The McLean-Harvard First-Episode Project:
Early Course in 114 Cases of First-Episode Nonaffective Psychoses

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ABSTRACT

Background: Early course in contemporary, clinically treated, nonaffective psychotic disorders other than schizophrenia remains incompletely defined.

Methods: We prospectively, repeatedly, and systematically assessed 114 patients hospitalized for a first episode of *DSM-IV-TR* nonaffective psychotic illness for ≥ 2 years (1989–1996) using structured (Structured Clinical Interview for *DSM-III-R,* Patient Edition; Clinical Global Impressions scale; Scale for the Assessment of Negative Symptoms; Scale for the Assessment of Positive Symptoms; and the expanded version of the Brief Psychiatric Rating Scale) and unstructured (best-estimate procedure, life charting) naturalistic follow-up procedures and survival analysis.

Results: Duration of untreated psychosis (22 ± 38 months) was longest with schizophrenia. Within 2 years, syndromal remission sustained for ≥ 8 weeks (recovery) was attained by 75 subjects (65.8%); median latency to syndromal recovery was 9.4 (95% CI, 5.7–13.3) weeks and was shorter with cycloid features, initial diagnosis of brief psychosis or schizophreniform disorder, and shorter initial hospitalization. Functional recovery within 2 years was achieved by 28 of 68 subjects (41.2%), more often without initial mood-psychomotor instability or homicidal ideation. New episodes occurred in 52 of 114 subjects (45.6%) and were more likely with less affective flattening, younger age, and white race. Median time to new episodes (43.7 [27.9–70.6] weeks) was earlier with initial first-rank auditory hallucinations, substance abuse, and functional nonrecovery. Diagnosis changed to other nonaffective, schizoaffective, or affective disorders within 2 years in 62 of 108 cases (57.4%).

Conclusions: Three-quarters of patients presenting in first lifetime, nonaffective psychotic episodes achieved recovery within 2 years, but only 41% returned to baseline functioning, and nearly half experienced new episodes. Patients with schizophrenia had the longest duration of untreated psychosis. A majority changed diagnosis, indicating instability of some *DSM* psychotic-disorder diagnoses.

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Nonaffective psychotic disorders are clinically heterogeneous. They include acute and transient conditions as well as chronic or recurrent disorders. *DSM* brief, schizophreniform, and unspecified psychotic disorders, in particular, vary in prognosis and long-term outcomes.[1–7] There are few reports of nonaffective psychotic disorders diagnosed by modern criteria and followed prospectively from first episodes.[1,6–12] Accordingly, we conducted a systematic, prospective, repeated comparison of 114 such patients followed up for a minimum of 2 years from a first lifetime major episode with psychiatric hospitalization, to quantify their courses and to identify outcome predictors.

METHODS

Baseline Measures

Subjects in a first lifetime psychiatric hospitalization for the first major episode of a psychotic illness at McLean Hospital in Belmont, Massachusetts, provided written, informed consent to participate in this naturalistic prospective, follow-up study, while continuing to receive clinically determined treatment. Patients were diagnosed according to *DSM* diagnostic criteria with the Structured Clinical Interview for *DSM-III-R,* Patient Edition (SCID-P)[13] that was performed at intake and 2 years after the index hospitalization, with raters blinded to baseline assessment, and updated to *DSM-IV-TR* criteria.[14] Admission clinical reports of all patients admitted to inpatient units of the McLean Hospital Bipolar and Psychotic Disorders Program were reviewed daily (1989–1996), and 784 patients were identified as potential first-episode psychotic disorder cases. Of these, 406 patients were recruited (consecutively) for the McLean-Harvard First-Episode Project. Among those patients screened with available demographic data for comparison (N = 1,009), 178 (17.6%) did not meet study criteria, 125 (12.4%) refused participation, and 323 (32.0%) were otherwise not recruited. Those recruited versus not recruited did not differ by race, education, or marital status, but more women than men were not recruited or refused study participation ($\chi^2_1 = 7.64$, $P = .006$). Data on prescribed medicines per person were available only for recruited subjects. Patient-subjects included were diagnosed with mania or bipolar mixed-states (with or without psychotic features), psychotic depression,

Clinical Points

- Our findings suggest that clinicians should be aware that recent onset nonaffective psychosis may change diagnosis within the first 2 years. Diagnostic instability appears to be particularly high in unspecified psychosis, brief psychosis, and delusional disorder.
- On the basis of DSM criteria, schizoaffective disorder may be a rare diagnosis in first-episode psychosis, but it may be a very common diagnosis in patients who initially were diagnosed with unspecified psychosis or brief psychosis.
- Within 2 years, most patients presenting in first lifetime, nonaffective psychotic episodes appear to achieve symptomatic recovery, but the majority do not return to baseline functioning. Of those who achieve symptomatic recovery, at least half will experience a recurrence.
- Compared to other patients suffering from nonaffective psychoses, those with schizophrenia appear to have the longest duration of untreated psychosis. This finding may have implications in terms of long-term outcome.

and various nonaffective psychoses. The present study is based on the 114 cases diagnosed at intake with a nonaffective or schizoaffective psychotic disorder (Table 1). Diagnoses updated to *DSM-IV-TR* criteria[14] included brief psychosis, schizophreniform disorder, delusional disorder, psychosis not otherwise specified (unspecified psychosis), schizoaffective disorder, and schizophrenia (Table 1).

