Sustained Remission in Drug-Free Schizophrenic Patients

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The inability to determine which schizophrenic patients do not require maintenance medication is a significant gap in current knowledge. This report describes 23 largely chronic DSM-III *schizophrenic patients who, after a period of inpatient treatment, sustained good outcome without maintenance antipsychotic medication over an average of 15 years. Retrospective study of these patients revealed that their distinguishing characteristics at admission included better premorbid social and occupational adjustment, higher levels of accrued psychosocial competence and acquired skills, fewer hebephrenic traits, and the preservation of affect (depressed mood). Hence, even within a largely chronic patient sample, classic predictors of good outcome may also be useful in predicting sustained remission without medication.*

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In view of the risks associated with long-term neuroleptics, our inability to determine which schizophrenic patients do not require maintenance medication constitutes a significant gap in current knowledge (1). A review of 29 controlled studies (2) demonstrates the powerful prophylactic effects of antipsychotic drugs but also documents the existence of a substantial, nonrelapsing, placebo subgroup over periods of observation ranging from 3 to 39 months. The most complete study (3–5) suggests that fully 20% of placebo-treated patients have not relapsed after 2 years. To our knowledge, neuroleptic maintenance has not been studied over longer periods, but it is clear that not all schizophrenic patients require continuous antipsychotic support (6, 7).

Although outcome prediction in schizophrenia per se has often been studied (8–10), specific efforts to characterize patients at low risk for relapse without medication have yielded conflicting results. Prien et al. (11) found that the phenothiazine dose at which patients had a therapeutic response predicted relapse after medication withdrawal. Patients receiving low maintenance doses were least likely to relapse. Two retrospective studies (12, 13) found that patients with acute illness—characterized as nonschizoid and nonparanoid, with good premorbid histories—who improved with placebo treatment had fewer rehospitalizations and better overall functioning at follow-up. In a study of chronic schizophrenic outpatients evaluated with the Hospitalization Proneness Scale, Rosen et al. (14, 15) found that among low-competence patients, phenothiazines reduced the occurrence of hospitalization, but among the high-competence group, phenothiazines were not distinguishable from placebo.

Leff and Wing (16) reported a relatively low (27%) 1-year relapse rate among placebo-treated, good prognosis patients in a double-blind study. They suggested that good prognosis patients (i.e., first episode, good premorbid personality, and short duration of illness) may not need maintenance medication. Kane et al. (17), however, noted that Leff and Wing (16) did not use a comparison group of good prognosis patients receiving phenothiazines. Kane et al. (17) studied 28 patients after remission from an acute first episode of schizophrenia; in the first year no drug-treated patient, but 41% of placebo-treated patients, relapsed. Similarly, among chronic schizophrenic outpatients, Goldberg et al. (18) found that those with good prognostic signs benefited most from neuroleptic prophylaxis over 2 years.

A study of the long-term course and outcome of patients discharged from Chestnut Lodge between 1950 and 1975 allowed the identification of a subgroup of schizophrenic patients who sustained good outcomes, without neuroleptics, over an average of 15 years. This report details the extent to which these patients could be identified retrospectively on the basis of demographic, premorbid, and clinical characteristics at admission.

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METHOD

A detailed methodologic outline of the Chestnut Lodge follow-up study has been presented elsewhere (19, 20). Included were all patients discharged from the hospital between 1950 and 1975 and a smaller cohort of nondischarged inpatients from a comparable period of time.

This report is concerned with two realms of independently collected data: baseline diagnostic/predictor and outcome. For baseline assessment, medical records were transposed and summarized onto a 25-page document called the Chart Abstract (blank forms available on request). Each patient was rated on a broad range of demographic and predictor variables, diagnostic sign and symptom variables, and several sets of diagnostic criteria, including *DSM-III*. Interrater reliabilities have been reported elsewhere (19).

Outcome data were collected an average of 15 years after discharge (range=2–32 years) through interviews with subjects and/or significant others by a member of the research team who was blind to the patient's baseline data. The information gathered was sufficient to rate multidimensional and global outcome with adequate reliability (20).

Minimal criteria for assigning follow-up patients to the drug-free, good outcome group included 1) clinical global outcome score of moderate or better, 2) never rehospitalized, and 3) no psychotropic medication use during the follow-up period. Twenty-three (14%) of 163 patients with an index diagnosis of schizophrenia met these criteria.

Overall, drug-free patients with good outcomes proved to be excellent informants and were among the highest functioning individuals in the study. They were employed for 80% of the follow-up period, and 70% (N=16) were married. Sixty-three percent (12 of 19) had attended college after discharge and 31% (six of 19) had obtained a degree. They spent an average of 2 years in psychosocially oriented outpatient treatment without the use of medications after index discharge. In most instances this treatment consisted of individual therapy with the psychiatrists who had treated them as inpatients. After this, most patients eschewed *any* further psychiatric assistance; at follow-up only 13% (N=3) of these patients were currently in treatment, compared to 74% (N=104) of the remaining schizophrenic patients.

