McLean-Harvard International First-Episode Project: Two-Year Stability of *ICD-10* Diagnoses in 500 First-Episode Psychotic Disorder Patients

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Objective: Because clinical and biologic research and optimal clinical practice require stability of diagnoses over time, we determined stability of *ICD-10* psychotic disorder diagnoses and sought predictors of diagnostic instability.

Method: Patients from the McLean-Harvard International First-Episode Project, conducted from 1989 to 2003, who were hospitalized for first psychotic illnesses (N = 500) were diagnosed by *ICD-10* criteria at baseline and 24 months, on the basis of extensive prospective assessments, to evaluate the longitudinal stability of specific categorical diagnoses and predictors of diagnostic change.

Results: Diagnostic stability averaged 90.4%, ranking as follows: schizoaffective disorder (100.0%) > mania with psychosis (99.0%) > mixed affective episode (94.9%) > schizophrenia (94.6%) > delusional disorder (88.2%) > severe depressive episode with psychotic symptoms (85.2%) > acute psychosis with/without schizophrenia symptoms = unspecified psychosis (all 66.7%) >> acute schizophrenia-like psychosis (28.6%). Diagnoses changed by 24 months of follow-up to schizoaffective disorder (37.5%), bipolar disorder (25.0%), schizophrenia (16.7%), or unspecified nonorganic psychosis (8.3%), mainly through emerging affective features. By logistic regression, diagnostic change was associated with Schneiderian first-rank psychotic symptoms at intake > lack of premorbid substance use.

Conclusions: We found some psychotic disorder diagnoses to be more stable by *ICD-10* than *DSM-IV* criteria in the same patients, with implications for revisions of both diagnostic systems.

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> *"The truth of aesthetically satisfying and didactically convenient classifications can be tested only in the actual application of them."*
>
> Karl Jaspers[1]

The importance of establishing sound categorical or syndromal clinical diagnoses of major psychiatric disorders with both cross-sectional validity and stability over time has long been recognized as clinically crucial and essential for progress in neurobiologic as well as clinical research.[1–3] International taxonomies represented by the World Health Organization's (*International Classification of Diseases* [*ICD*]) and American Psychiatric Association's (*Diagnostic and Statistical Manual of Mental Disorders* [*DSM*]) systems involve standardized and operationalized descriptive criteria and a longitudinal perspective.[4,5] More objective, biologically based methods to support psychiatric diagnoses continue to be sought but are unlikely to soon displace clinical, descriptive, phenomenological systems of diagnosis or limit the need for biologists and nosologists to collaborate.[6]

Diagnosis of psychotic disorders may be especially unstable, owing to factors that include: (1) insufficient and potentially unreliable information, especially if elicited only from patients; (2) fluctuating manifestations or detection of psychopathology over time and later emergence or change of initially unclear symptoms[7,8]; (3) symptom-modifying effects of treatment, substance abuse, comorbid psychiatric or medical disorders, and prolonged disability or institutional care[8]; premorbid temperamental characteristics or personality disorders[9] and developmental factors related to age[10,11]; as well as (4) standardized diagnostic schemes of potentially limited validity,[4,5] with simplified or arbitrary criteria for particular features, symptom duration, and functional impairment that belie the richness, complexity, fluidity, and nuances of illness phenomena arising early in most disorders.[11–19] In addition, some diagnostic concepts remain inadequately validated and may simply be unreliable, notably including transient acute psychotic disorders and schizoaffective syndromes, or may be applied differently to particular clinical, ethnic, sex, or age groups, highlighting the need to consider cultural variations in psychopathological presentations and illness stability over time.[20–23]

Given clinical and research requirements for more reliable diagnoses despite limited information and typically brief observation times, it is highly desirable that initial standardized, syndromal diagnoses remain longitudinally stable or follow predictable courses. It is, therefore, important to test diagnostic stability by systematic and prospective, long-term assessments, if only to document levels of longitudinal congruence of specific diagnoses and to identify early predictors