Patients ever given antipsychotic or antimanic medicines for more than 4 weeks before hospitalization were excluded. All participants were followed and treated clinically by nonstudy clinicians by prevailing community standards; treatments were not controlled by experimental protocols or specified therapeutic guidelines. Illness onset was rated as acute (≤ 4 weeks), subacute (5–26 weeks), or gradual (evolving over > 6 months).

Duration of untreated psychosis (DUP) was assessed retrospectively by chart review, by 2 reviewers working to consensus (P.S. and R.J.B.), and defined as the time between emergence of first lifetime psychotic symptoms and first antipsychotic treatment for psychotic symptoms. We also noted the presence at intake of specific psychopathological features reported to predict outcome, independent of their nosologic categorization, including suicidal ideation and attempts, homicidal ideation and behaviors, mood-psychomotor instability,[15] and cycloid psychosis as defined by the criteria of Perris and Brockington.[16–18]

Outcome Assessments

Functional recovery during follow-up was defined categorically (yes/no) as a return to individual best premorbid status, based on ratings for both occupational level and residential status as returning to or exceeding the highest levels within the preintake year,[19] considering information from subjects, family members, treating physicians, and medical records.[7,20–23] *Syndromal remission* was defined as reaching both a Clinical Global Impressions (CGI) scale[24] (score range = 1–7) score of ≤ 2 and a score of ≤ 3 on each of the *DSM-IV* criteria for each diagnostic entity, based on scores obtained with an expanded version of the Brief Psychiatric Rating Scale (BPRS-E).[7,25] *Syndromal recovery* was defined as remission sustained for at least 8 weeks. For schizophrenia and schizophreniform disorder, remission required that no *DSM-IV* "A" criterion was rated > 2 and fewer than 3 BPRS-E criteria were rated ≥ 2. For schizoaffective disorder, remission from psychosis was required plus, for depressive type, no major depression BPRS-E items rated > 3 and no more than 3 items rated 3 and with a CGI score ≤ 2. For schizoaffective disorder-bipolar type, remission was defined as remission from psychosis plus mania criteria "A" ≤ 3 and no more than 2 "B" criteria rated 3, with no "B" criteria > 3, and with a CGI score of ≤ 2. For delusional disorder, brief psychosis, and unspecified psychoses, no delusional or hallucinatory or affective symptoms were rated > 2.

Two years after the index hospitalization, an experienced and expert rater (C.A.Z.) administered the SCID-P diagnostic instrument for a second time, blinded to results of the SCID-P administered at intake, and using a best-estimate procedure based on all available information. A second formal SCID-P was conducted over the phone or in person at 24 months post hospital discharge by an investigator held blind to initial diagnoses. Diagnoses at intake, 2 years, and end of follow-up

Table 1. Initial Versus Final Follow-Up *DSM-IV* Diagnoses Among 114 First-Episode Psychotic Disorder Patients[a]

	Final	Initial Diagnoses, N						
Final Diagnosis	Cases, N	Unspecified Psychosis	Schizophrenia	Delusional	Schizophreniform	Brief	Schizoaffective	Other
Initial cases	114	49	32	13	12	7	1	0
Schizoaffective	43	17	12	5	6	2	**1**	0
Schizophrenia	27	4	**20**	0	3	0	0	0
Unspecified psychosis	20	**20**	0	0	0	0	0	0
Delusional disorder	10	1	0	**8**	0	1	0	0
Bipolar I	4	2	0	0	1	1	0	0
Major depression	1	0	0	0	1	0	0	0
Brief psychosis	3	0	0	0	0	**3**	0	0
Schizophreniform	0	0	0	0	**0**	0	0	0
Lost to follow-up	5	4	0	0	1	0	0	0
Refused follow-up	1	1	0	0	0	0	0	0
Final diagnoses	108	20	27	10	0	3	43	5
Changed diagnoses	62 (57.4%)	−29	−12, +7	−5, +2	−12	−4	+42	+5

[a]Boldface numerals indicate cases that retained initial diagnoses at 2-year follow-up. Note that all initial diagnostic categories underwent losses, with the exception of schizoaffective disorder and other affective disorders, with all final categories gaining cases.

