Depression During the Longitudinal Course of Schizophrenia

by James R. Sands and Martin Harrow

Abstract

This prospective research investigated the occurrence and persistence of depression during the longitudinal course of schizophrenia. The research goals were to (1) compare depression in schizophrenia with that in schizoaffective and major depressive disorders, (2) assess whether some schizophrenia patients are vulnerable to depression, and (3) assess the relationship of depression to posthospital adjustment in schizophrenia. A total of 70 schizophrenia, 31 schizoaffective depressed, 17 psychotic unipolar major depressed, and 69 nonpsychotic unipolar major depressed patients were assessed during hospitalization and prospectively assessed for depression, psychosis, and posthospital functioning at 4.5- and 7.5-year followups. A large number (30% to 40%) of schizophrenia patients evidenced full depressive syndromes at each followup, including a subgroup of patients who evidenced repeated depression. Even when considering the influence of psychosis on outcome, depression in schizophrenia was associated with poor overall outcome, work impairment, lower activity, dissatisfaction, and suicidal tendencies. During the post-acute phase assessed, neither the rates nor the severity of depressive syndromes differentiated depression in schizophrenia from schizodepressive or major depressive disorders. However, the depressed schizophrenia patients showed poorer posthospital adjustment in terms of less employment, more rehospitalizations, and more psychosis than the patients with primary major depression. The high prevalence of depression in schizophrenia warrants its incorporation into theory about the disorder. A continuum of vulnerability to depression contributes to the heterogeneity of schizophrenia, with some schizophrenia patients being prone to depression even years after the acute phase. Depression in schizophrenia is one factor, in addition to psychosis, associated with poor outcome and requires specific attention to the treatment strategies by psychiatrists.

Key words: Schizoaffective disorder, major depression, psychosis, longitudinal study, suicide, employment, rehospitalization.

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Despite a long history of debate, the presence of depression in schizophrenia remains quite controversial (Bartels and Drake 1988; Siris 1991). Recently, "Postpsychotic Depressive Disorder of Schizophrenia" was listed in the *Diagnostic and Statistical Manual of Mental Disorders-4th ed.* (*DSM–IV;* American Psychiatric Association 1994) as a possible diagnostic category requiring further research. The current research used a longitudinal design to investigate the occurrence of syndromally defined depression in schizophrenia at two successive followup assessments: at 4.5 years and at 7.5 years after index hospitalization. The research focused on the frequency and severity of depression during the course of schizophrenia compared with that in schizoaffective disorder, depressed type, and primary major depression; whether schizophrenia patients with depression can be differentiated from patients with schizoaffective depression and primary major depression; and the role of depression in the posthospital adjustment of schizophrenia patients.

In the 1970s, empirical research documented that a substantial number of schizophrenia patients experienced significant depression (estimates ranged up to 60%, with modal estimates of about 25%) (McGlashan and Carpenter 1976). Modern diagnostic systems (Research Diagnostic Criteria [RDC], Spitzer et al. 1978; *DSM–III*, American Psychiatric Association 1980) adopted a "narrow" definition of schizophrenia, with specific exclusionary criteria that precluded a diagnosis of schizophrenia for patients with prominent depression. Yet despite this exclusionary criteria, depression has been reported in 6 percent to more than 50 percent of patients from "narrow"

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schizophrenia samples (Siris 1991). The 25-percent modal estimate of prevalence is still applicable in modern samples (Bartels and Drake 1988; Siris 1991; Siris 1994). Research using narrow criteria has found depression among both chronic schizophrenia patients (Roy et al. 1983; Drake and Cotton 1986; Lindenmayer et al. 1991) and first-admission patients (Koreen et al. 1993). Depression occurred during the inpatient or acute phase (Van Putten and May 1978; Lerner and Moscovich 1985; Drake and Cotton 1986; Koreen et al. 1993), during long-term hospitalization (Barnes et al. 1989), during outpatient treatment or the posthospital phase of illness (Hogarty and Munetz 1984; Lerner and Moscovich 1985; Martin et al. 1985; House et al. 1987; Green et al. 1990; Birchwood et al. 1993), and preceding psychotic relapse (Heinrichs and Carpenter 1985; Johnson 1988; Green et al. 1990; Siris et al. 1994). Our own longitudinal research has found that between 30 and 40 percent of narrowly diagnosed schizophrenia patients show depression at a 2.1-year followup (Summers et al. 1983) and a 4.5-year followup (Harrow et al. 1994).

Many fundamental questions about depression in schizophrenia remain unanswered. Does syndromally defined depression in schizophrenia persist over multiple years? Previous research on this issue, which mostly focuses on short-term followups, shows mixed results (Roy et al. 1983; Hogarty and Munetz 1984; Becker et al. 1985; Lerner and Moscovich 1985; Siris et al. 1986; House et al. 1987; Barnes et al. 1989). What are the implications of depression in schizophrenia for nosology (Bartels and Drake 1988; Crow 1990; Brockington et al. 1991; Taylor 1992), particularly regarding the status of schizoaffective disorder (Taylor et al. 1974; Procci 1976; Pope and Lipinski 1978; Abrams and Taylor 1981; Harrow and Grossman 1985; Williams and McGlashan 1987; Grossman et al. 1991)? Is depression in schizophrenia associated with other aspects of outcome? Early formulations of schizophrenia, based on broad diagnostic criteria, viewed depression in schizophrenia as a favorable prognostic sign (Vaillant 1964; Stephens et al. 1966; Garmezy 1974). However, recent formulations have questioned this view (Hirsch 1982; Hogarty and Munetz 1984; Becker et al. 1985; Bartels and Drake 1988; Hogarty et al. 1988).