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of later diagnostic change. Several modern studies have considered the stability of some psychotic disorders followed from onset,[11,14,18,24–38] but few have considered predictors of particular diagnostic changes over a wide spectrum of disorders.[26,31,32,35–38] Specifically, studies of longitudinal stability of specific *ICD-10* psychotic disorder diagnoses include acute and transient psychotic disorder (ATPD) subtypes among acute polymorphic psychotic disorders (APPDs),[39–44] schizophrenia,[45,46] or mood disorders.[47–49] However, we found only 2 studies that investigated diagnostic stability over time in the broad range of *ICD-10* functional psychoses, and neither explored factors predicting diagnostic change or stability over time.[25,28]

On the basis of these considerations and our previous findings on diagnostic stability and its predictors among *DSM-IV* psychotic disorders,[38] we again evaluated diagnostic stability over 2 years of a broad range of initially considered psychotic disorders based on *ICD-10* criteria among 517 patients enrolled in the McLean-Harvard International First-Episode Project. We hypothesized that stability of some initial *ICD-10* diagnoses would vary over time and that early clinical factors might predict later diagnostic instability. As secondary aims, we considered how initial affective and psychotic components of illnesses changed over time and whether new diagnoses were more likely to emerge through newly prominent affective versus nonaffective features.

METHOD

Subjects and Diagnostic Assessments

Subjects were among the first 517 patients entering the McLean-Harvard International First-Episode Project based at McLean Hospital and the University of Parma from 1989 to 2003. Project protocols were reviewed annually and approved by the McLean Hospital Institutional Review Board and Ethical Committee of the University of Parma Medical Center through 2008. For inclusion, all subjects presented in a first lifetime episode of affective (manic, mixed, or depressive) or nonaffective psychotic illness and gave written informed consent for participation and anonymous, aggregate reporting of findings. Intake exclusion criteria were (1) acute intoxication or withdrawal associated with drug or alcohol abuse or any delirium; (2) previous psychiatric hospitalization, unless for detoxification; (3) documented mental retardation (Wechsler Adult Intelligence Scale–tested IQ < 70) or other organic mental disorder; (4) index 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 for analyses based on *ICD-10* criteria were made by a highly trained diagnostician with years of clinical research experience (P.S.), employing historical prospective methods[50] and kept blinded to initial (baseline) and follow-up consensus and Structured Clinical Interview for *DSM-III-R*, Patient Version (SCID-P)–based diagnoses.[51] All information on illness antecedents, prodromes, onset, presentation, and course was derived from medical records (including clinical narratives of hospital course and notes from initial and follow-up assessments and semistructured interviews with patients, families, and treating or primary care clinicians) as well as research records (including psychopathological rating scales and data derived from standardized clinical interviews, including the SCID[51])—all with diagnostic formulations excluded for this study. This information was reviewed to define the most appropriate *ICD-10* diagnosis in each case at baseline and again at 2 years. These 1,000 assessments were made in random order by the same expert investigator (P.S.) over several months, with 3 to 6 weeks between individual assessments, making recollection bias unlikely. In addition, as a test of reliability of the assessments, we drew a random sample of 50 patients with 2 categorical *ICD-10* diagnoses and found agreement in 46 (92.0%), even without correcting for effects of natural diagnostic change over time. Diagnostic procedures of the First-Episode Project for other studies applied *DSM-IV* criteria or updated diagnoses according to current *DSM* classifications on the basis of SCID-P evaluations at baseline and at 24 months.[37,38] We also estimated age at onset of primary illnesses, timing of premorbid features, and the presence and timing of lifetime comorbid psychiatric or substance use disorders (SCID-based), as well as general medical, neurologic, and personality disorders determined clinically and recorded systematically according to *DSM-IV* requirements. Primary diagnoses met current *ICD-10* criteria in 2008, based on the 1992 Clinical Descriptions and Diagnostic Guidelines,[4] and were compared to *DSM-IV-TR* diagnoses.[38] Clinical assessment methods have been detailed previously.[37,38]