were compared to determine their stability.[4,5] In addition, yearly follow-up assessments conducted by experienced masters-level research assistants were performed blinded to baseline assessments. All baseline (M.T. and S.M.S.) and follow-up (C.A.Z.) SCID-Ps were administered by psychiatrists trained in the use of the SCID-P and experts in the diagnosis of psychotic disorders. Interrater reliability was evaluated for SCID-P findings by intraclass correlation coefficients (ICC; ICC = 0.92 for primary and 0.90 for secondary diagnoses). High interrater reliability also was found for the 36-item BPRS-E (ICC = 0.96) administered by experienced masters-level research assistants trained in the use of the scale. In addition, there was excellent agreement between telephone and in-person interviews (ICC = 0.90)[20,26] conducted by experienced masters-level research assistants trained in the use of the outcome assessments.

Recurrence was defined as meeting *DSM-IV-TR* criteria for any major episode of a psychotic or affective disorder following initial syndromal recovery. *Relapse* was defined as again meeting diagnostic criteria for a new episode of major illness prior to 8 weeks of full recovery from the index episode.[7] For simplification, we considered as *new episodes*, the sum of relapses and recurrences. At follow-up assessments carried out at 6 and 12 months, and yearly thereafter, interval weekly morbidity status, including syndromal episodes, was reconstructed in life charts,[27] based on semistructured in-person or telephone interviews of patients and family members, as well as medical records and interviews by treating clinicians.

Symptomatic remission required scores equivalent to mild or absent (≤ 3) on relevant rating scales, including all BPRS-E psychosis symptoms, notably abnormal or flat affect; conceptual or behavioral disorganization; disorientation; hallucinations; suspiciousness; blunted affect; control, broadcasting, withdrawal, or insertion of thoughts; observed confusion or disorientation; and mannerisms or posturing.[7] Symptoms were also measured at baseline and follow-up using the Scale for the Assessment of Negative Symptoms (SANS)[28] and the Scale for the Assessment of Positive Symptoms (SAPS).[29]

Statistical Methods

Rates of defined outcomes were compared in subgroups of interest by bivariable logistic regression analysis. Median latencies to recovery and to new episodes (in weeks with 95% confidence intervals [CIs]) from the date of intake to recovery, or to new episodes from date of recovery, were compared by Kaplan-Meier life-table survival analyses, with Mantel-Cox log-rank (χ^2) tests. Median times to recovery or new illness (and 95% CI) in survival analysis were estimated as weeks by which 50% of subjects reached recovery or new illness. Variables with at least suggestive, preliminary bivariable associations ($P \leq .10$) with new episodes and times to new episodes were included in subsequent multivariable analyses.

We tested goodness of fit of multivariable models by deciles of fitted values and partial residual plot methods[30] and checked for compliance with the proportional hazards assumption and for goodness of fit of Cox models with Arjas plots and Schoenfeld residuals.[31] Explanatory variables with adjusted odds ratios (ORs; for logistic regression) or hazard ratios (HRs; for Cox regression) substantially different from 1.0 (at $P < .05$) were retained for final multivariable regression modeling. Interaction effects were tested for each multivariable model. The Kruskal-Wallis equality-of-populations rank test was used to compare DUP across diagnoses at intake and at 2 years, by sex and by stability of diagnosis. Statistical analyses employed commercial microcomputer software (Stata 10, StataCorp, College Station, Texas).

RESULTS

Baseline Characteristics

Subjects diagnosed at intake with a nonaffective or schizoaffective disorder (N = 114; Table 2) included 77 men (67.5%) and 37 women (32.5%), of mean intake age (31 years [SD = 13.2]); 90 (79.0%) were white. Most had at least high school education (86 patients; 75.4%), and most were unmarried (91 patients; 78.9%). Most prevalent diagnoses were unspecified psychosis, schizophreniform disorder, or brief psychosis, all with acute onset. Gradual onset was associated with schizophrenia and delusional disorder, as well as the 1 case initially meeting *DSM-IV-TR* criteria for schizoaffective disorder (Table 2). Many subjects (45 patients; 39.5%) met *DSM-IV-TR* criteria for substance or alcohol abuse or dependence, and 51 subjects (44.7%) had at least 1 general medical diagnosis. Suicide was attempted within 90 days of admission by 13 patients (11.4%), and 25 (21.9%) acknowledged homicidal ideation or behaviors at intake.