Potential predictors resided in a set of baseline variables traversing sociodemographic and family characteristics, historical items, premorbid functioning, and features of manifest illness (19, 20). Discriminating characteristics were identified by comparing drug-free patients with good outcomes to all other schizophrenic patients across these baseline dimensions by using chi-square analysis for categorical variables and t tests for continuous variables. The predictive power of a set of discriminating characteristics was then evaluated by using multiple regression and discriminant function analyses. Finally, the relationship between prognostic status and medication/outcome groups was explored.

TABLE 1. Significant Differences in Premorbid Characteristics Between 23 Drug-Free Schizophrenic Patients With Good Outcomes and 140 Other Schizophrenic Patients Followed Up

Variable[a]	Drug-Free Patients With Good Outcomes		Other Schizophrenic Patients		t	df	p
	Mean	SD	Mean	SD			
Asociality in latency (0=best; 18=worst)	6.5	4.0	8.7	4.8	2.19	33	.04
Acquisition of skills (4=best; 0=worst)	3.0	0.9	2.2	1.2	−3.81	35	.001
Quality of premorbid work (4=very competent; 0=incompetent)	2.9	0.8	2.4	1.3	2.39	41	.02
Heterosexual functioning (4=best; 0=worst)	2.4	1.2	1.9	1.3	−1.94	145	.05

[a]The percentages of the two groups that showed instability at work or school were 4% and 26%, respectively ($\chi^2=3.99$, df=1, p=.05).

RESULTS

Ten percent of the male (N=8 of 83) and 19% of the female (N=15 of 80) schizophrenic patients met the criteria for the drug-free, good outcome group. At admission, these 23 patients were comparable to the remaining schizophrenic cohort in age, marital status, and family socioeconomic condition. The mean±SD age for all subjects was 28±8.1 years, 25% (N=40) were married, and most were upper-middle class (mean±SD level=1.6±0.93; Hollingshead-Redlich). Fathers of the drug-free patients with good outcomes, however, had attained a significantly higher level of education than fathers of the remaining patients (mean±SD level=1.6±.77 versus 2.4±1.6; Hollingshead-Redlich; t=2.8, df=31, p<.009).

Significant differences in premorbid functioning are summarized in table 1. Before the onset of illness, drug-free patients with good outcomes demonstrated better functioning across a range of measures including social relations in latency, heterosexual relations, quality and stability of premorbid work functioning, and accrued psychosocial competence as reflected by acquisition of skills and interests.

Among the schizophrenic patients studied, comparison groups did not differ in age at onset (mean±SD=19.3±7.2 years), age at first hospitalization (23.3±6.5 years), months of prior outpatient treatment (17±23.4), or number of previous hospitalizations (3.1±2.2). By index admission, patients in both groups were

severely and chronically ill, although drug-free patients with good outcomes had spent a significantly shorter period of time hospitalized (10.9±11.7 versus 29.8±38.4 months; $t=4.62$, $df=114$, $p<.0001$).

At admission, drug-free patients with good outcomes were more likely to manifest depressed mood (48% [11 of 23] versus 24% [32 of 133]; $\chi^2=4.42$, $df=1$, $p<.04$) and derealization (39% [7 of 18] versus 14% [18 of 127]; $\chi^2=5.12$, $df=1$, $p<.02$). Although schizophrenic subtypes were not assessed, drug-free patients with good outcomes had significantly lower Elgin 10 scores (21), which measure the frequency and severity of hebephrenic-like symptoms (18.7±4.6 versus 22.4±7.4; $t=2.93$, $df=38$, $p<.006$). At index admission, drug-free patients with good outcomes had been continuously psychotic for a shorter interval as rated on the Elgin duration of psychosis subscale (3.9±2.2 versus 5.1±2.2; $t=2.34$, $df=160$, $p<.02$; average of 10 months to 1 year versus 1–2 years). In addition, they scored lower on a 7-point scale of admission global psychopathology (5.2±0.4 versus 5.5±0.6; $t=2.99$, $df=39$, $p<.005$).

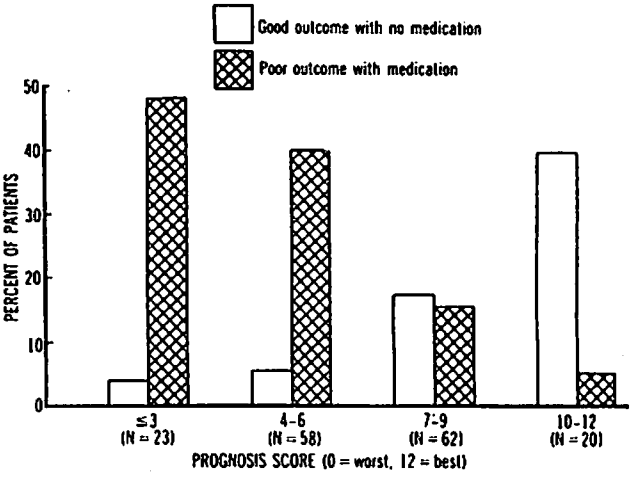
Length of hospitalization was similar in the drug-free patients with good outcomes and the comparison cohort (44±42 versus 49±49 months; n.s.). Drug-free patients with good outcomes, however, were significantly *more* likely to be discharged against medical advice (56% [9 of 16] versus 23% [22 of 97]) and were less likely to be transferred to another institution (19% [3 of 16] versus 57% [55 of 97]; $\chi^2=9.62$, $df=2$, $p<.008$).

