McLean-Harvard International First-Episode Project: Two-Year Stability of DSM-IV Diagnoses in 500 First-Episode Psychotic Disorder Patients

Paola Salvatore, M.D.; Ross J. Baldessarini, M.D.; Mauricio Tohen, M.D., Dr.P.H.; Hari-Mandir K. Khalsa, M.S.; Jesus Perez Sanchez-Toledo, M.D., Ph.D.; Carlos A. Zarate, Jr., M.D.; Eduard Vieta, M.D., Ph.D.; and Carlo Maggini, M.D.

Objective: Since stability of DSM-IV diagnoses of disorders with psychotic features requires validation, we evaluated psychotic patients followed systematically in the McLean-Harvard International First Episode Project.

Method: We diagnosed 517 patients hospitalized in a first psychotic illness by SCID-based criteria at baseline and at 24 months to assess stability of specific DSM-IV diagnoses.

Results: Among 500 patients (96.7%) completing the study, diagnoses remained stable in 77.6%, ranking as follows: bipolar I disorder (96.5%) > schizophrenia (75.0%) > delusional disorder (72.7%) > major depressive disorder (MDD), severe, with psychotic features (70.1%) > brief psychotic disorder (61.1%) > psychotic disorder not otherwise specified (NOS) (51.5%) >> schizophreniform disorder (10.5%). Most changed diagnoses (22.4% of patients) were to schizoaffective disorder (53.6% of changes in 12.0% of subjects, from psychotic disorder NOS > schizophrenia > schizophreniform disorder = bipolar I disorder most recent episode mixed, severe, with psychotic features > MDD, severe, with psychotic features > delusional disorder > brief psychotic disorder > bipolar I disorder most recent episode manic, severe, with psychotic features). Second most changed diagnoses were to bipolar I disorder (25.9% of changes, 5.8% of subjects, from MDD, severe, with psychotic features > psychotic disorder NOS > brief psychotic disorder > schizophreniform disorder). Third most changed diagnoses were to schizophrenia (12.5% of changes, 2.8% of subjects, from schizophreniform disorder > psychotic disorder NOS > brief psychotic disorder = delusional disorder = MDD, severe, with psychotic features). These 3 categories accounted for 92.0% of changes. By logistic regression, diagnostic change was associated with nonaffective psychosis > auditory hallucinations > youth > male sex > gradual onset.

Conclusions: Bipolar I disorder and schizophrenia were more stable diagnoses than delusional disorder or MDD, severe, with psychotic features, and much more than brief psychotic disorder, psychotic-disorder NOS, or schizophreniform disorder. Diagnostic changes mainly involved emergence of affective symptoms and were predicted by several premorbid factors. The findings have implications for revisions of DSM and ICD.

J Clin Psychiatry 2009;70(4):458–466

Received March 20, 2008; accepted June 10, 2008. *From the Department of Psychiatry and Neuroscience Program, Harvard Medical School, Boston, Mass. (Drs. Salvatore, Baldessarini, Tohen, and Vieta and Ms. Khalsa); the International Consortium for Bipolar and Psychotic Disorders Research, Mailman Research Center, McLean Hospital, Belmont, Mass. (Drs. Salvatore, Baldessarini, Tohen, Perez Sanchez-Toledo, Zarate, Vieta, and Maggini and Ms. Khalsa); the Section of Psychiatry, Department of Neuroscience, University of Parma, Parma, Italy (Drs. Salvatore and Maggini); Lilly Research Laboratories, Indianapolis, Ind. (Dr. Tohen); the Department of Psychiatry, University of Cambridge, United Kingdom (Dr. Perez Sanchez-Toledo); the Laboratory of Molecular Pathophysiology and Experimental Therapeutics, Mood and Anxiety Disorders Program, National Institute of Mental Health, National Institutes of Health, Bethesda, Md. (Dr. Zarate); and the Neuroscience Institute, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain (Dr. Vieta).*

Supported by grants from NARSAD (Dr. Salvatore); NIH grants MH-04844, MH-10948; by NIH grants MH-47370 and MH-73049, a grant from the Bruce J. Anderson Foundation, and the McLean Private Donors Research Fund (Dr. Baldessarini); the Spanish Ministry of Education and Science and CIBERSAM (Dr. Vieta); and a grant from the Atlas Foundation (Dr. Tohen).

Statistical advice was provided by Theodore Whitfield, D.Sc., and the late John Hennen, Ph.D., both of the International Consortium for Bipolar and Psychotic Disorders Research. Dr. Whitfield reports no financial or other relationship relevant to the subject of this article.

Financial disclosure appears at the end of this article.

Corresponding author and reprints: Paola Salvatore, M.D., International Consortium for Bipolar and Psychotic Disorders Research, Center Building G-07B, McLean Hospital, 115 Mill St., Belmont, MA 02478-9106 (e-mail: psalvatore@mclean.harvard.edu).

> *The task is to use clinical methods for the development of pictures of disease, in which as far as possible all the phenomena of the individual patient's life are evaluated for purposes of diagnosis and the whole course of the illness is taken into account.*
>
> —Karl Kahlbaum[1]

The importance of establishing sound clinical diagnoses of major psychiatric disorders with both cross-sectional coherence and stability over time has long been recognized.[1–3] Current leading international taxonomies represented by the American Psychiatric Association's DSM[4] and World Health Organization's ICD[5] systems involve standardized descriptive criteria, and consider a longitudinal perspective. More objective, biologically based methods to support psychiatric diagnoses continue to be sought but remain unlikely to dis-

place clinical, descriptive, phenomenological systems of diagnosis soon.[6]

Psychiatric diagnoses may be especially vulnerable to instability over time, owing to factors that include (1) insufficient information in individual cases and potential unreliability of information elicited only from patients; (2) symptom-modifying effects of treatment, substance abuse, comorbid medical disorders, and prolonged disability or institutional care as well as premorbid externalizing or internalizing nonpsychotic or personality disorders[7]; (3) changes or evolution of symptomatic manifestations over time; (4) use of standard diagnostic schemes[4,5] that rely on simplified and somewhat arbitrary criteria for required features, symptom duration, and functional impairment that contrast to the richness and nuances of phenomenology arising early in most disorders.[8–16] In addition, some current diagnostic concepts remain inadequately validated and may simply be unreliable, notably including acute psychotic and schizoaffective disorders.[17–19]