The present investigation provides new data on the persistence or recurrence of depression during the course of schizophrenia. The data come from repeated assessments of syndromally defined depression—at 4.5 years and again at 7.5 years after hospital discharge. We also assessed patients with schizoaffective depression and primary major depression to provide cross-diagnostic comparisons of depression and functional adjustment. The current research also examined the relationship of depression in schizophrenia to posthospital adjustment, while accounting for the influence of psychosis. Our analyses target the following specific questions:

1. Is posthospital depression in schizophrenia as frequent and severe as it is in schizoaffective depression and primary major depression?
2. Are some schizophrenia patients particularly prone to depression during the longitudinal course of illness, whereas others are unlikely to be depressed?
3. Is depression in schizophrenia patients associated with further impairments in posthospital adjustment beyond those associated with psychosis?
4. Do depressed or depression-prone schizophrenia patients show more severe impairments than schizoaffective depressed patients and psychotic depressed patients?

Methods

The current research is part of the Chicago Followup Study, a large multiyear research program investigating the longitudinal course of schizophrenia, major affective disorders, and other psychotic disorders (Harrow et al. 1985; Harrow and Quinlan 1985; Grossman et al. 1986; Grinker and Harrow 1987; Carone et al. 1991; Sands and Harrow 1994, 1995, and in press; Harrow et al. 1995). Investigators originally recruited a sample of young, early-phase patients into the Chicago Followup Study during an index psychiatric admission. Patients were admitted into this study if (1) they were between 18 and 35 years of age at index hospitalization and (2) they did not evidence cerebral pathology, mental retardation, or significant nonpsychiatric medical complications. Investigators recruited from among consecutively admitted patients. Our analyses have shown no systematic difference with regard to diagnosis, sex, marital status, social class, or previous hospitalizations between patients who participate in the Chicago Followup Study and those who refuse to participate. Informed written consent from the patients was obtained at each assessment period.

Patient Sample. The current research focuses on 70 schizophrenia patients. We also included a comparison group of 117 nonschizophrenia patients who presented with full depressive syndromes during their index hospitalization: 31 schizoaffective, depressed subtype (schizodepressive) patients; 17 psychotic unipolar major depressed patients; and 69 nonpsychotic unipolar major depressed patients. Diagnoses were made at index hospitalization using the third edition of the RDC and structured interviews and inpatient information. By definition, none of the 70 patients diagnosed with schizophrenia met full RDC criteria for major depression, because the third

edition precludes a diagnosis of schizophrenia when a full affective syndrome is present during the active phase of illness. Patients whose index diagnosis included residual schizophrenia, schizoaffective manic subtype, and bipolar disorder were excluded from the present sample.

Our previous longitudinal research of the Chicago Followup Study patient sample documented support for the validity of the diagnoses at index hospitalization. We found that (1) despite clinical improvement by some patients during the followup period, those diagnosed with schizophrenia show significantly poorer overall outcomes (Harrow et al. 1985; Harrow and Quinlan 1985; Grinker and Harrow 1987), significantly more sustained psychosis and more thought disorder over time (Harrow and Quinlan 1985; Harrow et al. 1995), (2) that patients diagnosed with psychotic depression are extremely likely to have psychosis during subsequent depressive episodes (Sands and Harrow 1994), and (3) that patients diagnosed with schizoaffective disorder show significantly worse outcomes than unipolar depressive patients (Grossman et al. 1991). Over the years, the consistency of these results across successive followup assessments supports the validity of the index diagnoses. Complete data for a *DSM–IV* diagnosis were available for 68 of the 70 RDC-diagnosed schizophrenia patients. Of these, 58 patients (85%) also met *DSM–IV* criteria for schizophrenia, 8 (12%) met criteria for schizophreniform disorder, and 2 (3%) met criteria for another psychotic disorder.

At index hospitalization, the patients' mean age was 23 years; (standard deviation [SD] = 3.5). All were of average intellectual ability and most (75%) had no or only one prior hospitalization. The overall sample was 51 percent male and 49 percent female. Most of the schizophrenia patients were male (66%), compared with 35 percent of the psychotic depressed and 39 percent of the nonpsychotic depressed patients.

Data on posthospital functioning at the 7.5-year followup were available for slightly more than 80 percent of the original sample. Patients included in the current study did not differ from the attrition sample with respect to age, intellectual functioning, number of previous hospitalizations, or age at first break.

Followup Assessments. The Schedule for Affective Disorders and Schizophrenia (SADS; Endicott and Spitzer 1978) was administered to all patients at the 7.5-year followup to assess depressive symptoms, delusions, and hallucinations during the 12 months prior to followup. Complete SADS data were also obtained for a subgroup of 46 schizophrenia patients at a previous 4.5-year followup (Harrow et al. 1994). Patients' work and social functioning, rehospitalization, and medication were assessed using a semistructured interview. Most of the followup interviews were conducted at the research offices of a psychiatric hospital, although the followup assessments were not part of the patient's routine clinical care. A small percentage of the interviews were conducted at the patients' homes, residential facilities, or hospitals, depending on circumstances at the time of the followup.

The presence of a major depressive syndrome during the followup year was rated using RDC criteria based on the SADS assessments of depressive symptoms. Each patient was assigned to one of four categories (1) *no depression*—having no or only one depressive symptom but not depressed mood; (2) *few depressive symptoms*—having either depressed mood and one other depressive symptom or having two or three depressive symptoms but not depressed mood; (3) *subsyndromal depression*—having depressed mood and two or three other depressive symptoms (equivalent to RDC "Minor Depression"), or having at least four depressive symptoms but not depressed mood; or (4) *full depressive syndrome*—meeting RDC criteria for a major depressive episode during the followup year. For some analyses, the depression rating was dichotomized so that subsyndromal depression and full depressive syndrome (ratings 3 and 4) were considered depressed, and no or only a few symptoms (ratings 1 and 2) were considered not depressed.