Data Analyses

We compared subjects with *ICD-10*–based categorical diagnoses considered stable versus changed by 24 months to assess associated patient characteristics, using 1-way analysis of variance (F) for continuous variables and contingency tables (χ^2 or Fisher exact P) for categorical factors, with defined degrees of freedom (df). We entered measures with at least suggestive differences ($P < .10$) in initial bivariate comparisons, stepwise, into a logistic regression model to identify factors independently associated with diagnostic change, reported as odds ratios (ORs) with their 95% confidence intervals (CI). Averages are means with standard deviations (± SD). Analyses were based on commercial statistical programs (Stata-9, StataCorp LP, College Station, Texas; Statview-5, SAS Institute Inc, Cary, North Carolina).

RESULTS

Subject Characteristics and Initial Diagnoses

Of 517 first-episode psychotic subjects assessed, 17 (3.3%) were lost to follow-up, leaving 500 (96.7%) for 2 (baseline and 2-year) diagnostic assessments (100.0%). Most subjects were men (55.0%), and estimated mean ± SD age at onset over the range of first psychotic syndromes averaged 31.7 ± 13.7 years. Patients enrolled at McLean Hospital (n = 406, 81.2%) and

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Table 1. Characteristics of 500 First-Episode *ICD-10* Psychotic Disorder Patients[a,b]

Characteristic	Value
Sex	
Male	275 (55.0)
Female	225 (45.0)
Age at onset by initial *ICD-10* diagnosis, mean ± SD, y	
Overall	31.7 ± 13.7
Delusional	41.4 ± 15.9
Psychotic depression	37.8 ± 18.2
Unspecified nonorganic psychosis	35.4 ± 13.0
Acute polymorphic without schizophrenic symptoms	33.3 ± 16.4
Manic or mixed affective episodes	31.5 ± 13.2
Acute polymorphic with schizophrenic symptoms	28.8 ± 10.8
Acute schizophrenia-like psychosis	28.0 ± 7.1
Schizophrenia	27.9 ± 8.9
Schizoaffective disorder	27.5 ± 10.3
DSM-IV comorbidities	
Substance use disorders	
All types	256 (51.2)
Alcohol	228 (89.1)
Drugs[c]	155 (60.5)
Both	126 (49.2)
Axis II personality disorders	115 (23.0)
Cluster A	39 (33.9)
Cluster B	55 (47.8)
Cluster C	21 (18.3)
Anxiety disorders	86 (17.2)
Phobias	35 (40.7)
Posttraumatic stress disorder	29 (33.7)
Panic disorder	26 (30.2)
Obsessive-compulsive disorder	25 (29.1)
Generalized anxiety disorder	9 (10.5)
Prevalence of initial *ICD-10* diagnoses (%, by rank)	
Mixed affective episode	156 (31.2)
Mania with psychosis	99 (19.8)
Schizophrenia	56 (11.2)
Depression with psychosis	54 (10.8)
Schizoaffective disorder	48 (9.6)
Acute polymorphic psychosis with schizophrenic symptoms	27 (5.4)
Acute polymorphic psychosis without schizophrenic symptoms	21 (4.2)
Delusional disorder	17 (3.4)
Unspecified nonorganic psychosis	15 (3.0)
Acute schizophrenia-like psychotic disorder	7 (1.4)
Changed initial diagnoses (%, by rank)	
Acute schizophrenia-like psychotic disorder	5/7 (71.4)
Acute polymorphic psychosis with schizophrenic symptoms	9/27 (33.3)
Acute polymorphic psychosis without schizophrenic symptoms	7/21 (33.3)
Unspecified nonorganic psychosis	5/15 (33.3)
Depression with psychosis	8/54 (14.8)
Delusional disorder	2/17 (11.8)
Schizophrenia	3/56 (5.4)
Mixed affective episode	8/156 (5.1)
Mania with psychosis	1/99 (1.0)
Schizoaffective disorder	0/48 (0.0)