Given clinical and research requirements for more reliable diagnoses despite limited information and typically brief observation times, it is highly desirable for initial standardized diagnoses to remain stable over time or to follow predictable courses. These considerations encourage testing of diagnostic stability by systematic and prospective, long-term assessments, if only to document levels of longitudinal stability of specific diagnoses and to identify early predictors of later diagnostic change. Several modern studies have considered the broad range of disorders with psychotic features, followed from onset.[10,12,15,20–28] Fewer have considered predictors of diagnostic change investigated among various psychoses at onset or during premorbid or prepsychotic stages.[22,26,27]

Based on the preceding considerations, we evaluated diagnostic stability of a broad range of initial Structured Clinical Interview for DSM-IV Disorders (SCID)–based, DSM-IV psychotic disorders, including a large subgroup of first psychotic episode mood disorders, over their initial 2 years, among 500 patients enrolled in the McLean-Harvard International First-Episode Project. We hypothesized that initial diagnoses would vary in stability over time and that particular early clinical factors might predict later diagnostic instability. As a secondary aim, we considered how initial affective and psychotic components change over time and whether new diagnoses are more likely to emerge through newly prominent affective or nonaffective features.

METHOD

Subjects and Diagnostic Assessments

Subjects were among 517 patients entering the International First-Episode Project, based at McLean Hospital and the University of Parma, from 1989 to 2003, and meeting entry criteria, following the same methods in a single multisite project. Project protocols have undergone annually updated review and approval by the McLean Hospital Institutional Review Board as well as the Ethical Committee of the University of Parma Medical Center, through 2008. For inclusion, all subjects presented in a first-lifetime episode of psychotic illness and gave written, informed consent for participation and anonymous, aggregate reporting of findings. Exclusion criteria at intake were (1) acute intoxication or withdrawal associated with drug or alcohol abuse, or any delirium; (2) previous psychiatric hospitalization, unless for detoxification; (3) presence of mental retardation (Wechsler Adult Intelligence Scale–tested IQ < 70) or other DSM-IV organic mental disorder; (4) index DSM-IV full syndromal illness present > 6 months or any previous syndromal episode; or (5) prior total treatment with an antipsychotic agent for ≥ 4 weeks or an antidepressant or mood stabilizer for ≥ 3 months.

Diagnoses were based on SCID-I/P assessments at baseline and again at 24 months by highly trained and experienced diagnosticians, blinded at 24 months to initial diagnoses, in a total of 500 cases (completion rate of 500/517 = 96.7%). The intake versus year 2, SCID-based diagnoses were the basis of the present analyses. In addition, we considered other premorbid or baseline clinical features obtained by investigators not held blind to the initial SCID-based diagnosis, from medical records, clinical notes, and reports of interviews with family members, treating and primary care clinicians, considering duration of episodes or other clinical features as required by DSM-IV. We also estimated age at onset or occurrence of primary illnesses as well as the timing of premorbid psychiatric clinical characteristics, and of neuromedical as well as substance use comorbidities both in antecedent and prodromal phases. We updated all diagnoses to meet DSM-IV-TR criteria in 2007. These clinical assessment methods were detailed previously.[29]

Data Analyses

We compared subjects with SCID-based diagnoses considered stable vs. changed by 24 months, using 1-way analysis of variance (F) for continuous variables, and contingency tables (χ^2 or Fisher exact p) for categorical factors, with defined dfs. Measures with at least suggestive differences ($p < .10$) in initial bivariate comparisons were entered into a logistic regression model to identify factors independently associated with diagnostic change, reporting odds ratios (ORs) with their 95% CIs. Averages are means with standard deviations (± SD). Analyses were based on commercial statistical programs (Stata-9, Stata Corp., College Station, Tex.; Statview-5, SAS Institute Inc., Cary, N.C.).

RESULTS

Subject Characteristics and Initial Diagnoses

Of 517 first-episode psychotic subjects assessed initially, 17 (3.3%) were lost to follow-up (1 died, 1 moved to another country, and 15 withdrew consent or were otherwise lost to follow-up), leaving 500 (96.7%) for analysis. Most subjects were men (55.0%), and estimated mean ± SD age at onset of first psychotic syndromes was 31.7 ± 13.7 years. Lifetime DSM-IV comorbid diagnoses at baseline included 51.2% with substance use disorders, 22.2% Axis II disorders, and 17.6% with any anxiety disorder (Table 1). Based on initial diagnoses, mean ± SD age at onset differed markedly among disorders ($F = 3.76$, $df = 8$, $p = .0003$), ranking as follows: schizoaffective disorder (20 ± 0.0 years) ≥ schizophreniform disorder (27.4 ± 8.6 years) ≥ psychotic disorder not otherwise specified (NOS; 28.1 ± 12.0 years) ≥ schizophrenia (29.4 ± 9.2 years) ≥ bipolar I disorder most recent episode mixed, severe, with psychotic features (31.0 ± 11.6 years) ≥ bipolar I disorder most recent episode manic, severe, with psychotic features (31.0 ± 13.6 years) > brief psychotic disorder (31.9 ± 14.6 years) > major depressive disorder (MDD), severe, with psychotic features (37.4 ± 17.5 years) ≥ delusional disorder (39.2 ± 14.7 years). Initial DSM-IV diagnoses included a majority (N = 308, 61.6%) of affective-psychotic disorders (bipolar I disorder or MDD, severe, with psychotic features), fewer (N = 191, 38.2%) nonaffective diagnoses (brief psychotic disorder, delusional disorder, schizophreniform disorder, schizophrenia, or psychotic disorder NOS), and rare (N = 1, 0.20%) schizoaffective disorder.