To evaluate whether our depression assessment was differentiated from negative symptoms, we analyzed the relationship between ratings of depressive syndrome (see above) and ratings of patients' flat affect for a subsample of 41 of the schizophrenia patients. We used a method of behavioral rating described in previous research (Pogue-Geile and Harrow 1984, 1985). Our ratings were unrelated to negative symptoms or flat affect ($r_s = 0.08$, $n = 41$, $p = 0.60$).

Psychosis, defined as delusions or hallucinations, was rated using a 3-point system: (1) absent, (2) equivocal or weak, and (3) definite. For some analyses, this variable was dichotomized so that ratings for equivocal psychosis (rating 2) were combined with definite psychosis (rating 3). This system has been used successfully in previous research (Harrow et al. 1985; Harrow and Quinlan 1985; Grossman et al. 1986; Grinker and Harrow 1987; Sands and Harrow 1994, 1995, and in press; Harrow et al. 1995). Our ratings of psychosis do not include formal thought disorder.

Posthospital adjustment was rated using standardized scales, focusing on the followup year. Overall posthospital adjustment was rated using a scale that considered work and social functioning, rehospitalization, symptoms, and self-support (Levenstein et al. 1966). Interrater reliability on this scale was good (intraclass correlation of 0.92). For some analyses, we divided this 8-point scale

into three broad outcome categories: good, moderate, and poor. We used the Strauss-Carpenter outcome scales (Strauss and Carpenter 1972) to rate work functioning, social functioning, and rehospitalization. These scales have been used successfully in research on posthospital adjustment (Grossman et al. 1986; Grinker and Harrow 1987; Williams and McGlashan 1987; Westermeyer et al. 1991; Goldberg et al. 1995). Interrater reliabilities were 0.96, 0.89, and 0.94 for work functioning, social functioning, and rehospitalization, respectively.

Medications. Slightly more than half (51%) of the subjects were receiving pharmacological treatment at the 7.5-year followup. Because the current research uses a naturalistic followup design, patients were not randomly assigned to medication groups. Thus, treatment conditions were due to several factors, including clinical status and the choice of treating psychiatrists.

As might be expected, significantly more schizophrenia patients (63%) and schizodepressive patients (61%) were taking neuroleptics (alone or in conjunction with other medications) when compared with the nonpsychotic and psychotic major depression patients (13% and 12%, respectively) ($\chi^2 = 47.1$, degrees of freedom [*df*] = 3, $p \leq 0.001$). When considering the rates of neuroleptic use, it is important to recognize that the data were obtained within a naturalistic, longitudinal research design. Some of these schizophrenia patients were in remission during the followup period, and others were not taking medications for other reasons. In general we have found that medications, such as neuroleptics, were more likely to have been prescribed for patients with more severe or persistent psychopathology than for patients with milder symptoms or patients who were symptom free for an extended period.

Relatively few schizophrenia patients (7%) and schizodepressive patients (6%) were taking antidepressants when compared with the patients with major depression (15%) ($\chi^2 = 8.3$, $df = 3$, $p < 0.05$). Almost all of the antidepressants were tricyclics. Dosage of antidepressants was not randomly assigned, but was established by the patient's treating psychiatrist. Data on the use of mood stabilizers (lithium) were available for a subgroup of the schizophrenia patients, only two of whom were taking lithium during the followup year. Because so few schizophrenia and schizoaffective patients were taking antidepressants or lithium, meaningful estimates of the relationship between the use of these medications, depressive syndromes, or outcome for these patients were not possible.

Our preliminary analyses have suggested a complex interaction between depression, psychosis, and neuroleptic use (Harrow et al. 1995; Sands et al., in preparation). Data on anticholinergic medications were available for 42 of the 44 patients who were taking neuroleptics at the 7.5-year followup. Among the patients taking neuroleptics, we found no significant differences in depression between those who were and those who were not taking anticholinergic medications (Mann-Whitney $U = 166.0$, $p > 0.50$). Thus, it is unlikely that our depression ratings are due to patients experiencing akinesia or extrapyramidal side effects.

Statistical Analyses. The data are presented in cross-tabular form (see tables 1 through 5), with dependent measures consolidated for simplicity and subgroup percentages presented for each analysis. Unless otherwise specified, all statistical procedures use the full range of scores. We used nonparametric techniques, including Kruskal-Wallis *H*, Mann-Whitney *U*, and Spearman correlations, to analyze ordinal and categorical data and multivariate analysis of variance (MANOVA) was to assess overall effects of factors (e.g., diagnosis and psychosis) on multiple aspects of posthospital adjustment. Univariate analyses, including *T*-tests, one-way analysis of variances (ANOVAs), and two-way ANOVAs, were subsequently used, as appropriate, to assess the effects of factors on single measures of adjustment.