[a]All data are presented as n (%) unless otherwise noted. [b]Overall diagnostic stability averaged 90.4% (452/500). [c]Drugs abused by 155/500 patients included cocaine (30.9%), hallucinogens (28.5%), heroin (18.4%), methylenedioxymethamphetamine ("ecstasy"; 14.5%), sedatives or hypnotics (14.0%), and stimulants (14.0%).

the University of Parma Medical Center (n = 94, 18.8%) followed identical protocols. Initial diagnoses included affective psychotic syndromes (mixed affective episode, mania with psychotic symptoms, severe depressive episode with psychotic symptoms; n = 309, 61.8%) and nonaffective disorders (schizophrenia, APPD, delusional disorder, unspecified nonorganic psychosis, and acute schizophrenia-like psychotic disorder; n = 143, 28.6%), as well as schizoaffective disorders (n = 48, 9.6%; Table 1). Among schizophrenia diagnoses at baseline (n = 56/500; 11.2%), the undifferentiated type was most prevalent (n = 22, 39.3%), the hebephrenic (n = 15, 26.8%) and paranoid types (n = 11, 19.6%) were intermediate, and the catatonic (n = 4, 7.1%) and simple (n = 1, 1.8%) types were uncommon.

At baseline, SCID-P–based lifetime comorbid diagnoses included substance use disorders (51.2%) and anxiety disorders (17.2%), and clinically determined Axis II lifetime comorbidity with personality disorders recorded according to *DSM-IV* requirements reached 23.0% (Table 1). Substance use disorders were associated (in descending incidence) with the following initial *ICD-10* diagnoses: mixed affective episode (69.2%), mania with psychosis (57.6%), schizoaffective disorder (56.3%), severe depression with psychosis (51.8%), acute schizophrenia-like disorder (42.9%), schizophrenia (33.9%), unspecified nonorganic psychosis (33.3%), APPD without symptoms of schizophrenia (23.8%), delusional disorder (11.8%), or APPD with symptoms of schizophrenia (11.1% of cases; $\chi^2_9 = 73.9$ $P < .0001$).

Based on initial diagnoses, mean age at onset was 31.7 years, and age at onset ranked by diagnosis as follows: delusional disorder (41.4) > severe depressive episode with psychotic symptoms (37.8) > unspecified nonorganic psychosis (35.4) > APPD without symptoms of schizophrenia (33.3) > mania with psychotic symptoms (31.5) = mixed affective episode (31.5) > APPD with symptoms of schizophrenia (28.8) ≥ acute schizophrenia-like psychotic disorder (28.0) ≥ schizophrenia (27.9) ≥ schizoaffective disorder (27.5 years; Table 1).

Changes in Diagnosis at 2-Year Follow-Up

Initial *ICD-10* diagnoses changed in 48/500 cases (9.6%), with a positive predictive value of initial diagnoses of 90.4%.[52] This overall stability contrasts with 77.6% found with *DSM-IV* consensus diagnoses of the same cases.[38] Positive predictive value was 1.2 times greater among subjects with *ICD-10* schizoaffective (48/48, 100.0%) or major affective episodes with psychotic features (292/309, 94.5%) than those diagnosed with *ICD-10* nonaffective psychoses (112/143, 78.3%; $\chi^2_2 = 35.1$, $P < .0001$; Tables 2 and 3).