Table 1. Characteristics of 500 First-Episode DSM-IV Psychotic Disorder Patients[a,b,c]

Characteristic	Value
Sex	
Male	275 (55.0)
Female	225 (45.0)
Age at onset, mean ± SD, y	31.7 ± 13.7
Comorbidities	
Substance use disorders	256 (51.2)
Axis II personality disorders	111 (22.2)
Anxiety disorders	88 (17.6)
Prevalence of initial DSM-IV diagnoses (%, by rank)	
Any bipolar I disorder	231 (46.2)
Bipolar I disorder (initially manic)	148 (29.6)
Bipolar I disorder (initially mixed)	83 (16.6)
Major depressive disorder	77 (15.4)
Psychotic disorder NOS	66 (13.2)
Schizophrenia	48 (9.6)
Brief psychotic disorder	36 (7.2)
Delusional disorder	22 (4.4)
Schizophreniform disorder	19 (3.8)
Schizoaffective disorder	1 (0.2)
Changed initial diagnoses (%, by rank)	
Schizophreniform disorder	17/19 (89.5)
Psychotic disorder NOS	32/66 (48.5)
Major depressive disorder	23/77 (29.9)
Brief psychotic disorder	14/36 (38.9)
Delusional disorder	6/22 (27.3)
Schizophrenia	12/48 (25.0)
Bipolar I disorder (initially mixed)	7/83 (8.4)
Bipolar I disorder (initially manic)	1/148 (0.7)
Any bipolar I disorder	8/231 (3.5)
Schizoaffective disorder	0/1 (0.0)

[a]All data are presented as N (%) unless otherwise noted.
[b]Diagnoses are based on initial SCID assessments.
[c]Overall diagnostic stability averaged 77.6% (388/500).
Abbreviations: NOS = not otherwise specified, SCID = Structured Clinical Interview for DSM-IV.

Changes in Diagnosis at Follow-Up

Among the 500 subjects analyzed (406 in the United States and 94 in Italy), initial diagnoses changed in 112 (22.4%). The proportion of initial diagnoses sustained at follow-up (N = 388, 77.6%), or the positive predictive value of initial diagnoses,[30] was 1.56 times greater among subjects with major affective disorders with psychotic features (stable/all affective cases = 277/308, 89.9%) than those diagnosed with nonaffective psychosis (stable/all nonaffective cases = 110/191, 57.6%; $\chi^2 = 71.8$, $df = 1$, $p < .0001$, omitting 1 initially schizoaffective case; Tables 2 and 3).

Most new diagnoses were of schizoaffective disorder (60 cases, 53.6% of the 112 revised diagnoses: 46 from initial nonaffective categories, and 14 from initial affective cases including 8 initial bipolar I disorder diagnoses and 6 initially considered MDD, severe, with psychotic features). New schizoaffective diagnoses involved later appearing affective features in previously nonaffective conditions 5.3 times more often than the opposite (46/191 [24.1%] initially nonaffective vs. 14/308 [4.54%] affective; $\chi^2 = 42.5$, $df = 1$, $p < .0001$). The second most prevalent new diagnosis was bipolar I disorder (25.9% of new diagnoses, involving 29 cases: 16 initially diagnosed MDD, severe, with psychotic features, 6 psychotic disorder NOS; 5 brief psychotic disorder, and 2, schizophreniform disorder). Third most likely were new diagnoses of schizophrenia (12.5% of changed diagnoses in 14 cases: 6, initially considered schizophreniform disorder; 5, psychotic disorder NOS; and 1 each from delusional disorder, brief psychotic disorder, and MDD, severe, with psychotic features). These 3 categories accounted for 103/112 new diagnoses (92.0%).

Initial DSM-IV diagnoses of bipolar I disorder held up best, at 96.5% (223/231), as only 3.46% (8/231) changed (all to schizoaffective disorder; 7/8 following mixed-state presentations). Also among major affective disorder diagnoses, 70.1% (54/77) of initial diagnoses of MDD, severe, with psychotic features, remained stable: 29.9% (23/77) changed (16 to bipolar I disorder, 6 to schizoaffective disorder, 1 to schizophrenia). Among nonaffective diagnoses, schizophrenia persisted at 75.0%, and delusional disorder at 72.7%. Most short-duration or initially nonspecific (NOS) disorders changed to various alternative diagnoses, with retention rates of 61.1% for brief

Table 2. Changes in DSM-IV Diagnosis: First-Episode Psychotic Disorders[a,b]

Initial diagnosis	N (%)	Final Diagnoses	N (%)
Schizophreniform disorder	19 (3.8)	Schizoaffective disorder	7 (36.8)
		Schizophrenia	6 (31.6)
		Schizophreniform disorder	2 (**10.5**)
		Major depressive disorder	2 (10.5)
		Bipolar I disorder	2 (10.5)
Psychotic disorder NOS	66 (13.2)	Psychotic disorder NOS	34 (**51.5**)
		Schizoaffective disorder	19 (28.8)
		Bipolar I disorder	6 (9.1)
		Schizophrenia	5 (7.6)
		Delusional disorder	1 (1.5)
		Major depressive disorder	1 (1.5)
Brief psychotic disorder	36 (7.2)	Brief psychotic disorder	22 (**61.1**)
		Bipolar I disorder	5 (13.9)
		Psychotic disorder NOS	4 (11.1)
		Schizoaffective disorder	3 (8.3)
		Delusional disorder	1 (2.8)
		Schizophrenia	1 (2.8)
Major depressive disorder	77 (15.4)	Major depressive disorder	54 (**70.1**)
		Bipolar I disorder	16 (20.8)
		Schizoaffective disorder	6 (7.8)
		Schizophrenia	1 (1.3)
Delusional disorder	22 (4.4)	Delusional disorder	16 (**72.7**)
		Schizoaffective disorder	5 (22.7)
		Schizophrenia	1 (4.5)
Schizophrenia	48 (9.6)	Schizophrenia	36 (**75.0**)
		Schizoaffective disorder	12 (25.0)
Bipolar I disorder, mixed	83 (16.6)	Bipolar I disorder	76 (**91.6**)
		Schizoaffective disorder	7 (8.4)
Bipolar I disorder, manic	148 (29.6)	Bipolar I disorder	147 (**99.3**)
		Schizoaffective disorder	1 (0.68)
Schizoaffective disorder	1 (0.2)	Schizoaffective disorder	1 (**100**)

[a]Listed in rank-order of worst-to-best diagnostic stability among 500 patients with SCID-based initial and 2-year assessments.
[b]Boldface indicates the proportion of initial diagnoses remaining unchanged (sensitivity).
Abbreviations: NOS = not otherwise specified, SCID = Structured Clinical Interview for DSM-IV.