Results

How Prevalent Is Depression During the Course of Schizophrenia? Table 1 presents the frequency of RDC depressive syndromes during the year preceding the 7.5-year followup: A total of 25 (36%) of the schizophrenia patients showed a full RDC depressive syndrome during the 7.5-year followup, and 10 patients (14%) showed subsyndromal depression. Moreover, the levels of depression did not differ across the four diagnostic groups studied (Kruskal-Wallis $H = 0.88$, $df = 3$, $p > 0.50$). The same result was also obtained at the 4.5-year followup for the 119 patients who had full SADS data at that time period (Kruskal-Wallis $H = 1.55$, $df = 3$, $p > 0.50$). We found no significant diagnostic differences in the mean *severity* of depressive symptoms for the full sample ($F = 1.04$, $df = 3,183$, $p > 0.35$) and for the subgroup of 69 patients with full depressive syndromes during the followup year ($F = 0.69$, $df = 3,65$, $p > 0.50$). Neither did we find significant sex effects for depression among the schizophrenia patients at the 7.5-year followup.

The frequency of posthospital depression during the 7.5-year followup was essentially unchanged when we grouped patients according to *DSM–IV* criteria. Among the 58 patients with a *DSM–IV* diagnosis of schizophre-

Table 1. The occurrence of depressive syndromes among schizophrenia patients, schizodepressed patients, psychotic depressed patients, and nonpsychotic depressed patients during the 7.5-year followup

Diagnosis at index hospitalization	Depressive syndromes during the 7.5-year followup							
	No depression		Few depressive symptoms		Subsyndromal depression		Full RDC depressive syndrome	
	n	%	*n*	%	*n*	%	*n*	%
Schizophrenia ($n = 70$)	17	24	18	26	10	14	25	36
Schizodepressed ($n = 31$)	9	29	5	16	3	10	14	45
Psychotic depressed ($n = 17$)	5	29	2	12	4	23	6	35
Nonpsychotic depressed ($n = 69$)	25	36	10	14	10	14	24	35

Note.—RDC = Research Diagnostic Criteria (Spitzer et al. 1978); Kruskal-Wallis $H = 0.88$, $df = 3$, $p > 0.50$.

nia, 21 (36%) had a full depressive syndrome during the 7.5-year followup and 8 (14%) evidenced subsyndromal depression. Also, 15 (26%) of these *DSM–IV* schizophrenia patients showed a few depressive symptoms. Only 14 *DSM–IV* schizophrenia patients (24%) were free from depression throughout the 7.5-year followup. The eight patients who met *DSM–IV* criteria for schizophreniform disorder showed a rate of depression similar to those who met *DSM–IV* criteria for schizophrenia. Three of the patients (37%) with a *DSM–IV* diagnosis of schizophreniform had a full depressive syndrome during the followup year.

Table 2 presents the occurrence of depression over time among the subgroup of schizophrenia patients with SADS assessments at both the 4.5-year followup and the 7.5-year followup. Of these 46 patients, 21 (46%) evidenced a full depressive syndrome at one or both followups. Only 16 patients (35%) did not evidence depression at followup and, thus, showed a paradigmatic "nonaffective" course of illness. A Wilcoxon Matched Ranks Test indicated no significant change in prevalence of depression across the two followups, suggesting that, after the acute phase, the depression is a stable feature among groups of schizophrenia patients.

Are a Subgroup of Schizophrenia Patients Prone to Depression? The data presented in table 2 can be viewed with regard to whether some schizophrenia patients are particularly prone to persistent or recurrent depression. Of the 14 schizophrenia patients with full depressive syndromes during the 4.5-year followup, most (57%) showed full depressive syndromes again during the 7.5-year followup. By contrast, of the 11 schizophrenia patients with no depression during the 4.5-year followup, only 1 (9%) had a full depressive syndrome during the 7.5-year followup. The tendency toward recurrence (or resistance to recurrence) of depression in schizophrenia patients was reflected in a significant correlation ($r_s = 0.54$, $n = 46$, $p < 0.001$) of depression across followup assessments. These analyses suggest that a subgroup of

Table 2. Depressive syndromes during the 7.5-year followup as a function of depressive syndromes during 4.5-year followup among schizophrenia patients

Depressive syndromes during the 4.5-year followup	Depressive syndromes during the 7.5-year followup							
	No depression		Few depressive symptoms		Subsyndromal depression		Full RDC depressive syndrome	
	n	%	*n*	%	*n*	%	*n*	%
No depression ($n = 11$, 24%)	7	64	1	9	2	18	1	9
Few depressive symptoms ($n = 13$, 28%)	5	38	3	23	3	23	2	15
Subsyndromal depression ($n = 8$, 17%)	2	25	2	25	0	0	4	50
Full RDC depressive syndrome ($n = 14$, 30%)	0	0	2	14	4	29	8	57
Total ($n = 46$)	14	30	8	17	9	20	15	33

Note.—RDC = Research Diagnostic Criteria (Spitzer et al. 1978); Spearman Correlation: $r_s = 0.54$, $p < 0.0001$.

schizophrenia patients could be particularly prone to persistent or recurrent depression during the early posthospital years, whereas other schizophrenia patients are more resistant to depression.

Is Depression a Factor in the Posthospital Adjustment of Schizophrenia Patients? Table 3 presents data on the functional adjustment among schizophrenia patients grouped according to the presence of (1) depression (dichotomized) and (2) psychosis (dichotomized) during the 7.5-year followup. MANOVA indicated that both depression and psychosis were significant factors in these schizophrenia patients' outcome during the 7.5-year followup (Wilks Lambda = 0.800, $F = 3.10$, $df = 5,62$, $p = 0.02$ for depression, and Wilks Lambda = 0.708, $F = 5,10$, $df = 5,62$, $p = 0.001$ for psychosis). The subsequent two-way ANOVAs suggest that depression is not uniformly associated with outcome. Rather, it is associated with specific areas of functioning.