Duration of Untreated Psychosis

Duration of untreated psychosis averaged 21.6 (SD = 37.7) months and differed significantly among intake ($\chi^2_5 = 30.3$, $P < .0001$) and 2-year diagnoses ($\chi^2_7 = 24.5$, $P = .0002$), but not by sex (Table 3). As expected, subjects diagnosed with schizophrenia had the longest DUP, and those with brief psychosis the shortest, based on both intake and 2-year diagnoses. The 6 subjects (diagnosed with unspecified [n = 5] or schizophreniform disorder [n = 1]) not followed-up had the longest DUP, nearly twice that in schizophrenia (Table 3).

Diagnostic Stability

Of the 114 initial participants, 108 (94.7%) were followed for at least 2 years from admission; only 6 (5.26%) were not followed-up. As shown in Table 1, a majority of subjects (56/108; 51.9%) required a change of diagnosis within 2 years: 47 (43.5%) to major affective or schizoaffective disorders, 7 (6.46%) to schizophrenia, and 2 (1.85%) to delusional disorder.

Among subjects initially diagnosed with schizophrenia, 37.5% (12 of 32) changed diagnosis, all to schizoaffective disorder. Of the 49 subjects initially diagnosed with

Table 2. Intake Characteristics and 2-Year Outcome of First-Episode Nonaffective Psychotic Disorder Patients by Intake *DSM-IV-TR* Diagnoses

Characteristic	All Cases	Unspecified	Schizophrenia	Delusional	Schizophreniform	Brief	Schizoaffective
Cases, n (%)	114 (100.0)	49 (43.0)	32 (28.1)	13 (11.4)	12 (10.5)	7 (6.1)	1 (0.9)
Sex, n (%)							
Men	77 (67.5)	33 (67.4)	21 (65.6)	8 (61.5)	10 (83.3)	4 (57.1)	1 (100.0)
Women	37 (32.5)	16 (32.7)	11 (34.4)	5 (38.5)	2 (16.7)	3 (42.9)	0 (0.0)
Age, mean (SD), y							
Onset	30.8 (13.3)	29.7 (12.9)	29.1 (10.6)	38.2 (13.4)	26.9 (7.7)	41.6 (25.5)	20.0
Intake	31.4 (13.2)	30.4 (12.7)	29.5 (10.3)	38.8 (13.3)	27.4 (7.6)	42.1 (25.3)	21.7
White, n (%)	90 (79.0)	35 (71.4)	28 (87.5)	12 (92.3)	7 (58.3)	7 (100.0)	1 (100.0)
Unmarried, n (%)	91 (79.8)	36 (73.5)	31 (96.9)	8 (61.5)	12 (100.0)	3 (42.9)	1 (100.0)
Education ≥ high school, n (%)	86 (75.4)	34 (69.4)	24 (75.0)	11 (84.6)	9 (75.0)	7 (100.0)	1 (100.0)
Onset type, n (%)							
Acute (≤ 1 mo)	49 (43.0)	25 (51.0)	9 (28.1)	4 (30.8)	6 (50.0)	5 (71.4)	0 (0.0)
Subacute (1–6 mo)	34 (29.8)	12 (24.5)	11 (34.4)	5 (38.5)	4 (33.3)	2 (28.6)	0 (0.0)
Gradual (> 6 mo)	31 (27.2)	12 (24.5)	12 (37.5)	4 (30.8)	2 (16.7)	0 (0.0)	1 (100.0)
Other diagnoses, n (%)							
Medical illness	51 (44.7)	22 (44.9)	13 (40.6)	8 (61.5)	5 (41.7)	3 (42.9)	0 (0.0)
Substance abuse	45 (39.5)	24 (49.0)	12 (37.5)	3 (23.1)	5 (41.7)	0 (0.0)	1 (100.0)
Alcohol	38 (33.3)	19 (38.8)	12 (37.5)	3 (23.1)	3 (25.0)	0 (0.0)	1 (100.0)
Drug	35 (30.7)	19 (38.8)	8 (25.0)	2 (15.4)	5 (41.7)	0 (0.0)	1 (100.0)
Learning disability	24 (21.1)	11 (22.5)	10 (31.3)	0 (0.0)	3 (25.0)	0 (0.0)	0 (0.0)
Personality disorder	24 (21.1)	10 (20.4)	10 (31.3)	2 (15.4)	0 (0.0)	2 (28.6)	0 (0.0)
Prior head trauma	15 (13.2)	6 (12.2)	5 (15.6)	0 (0.0)	3 (25.0)	1 (14.3)	0 (0.0)
Epilepsy	12 (10.5)	6 (12.2)	4 (12.5)	2 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)
Anxiety disorder	3 (2.6)	1 (2.0)	2 (6.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Posttraumatic stress disorder	3 (2.6)	2 (4.1)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Obsessive-compulsive disorder	1 (0.9)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Clinical features, n (%)							
Mood-psychomotor instability	64 (56.1)	29 (59.2)	16 (50.0)	7 (53.9)	7 (58.3)	5 (71.4)	0 (0.0)
Cycloid features	17 (14.9)	9 (18.4)	2 (6.3)	0 (0.0)	1 (8.30)	5 (71.4)	0 (0.0)
Capgras phenomena	12 (10.5)	5 (10.2)	1 (3.1)	1 (7.7)	3 (25.0)	2 (28.6)	0 (0.0)
Current homicidal ideation	25 (21.9)	9 (18.4)	8 (25.0)	3 (23.1)	5 (41.7)	0 (0.0)	0 (0.0)
Suicide attempt ≤ 90 d	13 (11.4)	8 (16.3)	2 (6.3)	3 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)
First-rank symptoms	102 (89.5)	43 (87.8)	29 (90.6)	12 (92.3)	12 (100.0)	5 (71.4)	1 (100.0)
Auditory hallucinations	72 (63.2)	33 (67.4)	25 (78.1)	0 (0.0)	10 (83.3)	3 (42.9)	1 (100.0)
Initial illness severity, mean (SD)							
BPRS-E total score	73.5 (18.8)	74.5 (19.4)	76.2 (19.1)	72.1 (15.3)	71.4 (16.2)	60.4 (22.0)	84.0 (0.0)
CGI severity score	3.70 (1.6)	4.20 (1.2)	3.20 (2.0)	3.10 (2.0)	3.60 (1.4)	3.50 (1.4)	5.00 (0.0)
SANS global scores	0.80 (1.2)	0.80 (1.2)	1.00 (1.6)	0.40 (1.0)	0.40 (0.7)	0.30 (0.8)	…
SAPS global scores	2.00 (1.9)	2.40 (1.9)	1.90 (1.8)	0.40 (0.7)	2.60 (2.3)	0.00 (0.0)	…
Initial hospitalization, mean (SD), d	29.9 (27.3)	25.7 (20.3)	38.2 (38.1)	33.2 (28.9)	30.8 (19.4)	15.9 (5.4)	14.0
Outcome latency, mean (SD), wk							
Syndromal remission	9.43 (1.8)	10.6 (1.3)	34.3 (17.7)	10.6 (1.31)	6.43 (1.6)	2.71 (0.6)	35.0
New illness	43.7 (6.4)	48.4 (27.4)	26.4 (17.6)	77.3 (48.7)	37.4 (2.4)	21.9 (16.4)	45.1