Table 3. Categorical Outcomes of Diagnoses During Follow-Up[a]

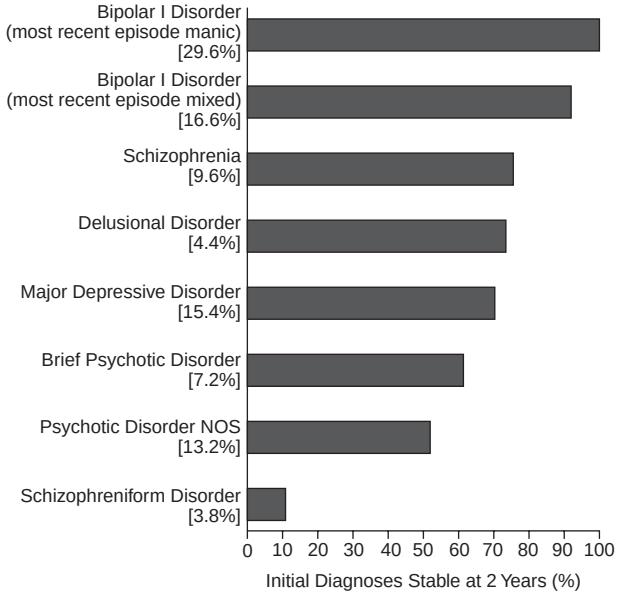
New Categories	From Nonaffective	From Affective	From Schizoaffective	From All Sources
To affective	16/81 (19.8%)	16/31 (51.6%)	0 (0.00%)	32/112 (28.6%)
To non-affective	19/81 (23.5%)	1/31 (3.20%)	0 (0.00%)	20/112 (17.9%)
To schizoaffective	46/81 (56.8%)	14/31 (45.2%)	0 (0.00%)	60/112 (53.6%)
All changes	81/191 (42.4%)	31/308 (10.1%)	0 (0.00%)	112/500 (22.4%)
Stable diagnoses	110/191 (57.6%)	277/308 (89.9%)	1/l (100%)	388/500 (77.6%)
Baseline Totals	191/191 (100%)	308/308 (100%)	1/1 (100%)	500/500 (100%)

[a]Diagnostic changes (22.4% of all cases) are specified in Table 2. Initially, there were 308 diagnoses of affective psychoses (61.6%), 191 of nonaffective disorders (38.2%), and 1 of schizoaffective disorder (0.20%). At follow-up, the distribution was affective (309; 61.8%), nonaffective (130; 26.0%), and schizoaffective (61; 12.2%), indicating a 60-fold increase of schizoaffective diagnoses, a 6.4% increase of affective disorder diagnoses, and 12.2% loss among nonaffective diagnoses ($\chi^2 = 393$, df = 4, $p < .0001$).

psychotic disorder, 51.5% for psychotic disorder NOS, and only 10.5% of initial schizophreniform disorder diagnoses (Figure 1).

Of 112 diagnostic changes, 81 (72.3%) involved diagnoses initially considered nonaffective (42.4% of 191 cases; Tables 2 and 3). These included 46/81 (56.8%) shifting to schizoaffective disorders, from initial psychotic disorder NOS (N = 19), schizophrenia (N = 12), delusional disorder (N = 5), schizophreniform disorder (N = 7), or brief psychotic disorder (N = 3). Changes to alternative nonaffective categories occurred in 19/81 (23.5%): from brief psychotic disorder to psychotic disorder NOS (N = 4), schizophrenia (N = 1) or delusional disorder (N = 1); psychotic disorder NOS to schizophrenia (N = 5) or delusional disorder (N = 1); schizophreniform disorder to schizophrenia (N = 6); and from delusional disorder to schizophrenia (N = 1). There were 16 shifts (19.8%) to new affective diagnoses: from psychotic disorder NOS to bipolar I disorder (N = 6) or MDD, severe, with psychotic features (N = 1), schizophreniform

Figure 1. Diagnostic Stability of Initial DSM-IV Diagnoses (with prevalences [%] from Table 1) Among 500 First-Episode Psychotic Disorder Patients at First-Lifetime Hospitalization, Ranked by Diagnostic Stability for the Same Subjects at 2-Year Follow-Up (% remaining unchanged)[a,b]



[a]One case initially and finally diagnosed as schizoaffective disorder is omitted.
[b]Diagnostic stability ranged from 96.5% for bipolar I disorder (best for pure mania) to only 10.5% for schizophreniform disorder.

disorder to MDD, severe, with psychotic features (N = 2) or bipolar I disorder (N = 2), and 5 from brief psychotic disorder to bipolar I disorder.

There were only 27.7% (31 of 112) changes of initial affective disorder diagnoses (of 308 cases: 10.1%), including 14 (45.2%) new schizoaffective diagnoses arising from bipolar I disorder (N = 8) or MDD (N = 6). Shifts within affective categories (N = 16) all involved new diagnoses of bipolar I disorder from initial MDD, severe, with psychotic features, owing to later manic (N = 10) or mixed episodes (N = 6). The one new nonaffective diagnosis was of schizophrenia from initial MDD, severe, with psychotic features.

Initial Diagnosis as Predictor of Final Diagnoses

Bayesian analyses[30] of final versus initial diagnoses (not shown) indicate that bipolar I disorder, in particular (96.5%), and, to a lesser extent, schizophrenia (75.0%), had relatively high levels of diagnostic stability or positive predictive value of initial SCID-based diagnoses. In contrast, initial SCID-based schizophreniform disorder, psychotic disorder NOS, and MDD, severe, with psychotic features, and brief psychotic disorder (10.5%–61.1%) diagnoses had lower consistency or predictive power (Table 2). Moreover, schizoaffective disorders were rarely diagnosed initially, indicating low diagnostic sensitivity without prolonged observation (Table 2). Sensitivity (diagnosed at both baseline and 24 months, or "true positive" rate) exceeded 90% only for bipolar I disorder and initially rare schizoaffective disorder (100%), with lower sensitivity for schizophrenia (75.0%), delusional disorder (72.7%), and MDD, severe, with psychotic features (70.1%), and much lower sensitivity for all other initial diagnoses, ranging from 61.1% for brief psychotic disorder to 10.5% for schizophreniform disorder. Specificity (not diagnosed at 24 months/not diagnosed at baseline, or "true negatives") in all categories equaled or exceeded 93%. These findings indicate that initial diagnoses vary greatly in their durability over time but that not having a diagnosis initially implies a low risk of being so diagnosed later.