Most changes involved later-diagnosed schizoaffective disorders (18 cases, 37.5% of the 48 revised diagnoses: 8 from initial nonaffective categories and 10 initially affective cases, including 8 initial mixed-episode diagnoses, 1 initially considered mania with psychotic symptoms, and another initially diagnosed as severe depression with psychotic symptoms). New schizoaffective diagnoses involved emerging affective features in previously nonaffective conditions, 1.8 times more often than the opposite (8/143 [5.6%] versus 10/309 [3.2%]; $\chi^2_4 = 771$, $P < .0001$).

The second most prevalent changed diagnosis was bipolar affective disorder (12/48 [25.0%]: 6 initially diagnosed severe depressive episode with psychotic symptoms, 3 APPD with symptoms of schizophrenia, 2 APPD without symptoms of schizophrenia, and 1 initial unspecified

Table 2. Changes in *ICD-10* Diagnosis: First-Episode Psychotic Disorders[a]

Initial Diagnosis	n (%)	Follow-Up Diagnoses	n (%)[b]
Acute schizophrenia-like psychotic disorder	7 (1.4)	Acute schizophrenia-like psychotic disorder	2 (**28.6**)
		Schizophrenia	4 (57.1)
		Recurrent depressive disorder[c]	1 (14.3)
Unspecified nonorganic psychosis	15 (3.0)	Unspecified nonorganic psychosis	10 (**66.7**)
		Schizoaffective disorder	3 (20.0)
		Bipolar affective disorder[c]	1 (6.7)
		Delusional disorder	1 (6.7)
Acute polymorphic psychosis with schizophrenic symptoms	27 (5.4)	Acute polymorphic psychosis with schizophrenic symptoms	18 (**66.7**)
		Bipolar affective disorder[c]	3 (11.1)
		Schizophrenia	3 (11.1)
		Recurrent depressive disorder[c]	1 (3.7)
		Mania with psychosis[d]	1 (3.7)
		Depression with psychosis[d]	1 (3.7)
Acute polymorphic psychosis without schizophrenic symptoms	21 (4.2)	Acute polymorphic psychosis without schizophrenic symptoms	14 (**66.7**)
		Unspecified nonorganic psychosis	4 (19.0)
		Bipolar affective disorder[c]	2 (9.5)
		Delusional disorder	1 (4.8)
Depression with psychosis	54 (10.8)	Any depressive disorder[e]	46 (**85.2**)
		Recurrent depressive disorder[c]	31 (57.4)
		Depression with psychosis[d]	15 (27.8)
		Bipolar affective disorder[c]	6 (11.1)
		Schizoaffective disorder	1 (1.9)
		Schizophrenia	1 (1.9)
Delusional disorder	17 (3.4)	Delusional disorder	15 (**88.2**)
		Schizoaffective disorder	2 (11.8)
Schizophrenia	56 (11.2)	Schizophrenia	53 (**94.6**)
		Schizoaffective disorder	3 (5.4)
Mixed affective episode	156 (31.2)	Any mixed or bipolar[e]	148 (**94.9**)
		Bipolar affective disorder[c]	126 (80.8)
		Mixed affective episode[d]	22 (14.1)
		Schizoaffective disorder	8 (5.1)
Mania with psychosis	99 (19.8)	Any manic or bipolar[e]	98 (**99.0**)
		Bipolar affective disorder[c]	84 (84.8)
		Mania with psychosis[d]	14 (14.1)
		Schizoaffective	1 (1.0)
Schizoaffective disorder	48 (9.6)	Schizoaffective disorder	48 (**100**)

[a]Listed in rank order of worst to best diagnostic stability among N = 500 patients with initial and 2-year *ICD-10* diagnoses. [b]Boldface indicates proportion of initial diagnoses remaining unchanged (positive predictive power). [c]Recurrent illnesses. [d]Single episode in 2 years of follow-up. [e]Total of single plus recurrent episodes.