Symbol: … = not applicable.
Abbreviations: BPRS-E = expanded version of the Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions scale, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms.

unspecified psychosis, as expected most (59.2%) changed diagnosis.

Syndromal and Symptomatic Remission

Of the 114 subjects followed for at least 2 years, 86 (75.4%) achieved syndromal remission, 82 (71.9%) achieved syndromal recovery (≥ 8 weeks sustained syndromal remission), and 28 (24.6%) achieved neither syndromal remission nor recovery within a mean of 3.44 years of follow-up. Syndromal recovery was attained by specific times following intake as follows: 57 patients (50.0%) by 3 months, 64 (56.1%) by 6 months, 69 (60.5%) by 1 year, and 75 (65.8%) by 2 years and 7 of 108 patients (6.48%) after 2 years follow-up. Symptomatic recovery was attained by 6, 12, and 24 months, by 29 of 114 (25.4%), 23 of 114 (20.2%), and 20 of 108 (18.5%) subjects, respectively, so that over 80% of subjects (88 of 108) were still symptomatic at 2 years after the index hospital admission. By multivariable logistic regression modeling, only co-occurring alcohol abuse and shorter hospitalization were significantly and independently associated with achieving syndromal recovery by 2 years (Table 4).

Functional Recovery

Among 68 subjects with data on vocation and living status at 2 years, 41.2% (28 of 68) attained functional recovery by 24 months. Likelihood of such recovery by initial diagnosis ranked as follows: brief psychosis (3 of 6 patients [50.0%]) ≥ schizophrenia (10 of 22 patients [45.5%]) ≥ schizophreniform disorder (3 of 7 [42.9%]) ≥ unspecified psychosis (10 of 26 [38.5%]) ≥ delusional disorder (2 of 7 [28.6%]) > schizoaffective disorder (0 [0.0%]). Factors associated with functional recovery, based on logistic regression modeling, were *absence* of initial homicidal ideation or behavior and of mood-psychomotor instability (Table 4).