Predictors of Diagnostic Instability

Initial bivariate contrasts indicated that subjects with changed versus stable diagnoses (in descending order of statistical significance) were (1) 2.5 times more likely to have an initial nonaffective diagnosis, (2) more likely to present with initial auditory hallucinations, (3) more likely to present with initial Schneiderian first-rank symptoms (FRS) of any type, (4) more likely to present with FRS of thought passivity-experience, (5) more likely to present with FRS of delusional perception, (6) 4.7 years younger at onset, (7) more likely to have had a gradual onset, (8) 1.3 times more often men than women, (9) more likely to have had recent homicidal behavior, (10) 1.7 times less likely to present with initial cycloid features, and (11) more likely to have had a previous head injury during prepsychotic either antecedent or prodromal phases (Table 4).

Several of these factors were sustained as independently associated with diagnostic change in a multivariate logistic regression model, with factors ranking by p value as (1) nonaffective versus affective psychotic disorders > (2) initial auditory hallucinations (including first-rank and other types) > (3) younger age at onset > (4) male sex > (5) gradual onset versus acute or subacute onset (Table 4). Additional factors not associated with changes in diagnosis included various prepsychotic or antecedent or prodromal comorbid psychiatric disorders (including cyclothymia, dysthymia, posttraumatic stress disorder or other anxiety disorders, eating disorders, or Axis II personality disorders, including clusters A–C, any form of substance abuse), as well as medical or neurologic illnesses or early learning disability, and study site (see Table 4 footnote).

DISCUSSION

Study Strengths and Limitations

Strengths of this study include its prospective and systematic follow-up of a large cohort of first-episode

Table 4. Factors Associated With Diagnostic Stability

Bivariate Analyses[a]				
Factor	Stable Diagnoses	Changed Diagnoses	F or χ^2	p Value
Initial nonaffective diagnoses, %	28.4	72.3	71.2	< .0001
Auditory hallucinations, %	42.3	65.2	18.3	< .0001
First-rank symptoms, %				
Any	75.3	92.0	14.6	.0001
Passivity	16.0	26.8	6.76	.009
Delusional perception	54.4	67.0	5.62	.02
Age at onset, mean ± SD, y	32.8 ± 14.5	28.1 ± 9.6	10.2	.002
Gradual onset, %	13.7	15.9	9.53	.008
Male sex, %	51.8	66.1	7.15	.008
Homicidal behavior within 1 wk, %	11.1	20.5	6.78	.009
Cycloid features, %	19.4	11.6	3.65	.06
Prior head trauma, %	6.96	12.5	3.55	.06
Multivariate Analysis[b]				
Factor	Odds Ratio (95% CI)		χ^2	p Value
Nonaffective disorders	5.59 (3.45 to 9.07)		48.8	< .0001
Auditory hallucinations	2.05 (1.27 to 3.31)		8.67	.003
Younger age at onset	1.03 (1.03 to 1.05)		5.28	.022
Male sex	1.64 (1.01 to 2.68)		4.01	.045
Gradual onset	1.80 (1.01 to 3.20)		3.99	.046

[a]Data are percentages of subjects with the stated features, or means ± SD; continuous variables are tested with analysis of variance (df = 1, N = 499); categorical variables were tested with contingency tables (χ^2 [df = 1], with factors in descending order by p values.) Other factors *not* associated with diagnostic stability included (1) months from initial symptoms to first syndromal illness; (2) prepsychotic anxiety disorders or posttraumatic stress disorder; (3) personality disorder or cluster-type; (4) other Schneiderian first-rank features; (5) Capgras misidentification features; (6) visual, olfactory, gustatory, tactile, or somatosensory hallucinations (7) substance abuse (drug or alcohol); (8) previous eating disorder; (9) head injury history; (10) significant prior or intake medical/surgical comorbidity, epilepsy, or allergy; (11) previous migraine; (12) prior epileptic seizures; (13) early learning disorder; or (14) study site.
[b]Logistic regression model: outcome is diagnostic change; factors are ranked by p values.

patients diagnosed with a broad range of DSM-IV affective and nonaffective psychotic disorders, based on early and 24-month full SCID assessments of 500 of 517 enrolled subjects (96.7%), with final SCID diagnostic assessments blinded to initial diagnosis. Notable limitations include relatively small samples of subjects (< 40 persons) in several categories at intake (especially brief psychotic, delusional, schizophreniform, and schizoaffective disorders), evidently reflecting their limited prevalence among patients sampled in this cohort. Such power limitations precluded statistical analysis of predictive factors for specific diagnostic changes, and the overall analyses reported may not apply to all disorders.

Stability of Specific Initial Diagnoses

A main finding is that bipolar I disorder with psychotic features was a highly robust diagnosis, stable for 2 years in 96.5% of cases, with changes only to schizoaffective disorder, particularly after mixed-state onset (Figure 1; Table 2). Schizophrenia was second most stable (75.0%), also changing only to schizoaffective disorder. Delusional disorder was somewhat less stable (at 72.7%), as 27.3% of such cases were later diagnosed with schizoaffective disorder or schizophrenia. Although uncommon (4.4%), delusional disorder diagnoses remained stable in nearly three quarters of cases (72.7%; Table 2). Delusional disorder has been associated with male sex and evolution into schizophrenia or schizoaffective diagnoses, with emergence of hallucinations or formal thought disorder, or affective features.[25] Its relationship to the schizophrenias and paraphrenias has remained ambiguous for a century.[2] Major depressive disorder, severe, with psychotic features, was similarly stable (70.1%), shifting, as expected, to bipolar I disorder as later manic or mixed episodes arose (20.8%), with fewer new schizoaffective diagnoses (7.8%), and rarely schizophrenia (1.3%). The diagnostic stability of bipolar I disorder compared to all other psychotic disorders may reflect genetic-psychobiological factors or the relatively consistent nature of mania and mixed states versus more heterogeneous acute or even chronic psychotic symptoms.