Depression was significantly associated with schizophrenia patients' employment ($F = 7.73$, $df = 1,66$, $p = 0.007$), as was psychosis ($F = 10.16$, $df = 1,66$, $p = 0.002$). Of the 28 patients with *both* psychosis and depression during the followup year, 68 percent were consistently unemployed. Of the 18 patients who were psychotic but *not* depressed, 33 percent were unemployed.

Given the high rates of unemployment in this group of schizophrenia patients, we assessed involvement in nonwork activities as an additional index of adaptive functioning. Depression was almost significantly associated with patients' overall activity level ($F = 3.73$, $df = 1,66$, $p < 0.06$), while psychosis had significant effect ($F = 11.46$, $df = 1,66$, $p = 0.001$). Patients with more severe psychopathology showed fewer activities, largely limited to sedentary activities at their place of residence (e.g., watching television). Depressed schizophrenia patients expressed less satisfaction with their nonwork activities ($F = 7.73$, $df = 1,66$, $p < 0.01$) and with their social func-

Table 3. The relationship of depression to outcome during the 7.5-year followup, controlling for psychosis among schizophrenia patients

	No psychosis at followup		Psychosis at followup		Two-way ANOVA significance of factors[1]	
Outcome measure	Not depressed ($n = 17$) %	Depressed ($n = 7$) %	Not depressed ($n = 18$) %	Depressed ($n = 28$) %	Depression	Psychosis
Employment						
Full time	47	29	6	11	$p = 0.007$	$p = 0.002$
Part time or some	47	14	61	21		
None	6	57	33	68		
Activity (nonwork) level						
Active	82	29	39	25	$p < 0.06$	$p = 0.001$
Marginal	12	71	33	28		
Minimal/none	6	0	28	46		
Social functioning						
Adequate	65	71	50	43	$p > 0.50$	$p = 0.006$
Restricted	35	29	22	32		
Impoverished	0	0	28	25		
Satisfaction (activity)						
Highly satisfied	23	0	28	11	$p < 0.01$	$p < 0.12$
Satisfied	53	29	50	61		
Dissatisfied	23	71	22	29		
Rehospitalization						
None	88	57	67	46	$p > 0.45$	$p < 0.13$
Less than 3 months	0	29	11	36		
3 months or more	12	14	22	18		
Suicidal ideation or behavior[2]						
None	100	71	74	50	$p < 0.04$	$p = 0.03$
Mild/moderate ideation	0	29	21	35		
Severe ideation/attempt	0	0	5	15		

Note.—Column percentages may not total 100 due to independent rounding; ANOVA = analysis of variance.

[1]Two-way ANOVA using a full range of scores on dependent measures.
[2]For this analysis, the presence of a depressive syndrome was calculated, excluding suicidal ideation or behavior. Psychotic and not depressed subgroup ($n = 19$), psychotic and depressed ($n = 26$). Not included in multivariate analysis of variance.

tioning ($F = 5.24$, $df = 1,66$, $p < 0.03$). Suicidal ideation and behavior were significantly related to both depression (recalculated without suicidal ideation as a criterion) ($F = 4.66$, $df = 1,65$, $p < 0.04$) and psychosis ($F = 4.93$, $df = 1,65$, $p = 0.03$). Depression was not significantly associated with either the occurrence of rehospitalization or its extent during the followup year, as measured by the Strauss-Carpenter scale.

To analyze depression's impact on adjustment in schizophrenia, we compared the 16 schizophrenia patients who were depressed during *both* followup years to the 16 schizophrenia patients who were *not* depressed during *either* followup year. The schizophrenia patients who were depressed during both followup years had significantly more psychotic symptoms (Mann-Whitney $U = 74.5$, $n = 32$, $p < 0.05$), worse overall outcome ($t = 3.10$, $df = 30$, $p = 0.004$), and lower employment ($t = 3.75$, $df = 30$, $p = 0.001$). They showed slight trends toward lower activity levels ($t = 1.64$, $df = 30$, $p = 0.11$) and toward more suicidal ideation ($t = 1.65$, $df = 30$, $p = 0.11$).

Do Schizophrenia Patients With Depression Show Worse Functional Adjustment Than Depressed Patients With Schizodepressive and Psychotic Depressive Disorder? The question of whether schizophrenia patients with depression can be distinguished from patients with schizodepressive disorder or psychotic depression was approached in two ways. First, we conducted cross-diagnostic comparisons of various measures of posthospital adjustment for the subgroup of patients who were depressed (with either subsyndromal depression or full depressive syndrome) during the 7.5-year followup (see table 4). Second, focusing on those patients with complete SADS data at *both* followups, we compared the 16 schizophrenia patients who were depressed during both the 4.5-year and the 7.5-year followups with a combined group of schizodepressed ($n = 8$) and psychotic depressed ($n = 5$) patients who were also depressed at both followups (see table 5).

In the first analyses, MANOVA results revealed that diagnosis was a significant factor in patients' outcome, even though the analysis included only patients who were depressed (Wilks Lambda = 0.597, $F = 3.33$, $df = 15,243$, $p < 0.001$). We found significant diagnostic differences in outcome on the scale of posthospital adjustment ($F = 8.32$, $df = 3,92$, $p = 0.001$). Only 9 percent of the depressed schizophrenia patients had good overall outcome. More of the depressed nonschizophrenia patients (although still only a minority) had a good outcome.