Table 3. Categorical Outcomes of *ICD-10* Diagnoses During Follow-Up[a,b]

Follow-Up Outcome	Baseline Diagnosis			
	Nonaffective	Affective	Schizoaffective	Any
Change				
To affective	10/16 (62.5)	6/16 (37.5)	0 (0.0)	16/48 (33.3)
To nonaffective	13/14 (92.9)	1/14 (7.1)	0 (0.0)	14/48 (29.2)
To schizoaffective	8/18 (44.4)	10/18 (55.6)	0 (0.0)	18/48 (37.5)
To any	31/143 (21.7)	17/309 (5.5)	0/48 (0.0)	48/500 (9.6)
Stable diagnosis	112/143 (78.3)	292/309 (94.5)	48/48 (100.0)	452/500 (90.4)

[a]All data are presented as n (%). [b]Diagnostic changes (9.6% of all cases) are specified in Table 2. Initially, there were 309 diagnoses of affective psychoses (61.8%), 143 of nonaffective disorders (28.6%), and 48 of schizoaffective disorder (9.6%). At follow-up, the distribution was 308 diagnoses of affective psychoses (61.6%), 126 of nonaffective disorders (25.2%), and 66 of schizoaffective disorder (13.2%), indicating a 1.4 fold increase of schizoaffective diagnoses, a 0.2% decrease of affective disorder diagnoses, and a 3.4% loss among nonaffective diagnoses ($\chi^2_4 = 771$, $P < .0001$).

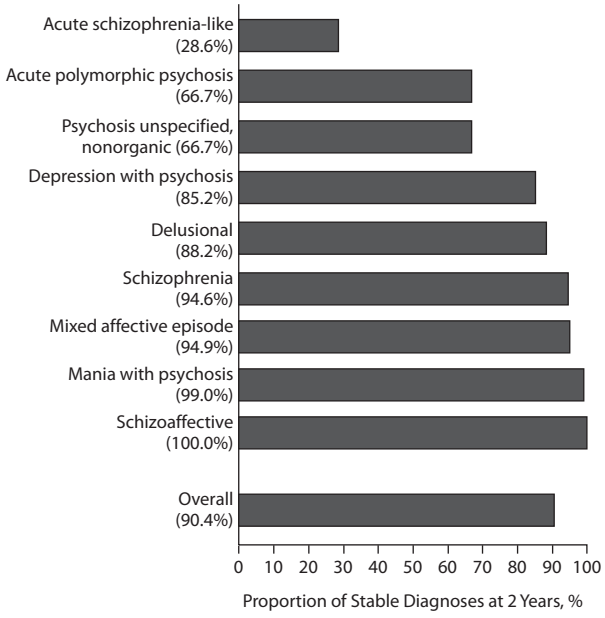
nonorganic psychosis). Third were new diagnoses of schizophrenia (8/48 changes, or 16.7%: 4 initially considered acute schizophrenia-like psychotic disorder, 3 initial APPD with symptoms of schizophrenia, and 1 with apparent severe depressive episode with psychotic symptoms). Fourth were shifts to unspecified nonorganic psychosis (4/48 = 8.3%, all from APPD without symptoms of schizophrenia). These 4 final categories accounted for 42/48, or 87.5%, of new *ICD-10* psychotic disorder diagnoses.

The remaining 6 new diagnoses (12.5%) included 2 cases of recurrent depressive disorder (1 each from acute schizophrenia-like psychotic disorder and APPD with symptoms of schizophrenia), 2 delusional disorder (1 each from unspecified nonorganic psychosis and APPD without schizophrenia symptoms), as well as 1 case each of mania with psychotic symptoms and severe depressive episode with psychotic symptoms, both being initially diagnosed as APPD with symptoms of schizophrenia.