Schizoaffective disorder, though least prevalent at baseline (0.20%), accounted for 12.2% of all 500 diagnoses at 2 years and 53.6% of new diagnoses—a 61-fold increase. Most new diagnoses of schizoaffective disorder arose due to newly perceived affective features among initially apparently nonaffective disorders (Table 3). Emergence of affective features led 24.1% of initial nonaffective cases to be diagnosed later as schizoaffective, whereas only 4.5% of initial affective disorder illnesses later manifested sustained psychotic features. That is, later emergence of affective features not present at intake was 5.4 times more likely than later emerging psychotic features as a route to schizoaffective diagnoses

(Table 3). In other studies, first-episode psychosis patients have received schizoaffective diagnoses during later follow-up, although relative contributions of later emerging nonaffective versus affective features were not specified.[15,21–23,31]

A striking example of such a change occurred with initial diagnoses of schizophrenia, 25.1% of which had changed to schizoaffective disorder by 24 months. This incidence of diagnostic change was unexpected, particularly given the DSM requirement of 6 continuous months of illness to support the diagnosis of schizophrenia.[4] Even in schizophrenia, some symptoms may require 12 to 24 months to stabilize.[32,33] For both disorders, prolonged observation, perhaps for more than 6 months, may be required to establish a diagnosis with confidence. DSM-IV schizoaffective disorder, as currently conceived, is widely considered to be similar to schizophrenia, in such features as severity, chronicity, disability, high rates of comorbidity, and relatively young age at onset.[10,20] This schizophrenia-like picture of contemporary schizoaffective disorders differs from Kasanin's original concept[34] of acute admixtures of features and recent formulations that include an episodic course.[26] Moreover, such "intermediate" disorders, lying between schizophrenia and manic-depressive disorders, challenge the fundamental Kraepelinian nonaffective/affective dichotomous core of current DSM and ICD diagnostic systems.[2,4,5,16,19,35]

The ambiguous category psychotic disorder NOS was expected to change over time, as it did in 48.5% of cases so diagnosed initially. Far more such cases shifted to affective categories (81.3%) than to nonaffective diagnoses (18.8%; Table 2), suggesting that affective features were not compelling initially. Despite its instability, such a working category may be required even as psychiatric diagnosis becomes more reliable, particularly as some acute psychotic disorders may not be fully expressed at onset.

Acute psychoses and other diagnoses of uncertain reliability changed in more than one third of cases, including initial schizophreniform disorder diagnoses (89.5%), psychotic disorder NOS (48.5%), and brief psychotic disorder (38.9%; Tables 1 and 2; Figure 1). These less-stable diagnoses shifted to various other categories (Table 2). There were particularly high levels of diagnostic instability of psychotic disorders expected to be acute, time-limited, and prognostically favorable, particularly schizophreniform disorder. Initially, this diagnosis was not common, but 89.5% of such cases changed to other diagnoses at 2 years, particularly schizoaffective disorder and schizophrenia (Table 2). Other studies have also found that schizophreniform disorder was associated with later schizophrenia or schizoaffective diagnoses, as well as being more common in men than women.[22,23,25,27,31,36] In contrast to schizophreniform disorder, DSM-IV brief psychotic disorder was a moderately stable category, since only 38.9% later changed, usually to bipolar I disorder or psychotic disorder NOS. Unlike schizophreniform disorder, brief psychotic disorders often are relatively acute and time-limited and may be episodic but rarely follow a chronic course and often appear in relatively well-functioning women.[12,15,17,18,24,25,37] Brief psychosis,[4] as well as "acute and transient psychoses" of ICD-10,[5] may be a more valid construct than schizophreniform disorder and appears to be associated with a more episodic-favorable course. In contrast, the DSM schizophreniform category appears to select more for a chronic later course. This difference may reflect their dissimilar DSM-IV duration criteria (up to 6 months for schizophreniform disorder vs. < 1 month for brief psychotic disorder), which may be useful but fail to take into account other descriptive differences. For example, the acute and transient psychoses of ICD-10,[5] as well as the related concepts of cycloid psychoses[38,39] and twilight psychogenic or epileptoid psychotic states,[40] that might serve to guide earlier definitive diagnoses.[41]

Comparisons With Earlier Studies

Several prospective studies have considered diagnostic stability of first-episode psychotic illnesses, although large, broad samples followed up for a year or longer[10,15,21,22,26,27] and evaluations of factors associated with diagnostic stability are rare.[22,26,27] These studies include evidence that bipolar I disorder is a very robust diagnosis. A detailed review of this work is beyond the scope of this report. However, the cited studies[10,15,21,22,26,27] averaged with our findings (Table 2) found DSM-IV schizophrenia to be a particularly stable mean ± SD initial diagnosis (90.6 ± 9.4%); bipolar I disorder to be similarly stable (87.5 ± 8.4%); MDD, severe, with psychotic features, less stable (54.4 ± 38.9%), and the pool of schizophreniform disorder, schizoaffective disorder, and psychotic disorder NOS diagnoses the least stable diagnoses (34.1 ± 26.6% of cases).

Predictive Factors

Predictive factors associated with diagnostic instability, in addition to an initial provisional or unstable diagnosis (such as schizophreniform disorder, psychotic disorder NOS, or brief psychotic disorder categories), included nonaffective initial disorders, any type of initial auditory hallucinations, younger age at syndromal onset, male sex, and gradual onset (Table 4). Comparable studies are rare. Schwartz et al.,[22] found that change between 6 and 24 months to schizophrenia or schizoaffective diagnoses was associated with poor adolescent adjustment, lack of early substance abuse, psychosis ≥ 3 months before hospitalization, more initial negative symptoms, prolonged hospitalization, and antipsychotic treatment at discharge. For Schimmelmann et al.,[26] higher initial Clinical Global Impressions and lower premorbid Global Assessment of Functioning scores predicted shifts from schizophreniform disorder to schizophrenia or schizoaffective dis-

order. Whitty et al.[27] associated diagnostic change in general with less education, milder initial psychopathology, and comorbid alcohol or substance abuse. Overall, relationships of substance abuse to risk or timing of new psychotic disorders remain unclear and the evidence inconsistent.[22,27,28]

Associations of particular early characteristics with later specific psychotic-disorder diagnoses encourage further study of potential predictive diagnostic value of antecedent and prodromal features[18] to guide earlier diagnosis and therapeutic interventions aimed at limiting morbidity and disability.[42,43] However, challenges of evaluating prepsychotic or premorbid phenomena during both antecedent and prodromal phases are great, especially in young patients, and early symptoms can obscure or delay diagnosis of psychotic disorders, particularly when prominent nonspecific features suggest neurotic, personality, or conduct disorders.[10,13,14,18,20,22,28,36,44–49]

CONCLUSIONS

Our findings underscore the wide diversity of diagnostic stability among DSM-IV psychotic disorder categories, based on 2 years of observation from onset, and they suggest 4 major diagnostic nodes, based on diagnostic stability: (1) high stability: bipolar I disorder > (2) moderate stability: schizophrenia, MDD, severe, with psychotic features, delusional disorder >> (3) low stability (particularly schizophreniform disorder, psychotic disorder NOS, and brief psychotic disorder); and (4) the schizoaffective disorders, which represent a special problem owing to a lack of consensus concerning diagnostic criteria. DSM-IV bipolar I disorder was particularly stable, and it appears to be even more robust as an initial diagnosis than schizophrenia or other psychotic disorders. Early allocation of individual patients to a particular diagnosis or to such diagnostic nodes might usefully consider the details of early psychopathology as well as presenting clinical features.