Additional one-way ANOVAs and post hoc analyses (Student Newman Keuls, $p \leq 0.05$) showed significant diagnostic effects in some specific outcome areas (see table 4). We observed diagnostic differences for employment: Most of the depressed schizophrenia patients (66%) were consistently unemployed during the followup year, as compared with substantially fewer of the primary major depressed patients (0% and 18%). The depressed schizophrenia patients also showed a lower ($p \leq 0.05$) nonwork activity level and more rehospitalization than the nonpsychotic major depressed patients. As expected, we saw significant diagnostic effects on level of psychosis (Kruskal-Wallis $H = 15.91$, $df = 3$, $p < 0.001$).

The second series of analyses investigated whether depression-prone schizophrenia patients (the subgroup with depression at two successive followups) differed from schizodepressive and psychotic depressive patients who also showed repeated depression (see table 5). The MANOVA indicated a near significant diagnostic effect on outcome measures (Wilks Lambda = 0.647, $F = 2.51$, $df = 5,23$, $p < 0.06$). However, on the single scale of overall outcome, the depression-prone schizophrenia patients had significantly poorer overall adjustment than the combined subgroup of schizodepressive and psychotic depressive patients ($t = 2.47$, $df = 27$, $p = 0.02$). The repeatedly depressed schizophrenia patients also showed significantly poorer work functioning ($t = 3.02$, $df = 27$, $p = 0.005$), even though relatively few patients from either subgroup had consistently maintained full-time employment. More of the depressed schizophrenia patients (63%) had been rehospitalized during the followup year when compared to the depressed schizodepressive and psychotic depressive patients ($\chi^2 = 9.15$, $df = 1$, Fishers Exact $p = 0.006$).

More than half (62%) of the depressed schizophrenia patients evidenced definite psychotic symptoms during the followup year, compared with 38 percent of the schizoaffective and psychotic patients with depression at both followups. However, in part due to the small number of patients, this was not statistically significant. It is important to note that, as shown in table 4, the depressed schizophrenia patients were different from the patients with index diagnoses of nonpsychotic depression on a number of outcome variables. Further, on other variables, the schizophrenia patients differed from both initially nonpsychotic and psychotic depressive patients.

Discussion

The current research investigated the prevalence and persistence of depression in schizophrenia, its relationship to clinical outcome, and the relationship of depression in schizophrenia to schizoaffective depression and primary major depression.

Table 4. Outcome among schizophrenia patients with depression during the 7.5-year followup compared with schizodepressed, psychotic depressed, and nonpsychotic depressed patients with depression during the 7.5-year followup

Outcome measure	Schizophrenia (Sz) (n = 35) %	Schizodepressed (SzD) (n = 17) %	Psychotic depressed (PD) (n = 10) %	Nonpsychotic depressed (NPD) (n = 34) %	One-way ANOVA[1] SNK comparisons[2]
Overall outcome[3]					
Good	9	24	20	42	F = 8.32 p = 0.001
Marginal	31	29	70	27	Sz < PD, NPD
Poor	60	47	10	31	SzD < NPD
Employment					
Full time	14	24	40	56	F = 11.71 p = 0.001
Part time or some	20	41	60	27	Sz, SzD < NPD
None	66	35	0	18	Sz < PD
Activity (nonwork) level					
Active	26	35	40	71	F = 4.86 p = 0.005
Marginal	37	47	50	18	Sz < NPD
Minimal/none	37	18	10	12	
Social functioning					
Adequate	49	59	40	56	F = 0.34 p = NS
Restricted	31	24	40	24	
Impoverished	20	18	20	21	
Satisfaction (activity)					
Highly satisfied	9	6	20	9	F = 1.17 p = NS
Satisfied	54	41	60	47	
Dissatisfied	37	53	20	44	
Rehospitalization					
None	49	76	90	73	F = 3.58 p < 0.02
Less than 3 months	40	24	10	27	Sz > NPD
3 months or more	11	0	0	0	
Suicidal ideation or behavior[3,4]					
None	53	47	50	59	F = 0.30 p = NS
Mild/moderate ideation	35	29	30	18	
Severe ideation/attempt	12	24	20	24	
Psychosis[3]					
None	20	29	50	68	K-W H[5] = 15.91 p < 0.001
Equivocal	23	24	10	18	
Definite	57	47	40	15	

Note.—Column percentages may not total 100 due to independent rounding; ANOVA = analysis of variance; MANOVA = multivariate analysis of variance; NS = not significant.

[1]ANOVAs calculated using a full range of scores on dependent measures; ANOVA have degrees of freedom [*df*] = 3,92.
[2]Student Newman Keuls (SNK) contrasts at $p \leq 0.05$.
[3]Variable not included in MANOVA.
[4]For this analysis, the rating for depressive syndrome excluded suicidal ideation or behavior.
[5]Kruskal-Wallis H (K-W H), df = 3.

Prevalence of Depression in Schizophrenia. Both cross-sectional and longitudinal analyses indicate that depression is a frequent concomitant of schizophrenia. At each followup, roughly one-third of schizophrenia patients evidenced full depressive syndromes. This finding is generally consistent with Siris's (1991, 1994) estimate of 25 percent and is similar to other reports assessing syndromally defined depression (Roy et al. 1983; Lerner and Moscovich 1985; Drake and Cotton 1986; Johnson 1988; Bermanzohn and Siris 1992; Harrow et al. 1994). Looked at from a longitudinal standpoint, nearly half of the schizophrenia patients experienced depression during one or both followups. These rates are much higher than the prevalence of major depression among the general population (Weissman et al. 1977; Boyd and Weissman 1981; American Psychiatric Association 1994).