Initial *ICD-10* diagnoses of both mania with psychotic symptoms and mixed affective episode held up best (99.0% [98/99] and 94.9% [148/156]), as only 1.0% (1/99) and 5.1% (8/156), respectively, changed to schizoaffective disorder at 2-year follow-up. These results were similar to our previous analyses of *DSM-IV* diagnoses.[38] Also among affective disorder diagnoses, 85.2% (46/54) of cases initially considered to have a severe depressive episode with psychotic symptoms remained stable, and 8 changed (6 to bipolar affective disorder, 1 each to schizoaffective disorder or schizophrenia). Among nonaffective diagnoses, schizophrenia persisted in 94.6% of patients (with only 3 changes to schizoaffective disorder, including 2 from paranoid and 1 from undifferentiated subtypes), and delusional disorder remained stable in 88.2% of cases. Most short-duration or initially nonspecific syndromes, not surprisingly, changed to various alternatives, with moderate retention rates for APPD with and without symptoms of schizophrenia (66.7%) as well as unspecified nonorganic psychosis (66.7%) and low persistence of initial acute schizophrenia-like psychotic disorder diagnoses (28.6%; Figure 1).

Of 48 total diagnostic changes, 31 (64.6%) involved diagnoses initially considered nonaffective (31/143 = 21.7%; Tables 2 and 3), of whom 8/31 (25.8%) shifted to schizoaffective disorders (from initial unspecified nonorganic psychosis [n = 3], schizophrenia [n = 3], or delusional disorder [n = 2]). Changes to alternative nonaffective categories occurred in 13/31 (41.9%) of initially nonaffective cases (4 from acute schizophrenia-like psychotic disorder to schizophrenia, 3 from APPD with symptoms of schizophrenia to schizophrenia, 5 from APPD without symptoms of schizophrenia to unspecified nonorganic psychosis [n = 4] or delusional disorder [n = 1], and 1 from unspecified nonorganic psychosis to delusional disorder). There were 10/31 shifts (32.3%) to new affective

Figure 1. Diagnostic Stability of Initial *ICD-10* Diagnoses (with prevalence [%] from Table 1) in 500 First-Episode Psychotic Disorder Patients at First Lifetime Hospitalization, Ranked by Diagnostic Stability (% remaining unchanged) for the Same Subjects at 24-Month Follow-Up[a]



[a]Diagnostic stability ranged from 100.0% for schizoaffective disorder (48 cases) to 28.6% for acute schizophrenia-like psychotic disorder (7 cases initially).
Abbreviation: *ICD-10* = *International Classification of Diseases, Tenth Revision*.

diagnoses (from APPD with symptoms of schizophrenia to bipolar affective disorder [n = 3], mania with psychotic symptoms [n = 1], recurrent depressive disorder [n = 1], or severe depressive episode with psychotic symptoms [n = 1]; from APPD without symptoms of schizophrenia to bipolar affective disorder [n = 2]; from acute schizophrenia-like psychotic disorder to recurrent depressive disorder [n = 1]; and from unspecified nonorganic psychosis to bipolar affective disorder [n = 1]).

There were only 17/48 (35.4%) changes of initial affective disorder diagnoses (of 309 initial affective cases, or 5.5%), including 10/17 (58.8%) new schizoaffective diagnoses arising from initial diagnoses of mixed affective episode (n = 8), mania with psychotic symptoms (n = 1), or severe depressive episode with psychotic symptoms (n = 1). Shifts within affective categories (n = 6) all involved new diagnoses of bipolar affective disorder from initial severe depression with psychotic symptoms, owing to later manic (n = 4) or mixed (n = 2) episodes. The 1 new nonaffective diagnosis was of schizophrenia, following an initial *ICD-10* diagnosis of severe depressive episode with psychotic symptoms.