Most changes were to the ambiguous "schizoaffective" diagnoses, which usually were anticipated by initial mixed states of bipolar I disorder as well as later emerging affective components of initially nonaffective psychotic illnesses, typically with unfavorable outcomes. This category challenges the standard psychotic/affective Kraepelinian dichotomy underlying both DSM-IV and ICD-10 and requires further study. The diagnosis of DSM-IV schizoaffective disorder may require prolonged observation, possibly more than 12 months, and may include acute and episodic as well as chronic forms.

We also recommend critical reevaluation of the DSM-IV categories of schizophreniform and brief psychotic disorders and related concepts. Development of improved diagnostic criteria for such supposedly good-prognosis and time-limited disorders and, more generally, for all diagnostic categories of psychotic illnesses, may require integration of categorical and dimensional approaches, with due consideration of premorbid and prodromal features and long-term outcomes.[1,50–54] Finally, we specifically encourage continued efforts to devise diagnostic methods and criteria to identify patients with psychotic disorders of favorable course as early as possible, if only to avoid unnecessarily pessimistic prognoses and overuse of antipsychotic medications and other costly or risky interventions.[39]

Financial disclosure: **Dr. Baldessarini** is a consultant or research collaborator to Janssen, JDS, Eli Lilly, Luitpold, and Novartis but is not a member of speakers bureaus, nor does he or any family member hold equity positions in pharmaceutical or biomedical companies. **Dr. Tohen** is an employee and stock shareholder of Eli Lilly. **Dr. Vieta** has been a consultant to or received research support from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Janssen-Cilag, Jazz, Merck, Novartis, Organon, Otsuka, Pfizer, Sanofi, and Servier. **Drs. Salvatore**, **Khalsa**, **Perez Sanchez-Toledo**, **Zarate**, and **Maggini** report no additional financial or other relationship relevant to the subject of this article.

REFERENCES

1. Kahlbaum KL. Catatonia. Levij Y, Pridan T, trans. Baltimore, Md: Johns Hopkins University Press; 1973
2. Kraepelin E. Psychiatrie: Ein Lehrbuch für Studierende und Ärzte [Textbook of Psychiatry]. Barclay RM, trans. Edinburgh, Scotland: E & S Livingstone; 1919
3. Robins E, Guze, SB. Establishment of diagnostic validity in psychiatric illness: application to schizophrenia. Am J Psychiatry 1970;126:983–937
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). Arlington, Va: American Psychiatric Press; 2000
5. World Health Organization. International Classification of Diseases, Tenth Revision (ICD-10). Geneva, Switzerland: World Health Organization; 1992
6. Baldessarini RJ. American biological psychiatry and psychopharmacology 1944–1994. In: Menninger RW, Nemiah JC eds. American Psychiatry After World War II (1944–1994). Washington, DC: American Psychiatric Association Press; 2000:371–412
7. Kramer MD, Krueger RF, Hicks BM. The role of externalizing and internalizing liability factors in accounting for gender differences in the prevalence of common psychopathological syndromes. Psychol Med 2008;38:51–61
8. Kendler KS. Toward a scientific psychiatric nosology: strengths and limitations. Arch Gen Psychiatry 1990;47:969–973
9. Kendler KS, Walsh D. Structure of psychosis: syndromes and dimensions. Arch Gen Psychiatry 1998;55:508–509
10. McClellan J, McCurry C. Early onset psychotic disorders: diagnostic stability and clinical characteristics. Eur Child Adolesc Psychiatry 1999;8(suppl 1):113–I19
11. Hollis C. Adult outcomes of child- and adolescent-onset schizophrenia: diagnostic stability and predictive validity. Am J Psychiatry 2000;157: 1652–1659
12. Valevski A, Ratzoni G, Sever J, et al. Stability of diagnosis: a 20-year retrospective cohort study of Israeli psychiatric adolescent inpatients. J Adolesc 2001 Oct;24(5):625–633
13. Peralta V, Cuesta MJ. Can schizophrenia be diagnosed in the initial prodromal phase? Arch Gen Psychiatry 2002;59:664–665
14. Drake RJ, Dunn G, Tarrier N, et al. Evolution of symptoms in the early course of non-affective psychosis. Schizophr Res 2003;63:171–179
15. Jarbin H, von Knorring AL. Diagnostic stability in adolescent onset psychotic disorders. Eur Child Adolesc Psychiatry 2003 Jan;12(1):15–22
16. Peralta V, Cuesta MJ. Nosology of psychotic disorders: comparison among competing classification systems. Schizophr Bull 2003;29: 413–425
17. Susser E, Fennig S, Jandorf L, et al. Epidemiology, diagnosis, and course of brief psychoses. Am J Psychiatry 1995;152:1743–1748

