockville, MD: National Institute of Mental Health, DHHS Publication No. (ADM) 90-1708, 1990.

McGuire, T.G. Measuring the economic costs of schizophrenia. *Schizophrenia Bulletin,* 17(3):375–388, 1991.

Nicholson, I.R. Factors involved in failure to keep initial appointments with mental health professionals. *Hospital and Community Psychiatry,* 45:276–278, 1994.

Parkes, C.M.; Brown, G.W.; and Monck, E.M. The general practitioner and the schizophrenic patient. *British Medical Journal,* 1:972–976, 1962.

Raskin, M., and Dyson, W.L. Treatment problems leading to readmission of schizophrenic patients. *Archives of General Psychiatry,* 19:356–360, 1968.

Renton, C.A.; Affleck, J.W.; Carstairs, G.M.; and Forrest, A.D. A follow-up of schizophrenic patients in Edinburgh. *Acta Psychiatrica Scandinavica,* 39:548–581, 1963.

Rice, D.R.; Kelman, S.; Miller, L.S.; and Dunmeyer, S. *The Economic Costs of Alcohol and Drug Abuse and Mental Illness.* Rockville, MD: Alcohol, Drug Abuse, and Mental Health Administration, (ADM) 90-1694, 1990.

Salit, S.A., and Marcos, L.R. Have general hospitals become chronic care institutions for the severely mentally ill? *American Journal of Psychiatry,* 148:892–897, 1991.

Schooler, N.R.; Levine, J.; Severe, J.B.; Brauzer, B.; DiMascio, A.; Klerman, G.; and Tuason, V.B. Prevention of relapse in schizophrenia: An evaluation of fluphenazine decanoate. *Archives of General Psychiatry,* 37:16–24, 1980.

Scottish Schizophrenia Research Group. The Scottish first episode schizophrenia study: V. One-year follow-up. *British Journal of Psychiatry,* 152:470–476, 1988.

Serban, G. Adjustment of schizophrenics in the community. In: Serban, G., ed. *Adjustment of Schizophrenics in the Community.* New York, NY: Spectrum Publications, 1980. pp. 205–233.

Serban, G., and Thomas, A. Attitudes and behaviors of acute and chronic schizophrenic patients regarding ambulatory treatment. *American Journal of Psychiatry,* 136:991–995, 1974.

Stein, L., and Test, M.A. Alternative to mental hospital treatment: I. Conceptual model, treatment program, and clinical evaluations. *Archives of General Psychiatry,* 37:392–397, 1980.

Sunshine, J.H.; Witkin, M.J.; Atay, J.E.; Fell, A.S.; and Manderscheid, R.W. *State and County Mental Hospitals, United States and Each State, 1986.* Rockville, MD: National Institute of Mental Health, DHHS Publication No. (ADM) 90-1706, 1990.

Taube, C.A. Funding and expenditures for mental illness. In: Manderscheid, R.W., and Sonnenschein,

M.A., eds. *Mental Health, United States, 1990.* Rockville, MD: National Institute of Mental Health, DHHS Publication No. (ADM) 90–1708, 1990. p. 223.

Thomas, B.H.; Ernst, C.; and Ernst, K. Wie erricht man compliance? Zur nachbehandlung psychischkranker nach dem klinikaustritt. *Nervenarzt,* 63:442–443, 1992.

Troshinsky, C.H.; Aaronson, H.G.; and Stone, R.K. Maintenance phenothiazines in aftercare of schizophrenic patients. *Pennsylvania Psychiatric Quarterly,* 2:11–15, 1962.

U.S. Bureau of Labor Statistics. *Consumer Price Index, Detailed Report.* Washington, DC: The Bureau, 1994.

Weiden, P.J.; Dixon, L.; Frances, A.; Appelbaum, P.; Haas, G.; and Rapkin, B. Neuroleptic noncompliance in schizophrenia. In: Tamminga, C.A., and Schulz, S.C., eds. *Advances in Neuropsychiatry and Psychopharmacology: Schizophrenia Research.* Vol. 1. New York, NY: Raven Press, 1991. pp. 285–296.

Wistedt, B.; Wiles, D.; and Jorgensen, A. A depot neuroleptic withdrawal study: Neurologic effects. *Psychopharmacology,* 80:101–105, 1983.

Wyatt, R.J., and Clark, K.P. Calculating the cost of schizophrenia. *Psychiatric Annals,* 17:589–591, 1987.

Wyatt, R.J.; de Saint Ghislain, I.; Leary, M.C.; and Taylor, E. An economic evaluation of schizophrenia—1991. *Journal of Social and Psychiatric Epidemiology,* in press.

Zygmunt, A., and Weiden, P.J. "Predictors of Noncompliance in Schizophrenia." Presented at the Annual Meeting of the American Psychiatric Association, Washington, DC, May 1992.

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