Our repeated assessments of depression showed that post-acute phase depression is a stable longitudinal characteristic among groups of schizophrenia patients, given that its prevalence does not change appreciably over the

Table 5. Outcome among schizophrenia patients with recurrent or persistent depression across two followup assessments compared with schizodepressed and psychotic depressed patients with recurrent or persistent depression across two followup assessments

Outcome measure	Schizophrenia (n = 16) %	Psychotic depressed and schizodepressed (n = 13) %	T-test[1]	Significance
Overall outcome[2]				
Good	6	15	t = 2.47	p = 0.02
Marginal	25	54		
Poor	69	31		
Employment				
Full time	12	23	t = 3.02	p = 0.005
Part time or some	6	61		
None	81	15		
Activity (nonwork) level				
Adequate	19	46	t = 0.95	p > 0.25
Marginal	50	38		
Minimal/none	31	15		
Social functioning				
Adequate	50	54	t = 0.09	p > 0.25
Restricted	31	23		
Impoverished	19	23		
Satisfaction (activity)				
Highly satisfied	19	23	t = 0.91	p > 0.25
Satisfied	44	46		
Dissatisfied	37	31		
Rehospitalization				
None	37	92	t = 2.93	p = 0.007
Less than 3 months	37	8		
3 months or more	25	0		
Suicidal ideation or behavior[2,3]				
None	56	54	t = 0.69	p > 0.25
Mild/moderate ideation	31	23		
Severe ideation/attempt	12	23		
Psychosis[2]				
None	19	31	M-W U[4] = 79.0	p > 0.25
Mild/equivocal	19	31		
Definite	62	38		

Note.—Column percentages may not total 100 due to independent rounding.

[1] T-tests calculated using a full range of scores on dependent measures; degrees of freedom = 27.
[2] Variable not included in multivariate analysis of variance.
[3] For this analysis, the rating for depression excluded suicidal ideation or behavior.
[4] Mann-Whitney U (M-W U) test.

years. Moreover, only one-third (35%) of the schizophrenia patients had essentially *no* depression (i.e., neither subsyndromal depression nor full depressive syndrome) during *both* followup years. These data indicate that only a minority of schizophrenia patients have a paradigmatic "nonaffective" course of illness.

Distinguishing depression from negative symptoms and from extrapyramidal side effects (particularly akinesia) can be quite challenging and requires careful assessment (McGlashan 1982; Bartels and Drake 1988; Lindenmayer et al. 1991; Hogarty et al. 1995). Depression, akinesia, and negative symptoms share some clinical features, particularly vegetative symptoms. However, depression can be differentiated from akinesia and negative symptoms when mood symptoms, including sad or blue emotional states, negative self-esteem, guilt, and pessimism are considered. Our ratings of depression were based on RDC criteria, which included these depressive mood symptoms. It is unlikely that the full RDC depressive syndromes shown by the current group of schizophrenia patients were due to negative symptoms or extrapyramidal side effects (akinesia). However, it is pos-

sible that some of the depressed schizophrenia patients in our study were experiencing comorbid extrapyramidal side effects or negative symptoms.

The relationship between neuroleptics and depression has been particularly controversial (Van Putten and May 1978; Ananth and Ghadirian 1980; Galdi et al. 1981; Johnson 1981; Mandel et al. 1982; Becker 1983; Galdi 1983; Hogarty and Munetz 1984; Bartels and Drake 1988; Hogarty et al. 1988, 1995; Siris et al. 1988; Siris 1991). Experts report that the role of neuroleptics in schizophrenia patients' depression may be less than previously thought (Hogarty and Munetz 1984; Hogarty et al. 1988, 1995; Siris et al. 1988; Siris 1991). In a major double-blind study, Hogarty and colleagues (1995) concluded that affective disruption in schizophrenia could not be attributed to extrapyramidal side effects in patients who were maintained on a reasonable dose of anti-Parkinson medication, and the dose of antipsychotic drugs does not account for affective disruption in schizophrenia.

Vulnerability to Depression: A Factor in the Heterogeneity of Schizophrenia. Our longitudinal analyses indicate that a subgroup (17%) of schizophrenia patients are particularly prone to depression at multiple time periods over the years, raising the possibility that the vulnerability to depression could be one factor in the heterogeneity of schizophrenia. The idea that some schizophrenia patients are prone to depression presents some complex issues. Discussions about proneness to or predisposing factors for depression in schizophrenia typically occur in the context of discussions of possible pathogenic factors, which are themselves heterogeneous and controversial (Bartels and Drake 1988, 1989; Siris 1991, 1994). These hypothesized predisposing factors include genetic factors or family history factors (Galdi et al. 1981; Galdi 1983; Kendler and Hays 1983), psychosis or psychotic relapse (Heinrichs and Carpenter 1985; Johnson 1988; Green et al. 1990; Koreen et al. 1993; Harrow et al. 1994), neuroleptics (Van Putten and May 1978; Ananth and Ghadirian 1980; Galdi et al. 1981; Mandel et al. 1982; Galdi 1983; Bartels and Drake 1988; Siris 1991), personality characteristics (Becker 1983; Siris 1991; Birchwood et al. 1993; Liddle et al. 1993), and substance abuse (Bartels and Drake 1988). It is also compelling that a subgroup of schizophrenia patients could be resistant to depression or have a trait-like reduction in affective experience. An important area for future research is identifying factors that contribute to the vulnerability to depression among schizophrenia patients.