18. Singh SP, Burns T, Amin S, et al. Acute and transient psychotic disorders: precursors, epidemiology, course and outcome. Br J Psychiatry 2004;185:452–459
19. Vollmer-Larsen A, Jacobsen TB, Hemmingsen R, et al. Schizoaffective disorder: reliability of its clinical diagnostic use. Acta Psychiatr Scand 2006;113:402–407
20. McClellan JM, Werry JS, Ham M. A follow-up study of early onset psychosis: comparison between outcome diagnoses of schizophrenia, mood disorders, and personality disorders. J Autism Dev Disord 1993 Jun;23(2):243–262
21. Amin S, Singh SP, Brewin J, et al. Diagnostic stability of first-episode psychosis: comparison of ICD-10 and DSM-III-R systems. Br J Psychiatry 1999;175:537–543
22. Schwartz JE, Fennig S, Tanenberg-Karant M, et al. Congruence of diagnoses two years after a first-admission diagnosis of psychosis. Arch Gen Psychiatry 2000;57:593–600
23. Veen ND, Selten JP, Schols D, et al. Diagnostic stability in a Dutch psychosis incidence cohort. Br J Psychiatry 2004;185:460–464
24. Amini H, Alaghband-rad J, Omid A, et al. Diagnostic stability in patients with first-episode psychosis. Australas Psychiatry 2005 Dec;13(4): 388–392
25. Baldwin P, Browne D, Scully PJ, et al. Epidemiology of first-episode psychosis: illustrating the challenges across diagnostic boundaries through the Cavan-Monaghan study at 8 years. Schizophr Bull 2005 Jul;31(3):624–638
26. Schimmelmann BG, Conus P, Edwards J, et al. Diagnostic stability 18 months after treatment initiation for first-episode psychosis. J Clin Psychiatry 2005 Oct;66(10):1239–1246
27. Whitty P, Clarke M, McTigue O, et al. Diagnostic stability four years after a first episode of psychosis. Psychiatr Serv 2005;56:1084–1088
28. Caton CL, Hasin DS, Shrout PE, et al. Stability of early-phase primary psychotic disorders with concurrent substance use and substance-induced psychosis. Br J Psychiatry 2007;190:105–111
29. Tohen M, Zarate CA Jr, Hennen J, et al. McLean-Harvard First-Episode Mania Study: prediction of recovery and first recurrence. Am J Psychiatry 2003;160:2099–2107
30. Baldessarini RJ, Finklestein S, Arana, GW. Predictive power of diagnostic tests and the effect of prevalence of illness. Arch Gen Psychiatry 1983;40:569–573
31. Addington J, Chaves A, Addington D. Diagnostic stability over one year in first-episode psychosis. Schizophr Res 2006;86:71–75
32. Rey ER, Bailer J, Brauer W, et al. Stability trends and longitudinal correlations of negative and positive syndromes within three-year follow-up of initially hospitalized schizophrenics. Acta Psychiatr Scand 1994;90:405–412
33. Reichemberg A, Rieckmann N, Harvey PD. Stability in schizophrenia symptoms over time: findings from the Mount Sinai Pilgrim Psychiatric Center Longitudinal Study. J Abnorm Psychol 2005;114:363–372
34. Kasanin J. The acute schizoaffective psychoses (1933). Am J Psychiatry 1994 Jun;151(suppl 6):144–154
35. Malhi GS, Green M, Fagiolini A, et al. Schizoaffective disorder: diagnostic issues and future recommendations. Bipolar Disord 2008;10:215–230
36. Bromet EJ, Naz B, Fochtmann LJ, et al. Long-term diagnostic stability and outcome in recent first-episode cohort studies of schizophrenia. Schizophr Bull 2005 Jul;31(3):639–649
37. Pillmann F, Haring A, Balzuweit S, et al. Concordance of ICD-10 acute and transient psychosis and DSM-IV brief psychotic disorder. Psychol Med 2002;32:525–533
38. Kleist K. On Karl Kleist. Chapt 12. In: Hirsch SR, Shepherd M, eds. Themes and Variations in European Psychiatry: An Anthology, translated by Marshal H. Charlottesville, Va: University of Virginia Press; 1974:295–331
39. Leonhard K. Classification of Endogenous Psychoses and Their Differentiated Etiology, edited by Beckmann H, 2nd ed. New York, NY: Springer-Verlag; 1999
40. Bonhoeffer K. How far should all psychogenic illnesses be regarded as hysterical? In: Hirsch SR, Shepherd M, eds. Translated by Marshal H. Themes and Variations in European Psychiatry: An Anthology. Charlottesville, Va: University of Virginia Press; 1974:53–64
41. Marneros A, Pillmann F, Haring A, et al. Is the psychopathology of acute and transient psychotic disorder different from schizophrenic and schizoaffective disorders? Eur Psychiatry 2005;20:315–320
42. McGorry PD. Evaluating the importance of reducing the duration of untreated psychosis. Aust N Z J Psychiatry 2000 Nov;34(suppl): S145–S149
43. van Rossum I, Haro JM, Tenback D, et al. Stability and treatment outcome of distinct classes of mania. Eur Psychiatry 2008;;23(5):360–367
44. Fennig S, Bromet EJ, Craig T, et al. Psychotic patients with unclear diagnoses: descriptive analysis. J Nerv Ment Dis 1995;183:207–213
45. Klosterkötter J, Ruhrmann S, Schultze-Lutter F, et al. The European Prediction of Psychosis Study (EPOS): integrating early recognition and intervention in Europe. World Psychiatry 2005;4:161-167
46. Addington J, Cadenhead KS, Cannon TD, et al. North American Prodrome Longitudinal Study: a collaborative multisite approach to prodromal schizophrenia research. Schizophr Bull 2007;33:665–672
47. Schultze-Lutter F, Ruhrmann S, Picker H, et al. Basic symptoms in early psychotic and depressive disorders. Br J Psychiatry Suppl 2007 Dec;51:S31–S37
48. Cannon TD, Cadenhead K, Cornblatt B, et al. Prediction of psychosis in youth at high clinical risk: multisite longitudinal study in North America. Arch Gen Psychiatry 2008;65:28-37
49. Nelson B, Yung AR, Bechdolf A, et al. Phenomenological critique and self-disturbance: implications for ultra-high risk (“prodrome”) research. Schizophr Bull 2008;34:381–392
50. Peralta V, Cuesta MJ. The underlying structure of diagnostic systems of schizophrenia: a comprehensive polydiagnostic approach. Schizophr Res 2005;79:217–229
51. Allardyce J, Suppes T, Van Os J. Dimensions and the psychosis phenotype. Int J Methods Psychiatr Res 2007;16(suppl 1):S34–S40
52. Häfner H. [Is the schizophrenia diagnosis still appropriate?]. Psychiatr Prax 2007;34:175–180
53. Vieta E, Phillips ML. Deconstructing bipolar disorder: a critical review of its diagnostic validity and a proposal for DSM-V and ICD-11. Schizophr Bull 2007;33:886–892
54. Krueger RF, Markon KE. Understanding psychopathology: melding behavior genetics, personality, and quantitative psychology to develop an empirically based model. Curr Dir Psychol Sci 2008;15:113–117