Table 3. Months of Untreated Psychosis[a]

Factor	Duration of Untreated Psychosis (mo)[b]	χ^2 (*df*)	*P* Value
All	21.6 (37.7)		
Sex			
Male	22.9 (40.1)	0.001 (1)	.98
Female	19.0 (32.6)		
Intake diagnosis			
Schizophrenia	33.4 (33.5)	30.3 (5)	<.0001
Delusional	24.9 (35.2)		
Unspecified psychosis	20.6 (45.5)		
Schizoaffective	20.8 (0.0)		
Schizophreniform	3.4 (6.0)		
Brief	0.7 (1.0)		
2-Year diagnosis			
Lost to follow-up	56.9 (98.1)	24.5 (7)	.0002
Schizophrenia	33.9 (35.9)		
Schizoaffective	22.9 (35.4)		
Delusional	15.0 (19.3)		
Unspecified psychosis	3.4 (07.8)		
Bipolar I	1.9 (03.4)		
Brief	0.3 (0.4)		

[a]There was no significant difference in duration of untreated psychosis between subjects with a stable (19.5 months) versus changed (19.8 months) diagnosis ($\chi^2_1 = 0.18$, $P = .67$).
[b]Values are given as mean (SD).

Table 4. Factors Associated With Achieving Syndromal and Functional Recovery and Experiencing New Episodes: Multivariable Logistic Modeling Within 2 Years

Factor	Odds Ratio (95% CI)	*z* Score	*P* Value
Syndromal recovery			
Alcohol use disorder	2.64 (1.05–6.66)	2.06	.04
Shorter index hospitalization	1.02 (1.00–1.04)	2.21	.03
Functional recovery			
No homicidal ideation or behavior	6.42 (1.40–29.5)	2.39	.02
No initial mood-psychomotor instability	2.94 (1.03–8.42)	2.01	.04
New episode[a]			
White	3.71 (1.10–12.6)	2.11	.04
Younger at intake	2.02 (1.32–3.11)	3.21	.001
Less initial affective flattening (SANS)	1.58 (1.04–2.41)	2.13	.03

[a]For each 10 years younger at intake, odds of a new episode increased 1.81 times.
Abbreviation: SANS = Scale for the Assessment of Negative Symptoms.

Table 5. Factors Associated With Shorter Latency to Syndromal Remission and to New Episodes: Multivariable Cox Modeling of Survival Functions

Factor	Hazard Ratio (95% CI)	*z* Score	*P* Value
Syndromal recovery[a]			
Cycloid features	2.70 (1.51–4.83)	3.36	.001
Intake diagnosis	2.00 (1.12–3.57)	2.34	.02
Shorter hospitalization	1.02 (1.01–1.03)	3.12	.002
New episode			
Substance misuse at intake	2.93 (1.41–6.11)	2.87	.004
Not functionally recovered by 2 years	2.14 (1.09–4.22)	2.21	.03
First-rank auditory hallucinations	1.96 (1.00–3.89)	1.94	.05

[a]Length of stay adjusted for year of admission. Intake diagnosis: schizophreniform or brief psychosis versus other.

Time to Syndromal Recovery

Since most subjects met criteria for syndromal recovery, we considered factors associated with syndromal recovery and median latency to syndromal recovery. Median time to syndromal recovery was 9.43 (95% CI, 5.71–13.3) weeks across all 114 subjects. This latency measure was shortest for brief psychosis (2.7 weeks) and longest for schizophrenia (34.3 weeks). Of note, all patients with brief psychosis recovered, but only 61.5% of those diagnosed with delusional disorders attained syndromal recovery within 2 years. Based on multivariable Cox regression modeling, cycloid features, diagnosis of brief or schizophreniform psychosis, and shorter index hospitalization were associated with *earlier* syndromal recovery (Table 5).

New Episodes Following Syndromal Remission

New major episodes of illness were experienced by 52 of 114 subjects (45.6%) within 3.44 years of follow-up (13.3% per year) with a mean of 1.97 (95% CI, 1–10) episodes per person. Four of 114 subjects (3.5%) relapsed before reaching 8 weeks of syndromal remission. Among 75 subjects who achieved syndromal recovery (≥ 8 weeks sustained syndromal remission), 65.3% (49 of 75) experienced a recurrence within 2 years, and the remaining 4.0% (3 of 75) did so by 2.6 years. Among the 69.3% (52 of 75) experiencing a recurrence post syndromal recovery, their syndromal recurrence types ranked as follows: brief psychotic episode (29 of 52 [55.8%]) > major depressive episode (16 of 52 [30.8%]) > manic episode (3 of 52 [5.8%]) > hypomania (2 of 52 [3.9%]) = mixed manic-depressive state (2 of 52 [3.9%]). New major affective episodes were associated with a change of diagnosis to schizoaffective (n = 42), bipolar I (n = 4), or major depressive disorders (n = 1), and in 1 case, a review of all available data on course, episodes, and subthreshold symptoms warranted rediagnosis to delusional disorder (Table 3). In multivariable logistic regression modeling, factors associated independently with the occurrence of new episodes were (*a*) white race, (*b*) younger age at intake, and (*c*) less affective flattening (lower SANS global score). On the basis of diagnosis stratified at intake, the most frequent type of new episode was nonaffective psychosis, except in subjects initially diagnosed with brief psychosis, among whom all new episodes were affective.