Among baseline variables associated with the drug-free group with good outcomes at a trend level, stepwise multiple regression indicated that, independent of all other variables, premorbid acquisition of skills and interests was the best single predictor. Although the entire multiple regression set was highly statistically significant, its predictive power was relatively modest, accounting for only about one-quarter of the outcome variance (multiple $R=.48$, $R^2=.23$, $p<.0001$). Stepwise linear discriminant function analysis correctly classified about three-quarters of the patients possessing all discriminating characteristics into the drug-free group with good outcomes (sensitivity).

A prognostic scale for chronic schizophrenia was constructed that conceptualizes prognosis as a dynamic interplay between an individual's highest level of adaptive occupational and social functioning and the "invasiveness" of his or her axis I disorder as estimated by family history of schizophrenia, preservation of affect in psychopathology (depressed mood), and erosion of reality testing (psychotic assaultiveness) (10, 22). Scores ranged from 12 (excellent premorbid social and work functioning, affect preserved, and absence of family history and assaultiveness) to 0 (poor premorbid social and work functioning, absence of affect, positive family history, and assaultiveness).

Figure 1 shows the proportion of drug-free patients with good outcomes in each of four prognostic intervals. Shown for comparison is the proportion of schizophrenic patients at each prognostic interval who demonstrated poor outcome (global scores of 0 or 1) in spite of continuous maintenance neuroleptic treatment over the entire follow-up period. Forty percent of the patients with the best prognosis sustained remission over the long term without medications. This proportion decreased progressively down the prognostic ladder. On the other hand, the fact that few good prognosis but many poor prognosis patients did poorly while using medication may help explain contradictory findings from prospective studies with prognostically mixed patient samples.

FIGURE 1. Percent of Two Groups of Schizophrenic Patients at Various Prognostic Levels[a]



[a]The number of patients at each prognostic level is as follows: score of 3 or less, one good outcome patient with no medication and 11 poor outcome patients with medication; score of 4–6, three and 23 patients, respectively; score of 7–9, 11 and 10 patients, respectively; and score of 10–12, eight patients and one patient, respectively.

DISCUSSION

The patients we studied were treated and discharged during an era when institutional ideology discouraged the use of medication. Most drug-free patients with good outcomes (78%, N=18) were not taking neuroleptics at the time of admission, and those who were had phenothiazines discontinued during their hospitalization. By today's standards, far fewer patients would likely be drug free. Nevertheless, the data presented here demonstrate that over a prolonged postdischarge period, a definite proportion of *DSM-III* schizophrenic patients sustained good outcome without medication. Furthermore, since drug-free patients with good outcomes did not need and/or were prone to avoid further psychiatric treatment, clinicians and researchers may have underestimated their numbers.

Studied retrospectively, our patients were distinguished by certain demographic, premorbid, and clin-

ical features that, by and large, encompassed classic predictors of outcome in schizophrenia. Duration of illness per se was not predictive, however, since this was largely a chronic sample. Rather, what appeared important was the extent to which, at any time before becoming ill, the patient had acquired skills allowing him or her to embark on a meaningful life path.

Having found variables correlated with sustained remission without medication, we must urge caution in ascribing prospective predictive power to them. Multivariate analyses suggested that drug-free patients with good outcomes derived from the group of patients with good prognostic signs but underscored our limited ability to predict specifically which of these good prognosis patients would do well without medication. It appears that only a subgroup of good prognosis patients, currently unidentifiable, can sustain remission without medication. Taken with the observation that many poor prognosis patients remain continuously disabled despite medication, this hypothesis may explain conflicting reports in the literature. Patients who have done well without medication, when identified and characterized *retrospectively*, appear as good prognosis patients (12–14). Poor prognosis patients, as a group, tend to relapse with or without medication (23). Therefore, when a prognostically mixed group of schizophrenic patients are followed *prospectively* in a drug/placebo trial, the good prognosis patients will be found to benefit most from prophylactic medication (18). Thus, we reach the apparent contradiction that good prognosis schizophrenic patients are not only most likely to respond to neuroleptic medications but are also most likely to do well without them.

A second source of inconsistencies across studies is the likelihood that a large portion of outcome variance is explained by characteristics of the social environment to which the patient returns (24). Future studies assessing both patient and environmental prognostic characteristics such as expressed emotion will likely provide the most powerful discriminative models.

Currently we have no established guidelines for identifying which patients have a low risk of relapse without pharmacotherapy; the decision to attempt a trail off of medication remains largely based on clinical judgment. Data presented here and elsewhere, however, suggest that relative risk may best be assessed by the extent to which the skills and capacities of the patient measure up against the complexity and demands of his or her living situation.

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