Is Depression Relevant to the Course and Outcome of Schizophrenia? The current research demonstrates that many schizophrenia patients, as well as some nonschizophrenia patients, show poor adjustment, even multiple years after hospital discharge. The functional impairments in schizophrenia are typically understood in terms of the effects of positive symptoms (psychosis) or negative symptoms, or both. However, recent research, including that by our group, has suggested that depression or other forms of affective disturbance in schizophrenia are also associated with poor outcome or functional impairments (Glazer et al. 1981; Bartels and Drake 1988; Johnson 1988; Fichtner et al. 1989; Birchwood et al. 1993; Harrow et al. 1994). The current research is among the first to examine the relative effects of both depression and psychosis on multiple aspects of posthospital adjustment. It is important to recognize that a multifactorial model may be needed to fully understand the role of possible factors mediating the relationship between depression and outcome. For example, additional research is needed to clarify whether substance abuse might be a confounding factor in the association between depression and poor outcome among schizophrenia patients.

Our analyses showed that, even when considering the influence of psychosis, posthospital depression is significantly associated with impairments in some (but not all) areas of schizophrenia patients' functioning, quality of life, and subjective well-being. Consistent with other reports (Birchwood et al. 1993), depression was significantly associated with schizophrenia patients' work functioning and activity level. Depression is also associated with schizophrenia patients' subjective satisfaction with their daily activities. During the posthospital period, both depression and psychosis increase schizophrenia patients' suicidal ideation or behavior, a noteworthy finding given that suicide is a major cause of death for schizophrenia patients (Breier and Astrachan 1984; Black et al. 1985; Caldwell and Gottesman 1990; Dingman and McGlashan 1986, 1988; Drake and Cotton 1986; Roy 1989; Westermeyer et al. 1991). This further underscores the need to understand which schizophrenia patients get depressed and which factors might contribute to the vulnerability to depression in schizophrenia.

Does Depression in Schizophrenia Imply a Continuum With Major Depression? Our findings on the presence of depression in schizophrenia (especially identifying a possible subgroup of depression-prone schizophrenia patients) are relevant to the nosological debate about the relationships among schizophrenia, schizoaffective disorder, and psychotic affective disorder (Taylor et al. 1974; Procci 1976; Pope and Lipinski 1978; Abrams and Taylor 1981; Kendler and Hays 1983; Harrow and Grossman 1985; Kendler et al. 1985, 1993; Williams and McGlashan 1987; Grossman et al. 1991; Taylor 1992; Dieperink and Sands 1996). Our data indicate that neither the occur-

rence rates of depressive syndromes nor their severity differentiates depression in schizophrenia from depression in schizodepressive or major depressive disorders. We found similar findings at earlier followups and using different instruments (Summers et al. 1983; Harrow et al. 1994). Comparing *outcome* for depressed schizophrenia patients with that of depressed patients with schizoaffective, psychotic depression, and nonpsychotic depression suggested that these diagnoses fall along a continuum, with some significant differences between the extremes.

These data could provide some support for a continuum model (Crow 1990; Brockington et al. 1991; Taylor 1992), yet Kraepelin's (1919/1921) dichotomy is not obviated. Within a dichotomized framework, the analyses could support the view that schizodepression is not a variant of major affective disorder (Pope and Lipinski 1978; Harrow and Grossman 1985; Williams and McGlashan 1987). Ultimately, nosological systems other than a dichotomous model or a unidimensional continuum model may better account for these data. The current understanding that both schizophrenia and major depression are heterogeneous rather than single disease entities (Akiskal 1989; Andreasen and Carpenter 1993; Andreasen et al. 1995) and the continued failure to identify pathognomonic clinical or biological markers warrant consideration of either a more relational, multidimensional nosological model (Strik et al. 1989) or a model that stresses integration across diagnoses (Swerdlow and Koob 1987).

Depression, the Concept of Schizophrenia, and Its Treatment. A number of early theories considered depression to be a "core" component of schizophrenia (Shanfield et al. 1970; Donlon et al. 1976; Johnson 1981; Hirsch 1982). Recent research reporting a positive association between psychosis and depression in schizophrenia (Hogarty and Munetz 1984; Heinrichs and Carpenter 1985; Green et al. 1990; Siris et al. 1990, 1994) has led some to reconsider the role of affective disruption in the underlying diathesis of even modern "narrow-diagnosed" schizophrenia patients (Leff et al. 1988; Siris et al. 1988, 1994; Koreen et al. 1993). However, modern formulations that define the core features of schizophrenic pathology (Andreasen and Carpenter 1993; Andreasen et al. 1995; Arndt et al. 1995) focus exclusively on nonaffective positive symptoms and negative symptoms. While nonaffective pathology is obviously important, a convergence of evidence indicates that clinically meaningful depression is sufficiently prevalent in schizophrenia that it should be incorporated into theory about the psychopathology of schizophrenia.

The prevailing concept of schizophrenia could potentially affect how treating clinicians perceive individual schizophrenia patients. Symptoms of depression in schizophrenia can be overlooked or misinterpreted and require careful assessment (Becker et al. 1985; Bartels and Drake 1989; Plasky 1991; Siris 1994). In the current group of schizophrenia patients, only 20 percent of those with full depressive syndromes were receiving antidepressant medications. Research has shown that antidepressants often effectively reduce affective distress in depressed schizophrenia patients (Siris et al. 1987, 1994; Bartels and Drake 1989; Siris 1991; Hogarty et al. 1995), although some research has yielded negative findings (Becker 1983; Becker et al. 1985; Kramer et al. 1989). Other researchers have suggested that while antidepressants may reduce depressive symptoms among schizophrenia patients, these medications could also exacerbate thought disorder (Prusoff et al. 1979). Authorities on the treatment of depression in schizophrenia suggest that a reduction of neuroleptics to a minimum effective dose and a trial of anticholinergic medications should be considered before instituting antidepressants (Siris 1991; Hogarty et al. 1995).

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