Time to a New Episode

Median latency to new illness episodes was 43.7 (95% CI, 27.9–70.6) weeks. In multivariable Cox regression modeling, factors associated significantly with *shorter* time to a new episode were (*a*) co-occurring substance abuse or dependence at intake, (*b*) lack of functional recovery at 24 months, and (*c*) presence of first-rank auditory hallucinations (Table 5). There were no interaction effects among factors in any of the final multivariable models.

Treatment at Discharge and 2-Year Follow-Up

The number of psychotropic medicines per person prescribed at discharge (to 102 patients) and at 2-year follow-up (to 88 patients) differed among drug classes. Their

respective frequencies of use at these sampling times were antidepressants (23 [22.5%] and 13 [14.8%]), antipsychotics (21 [20.6%] and 38 [43.2%], a 2.1-fold increase), mood stabilizers (including lithium and anticonvulsants, 35 [34.3%] and 19 [21.6%]), sedative-anxiolytics (28 [27.5%] and 8 [9.1%]), and anticholinergics (56 [54.9%] and 1 [1.1%]). These data indicate increasing use of antipsychotics and stable or declining use of all other drug types during post hospital follow-up, as the total number of psychotropic drugs per person decreased by 48%.

DISCUSSION

This study is one of very few[7,11] involving first-episode patients with a range of nonaffective psychotic illnesses, regardless of specific diagnosis save for exclusion of cases of delirium or intoxication. A notable finding is that a majority of patients (62 of 108 [57.4%]) later met *DSM-IV-TR* diagnostic criteria for a different disorder within 2 years of their presenting, first lifetime episode of psychotic illness leading to psychiatric hospitalization. The most frequent initial diagnosis at onset was unspecified psychosis (43.0%), and this category required a different diagnosis 3.1-times more often than others (57.0% vs 18.5% of all subjects during follow-up). Bromet and colleagues[6] similarly noted that 51% of 470 patients with first-episode psychotic disorder underwent diagnostic change during follow-up over 10 years. However, their Suffolk County, New York, sample had a larger proportion of patients initially diagnosed with schizophrenia than in the present sample, and this proportion increased during follow-up,[1,6] whereas the number of patients diagnosed with schizophrenia decreased in the present sample. In both studies, the proportion of unspecified psychoses decreased. Kingston and colleagues[12] also found unspecified disorders in 13 of 196 new cases of psychotic illnesses (6.63%), and two-thirds of initially unspecified cases later met *DSM-IV* criteria for a specific diagnosis within 6 years. These several findings underscore the point that initial diagnoses of "unspecified psychosis" should be considered tentative and likely to change with further observation. However, despite its instability, an unspecified working diagnostic category may be necessary to allow time for unfolding of final diagnoses.

The McLean-Harvard First-Episode Study has included psychotic depression and mania with or without psychotic features among affective disorders and schizoaffective disorders with nonaffective psychoses. In the present sample, only 1 subject was diagnosed initially as schizoaffective by *DSM-IV-TR* criteria, whereas this diagnosis was given to 43 of 108 cases (39.8%) by 2 years to become the most frequent final diagnosis. Most subjects (25 of 43 [58.1%]) who eventually met criteria for a schizoaffective diagnosis were considered initially to have a nonaffective psychotic disorder (brief psychotic, delusional, schizophreniform disorder, or schizophrenia), indicating the necessity for longer follow-up to confirm diagnosis. Longitudinal assessment for schizoaffective diagnoses has become even more important with *DSM-5*. Of 49 subjects initially considered unspecified, 17 (34.7%) were eventually diagnosed as schizoaffective, indicating utility of an unspecified diagnostic category at first. In contrast, if *ICD-10* diagnostic criteria were applied, many more cases would have been diagnosed as schizoaffective, and probably even fewer with *DSM-5* criteria, indicating that *DSM* diagnostic criteria for schizoaffective disorder require reconsideration and improvement.[5,32,33] Our findings are similar to those reported by Castro-Fornieles and colleagues[34] regarding the relative stability of the "schizophrenia spectrum" disorders (90.0%) and the low stability for unspecified psychosis (11.8%) and brief psychotic disorder in juvenile cases, whereas we have found a high rate of shift to schizoaffective disorder from these initial categories in adults.

The provisional diagnostic status of schizophreniform disorder has been noted previously.[4,35–37] In addition, among the 7 cases initially diagnosed as brief psychosis, 57% were re-diagnosed (as schizoaffective, delusional, or bipolar disorder), indicating a potentially high risk for subsequent major illness, rather than a favorable prognosis, in this diagnostic category.[12] In general, the present findings encourage a generally cautious and tentative approach to diagnosis of psychotic disorders at their initial presentation, with the expectation that prolonged observation will be required to establish a secure diagnosis. Of note, however, all required changes of diagnosis occurred within 2 years of follow-up, and no more were encountered up to an average of 3.4 years and a maximum of over 8 years.

Initial diagnoses of substance-induced psychotic disorder and psychosis due to a general medical condition were excluded, and no patient was rediagnosed at the 2-year assessment to either of these diagnoses. However, alcohol or drug abuse was recognized at intake in one-third of the present sample, mostly among subjects initially diagnosed with unspecified psychosis, but none diagnosed with brief psychosis. Other observations indicate that the proportion of cases with substance abuse may be larger among psychotic disorder patients with chronic versus acute illnesses (35%–44%).[38] Substance abuse had an adverse prognostic impact, as latency to a new episode following initial remission was less than half as long among subjects diagnosed with substance abuse (median: 40 vs 90 weeks). It is important to determine whether early interventions aimed at limiting substance abuse among patients with psychotic disorder can effectively limit future morbidity.[39]

As expected, patients with schizophrenia had the longest estimated DUP (33.4 months), whereas those diagnosed with brief or schizophreniform psychosis, as expected, had the shortest (0.7–3.4 months). It also follows that DUP was more than twice as long with gradual (mean 32.8 months) versus rapid onset (mean 15.5 months) of first episodes. These marked differences evidently reflect the natural history of chronic versus acute psychotic disorders, and plausibly greater likelihood of prompt intervention in more acute conditions. As would be expected of more chronic illnesses, longer DUP has been found to predict relatively

poor prognosis, including more impaired cognition and other aspects of disability.[40] The nearly twice greater DUP among the few present subjects who were not retained for follow-up (56.9 [98.1] vs 19.7 [31.3] months) encourages clinical investigators to assess access-to-care of research participants and underscores the potential for severe cases to disengage from treatment.[41] Other criteria for remission have been proposed. Andreasen and colleagues[42] proposed criteria based on symptom rating scales' minimum severity scores for a minimum of 6 months. Our criteria are similar except for minimum duration of months; therefore, comparison with studies using other criteria would not be appropriate.

Functional recovery was attained by 2 years in 41% of subjects and among 50% of those initially diagnosed with brief psychosis. Functional nonrecovery was associated with shorter times to new illness episodes and was 1.9-times more likely among patients without initial homicidal ideation, aggressive behaviors, or mood-psychomotor instability. The presence of cycloid features in first-psychosis episodes has been reported to predict relatively favorable outcomes,[16–18] specifically predicting both full recovery in single episode of psychosis course as well as relative good functioning and absence of residual symptoms during intervals in multiple-episode recurrent psychoses.[43] Schwartz and colleagues[44] found significant associations of homicidal ideation and intent with impaired global functioning among inpatients with schizophrenia. Our findings also suggest an association of homicidal ideation and behaviors with lower functioning at 2 years. We found first-rank auditory hallucinations to be a predictor of shorter time to new illness. As mood-psychomotor instability may predict the emergence/persistence[15,45] of psychotic symptoms such as first-rank phenomena, it may be useful for clinicians to identify such features at first presentation.

Limitations of this study include moderate-sized samples of some initial diagnostic groups and uncontrolled and clinically determined treatment that may affect illness course. In addition, demographic characteristics of the present participants (most were white, relatively well educated, and older than in some other studies[1,8,9]) suggest that some findings may not generalize to other settings. That only hospitalized patients were included may limit generalization of the findings beyond relatively severely ill, hospitalized patients with psychotic disorder or those with insidious, slowly evolving illnesses. Also as reported by Baca-Garcia and colleagues,[46] clinical settings can affect the case mix and alter rates of diagnostic stability. However, participants were evaluated systematically by an experienced research team, with very few cases lost to follow-up (5%). These characteristics are likely to enhance the reliability of the findings.

In conclusion, nonaffective psychotic disorders as defined by *DSM-IV-TR* criteria were heterogeneous in rates and latencies to remission, and in odds of new episodes, as expected. Nearly half of the subjects did not meet a specific *DSM* diagnosis at intake ("unspecified psychosis"), whereas most met criteria for specific diagnoses within 2 years of prospective follow-up. Additionally noteworthy is that most patients (57%) changed diagnosis within 2 years of follow-up, mainly to a schizoaffective disorder. These findings may reflect limitations of the *DSM-IV* diagnostic system, and probably pertain to most *DSM-5* categories as well. Further study of relatively acute psychotic disorders and the large but poorly characterized group of schizoaffective disorders is needed.

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