Initial Diagnosis as Predictor of Final Diagnoses

Bayesian analyses[52] of final versus initial diagnoses (not shown) indicate that schizoaffective disorder (100.0%), mania with psychotic symptoms (99.0%), mixed affective episode (94.9%), schizophrenia (94.6%), delusional disorder (88.2%), and severe depressive episode with psychotic symptoms (85.2%) had relatively high levels of diagnostic stability or positive predictive value (> 85.0%). In contrast, initial *ICD-10*–based acute schizophrenia-like psychotic disorder (28.6%) and diagnoses of unspecified nonorganic psychosis and APPD with and without symptoms of schizophrenia (3 categories, 66.7%) had lower predictive value (Table 2). Specificity (1.0 minus the false-positive rate) in all categories was ≥ 83.0% except for the acute and transient (50.0%) or unspecified psychotic disorders (64.3%). Sensitivity (1.0 minus the false-negative rate) exceeded 86.0% in all but 2 of the following categories: acute schizophrenia-like psychotic disorder and APPD with and without symptoms of schizophrenia (100.0%), bipolar affective disorder (95.0%), severe depressive episode with psychotic symptoms (94.1%), schizophrenia (86.9%), and delusional disorder (86.7%), but not unspecified nonorganic psychosis (71.4%) and schizoaffective disorder (72.7%).

Predictors of Diagnostic Instability

Initial bivariate regression modeling indicated that subjects with changed (n = 48) versus stable (n = 452) *ICD-10* diagnoses ranked by statistical significance as (1) 4.7 years younger at onset, (2) more likely to present initial Schneiderian first-rank symptoms (FRS)[53] of any type (audible thoughts, arguing, commenting, or imperative hallucinated voices; thought withdrawal, broadcasting, or insertion; external influences on bodily functions, arousal, sensations, or volition; and delusional perception or attribution of abnormal meanings to real perceptions), (3) experiencing more initial auditory hallucinations, (4) less likely to have a previous substance use disorder diagnosis, and (5) more likely to present with initial Schneiderian FRS of influence or hallucinations (Table 4).

Two of these factors were independently associated with diagnostic change in multivariate logistic regression modeling, with the factors ranking (by statistical significance) as (1) any Schneiderian FRS at presentation > (2) lack of an earlier substance use disorder diagnosis (Table 4). Other demographic and clinical factors not associated with diagnostic changes included the following: sex; onset type; latency of first-episode symptoms to full syndrome; specific Schneiderian FRS other than auditory hallucinations and experiences of influence; non-FRS visual, olfactory, gustatory, tactile, or somatosensory hallucinations; Capgras misidentification features; cycloid features; various prepsychotic comorbid *DSM* psychiatric disorders (including cyclothymia, dysthymia, posttraumatic stress disorder, other anxiety disorders, eating disorders, or Axis II personality disorders, including clusters A–C), as well as medical or neurologic illnesses; early learning disability; and study site (see Table 4 footnote).

Correlation of *ICD-10* Versus *DSM-IV* Diagnoses

Based on categories considered comparable in the 2 leading, modern diagnostic systems, estimates of diagnostic stability were highly correlated. However, for nearly all categories of psychotic disorder diagnoses, stability of

Table 4. Factors Associated With *ICD-10* Diagnostic Stability

Bivariate Analyses: Factors Favoring Diagnostic Change[a]				
Factor	Stable Diagnoses[b]	Changed Diagnoses[b]	*F* or χ^2	*P* Value
Onset age	32.8 ± 14.5[c]	28.1 ± 9.6[c]	10.2	.0015
Any first-rank symptoms	77.1	95.8	9.1	.0025
Auditory hallucinations	44.1	64.6	7.2	.0072
Any substance use disorder	52.8	35.4	5.2	.021
First-rank influence feelings	17.7	31.3	5.2	.023
First-rank hallucinations	43.8	58.3	3.7	.05
Multivariate Analysis: Factors Favoring Diagnostic Change[d]				
Factor	Odds Ratio (95% CI)		χ^2	*P* Value
Any first-rank symptoms	6.55 (1.56–27.5)		6.60	.010
Lack of any substance use disorder	1.94 (1.04–3.62)		4.30	.038

[a]Continuous variables are tested with ANOVA ($F_{1,499}$); categorical variables were tested with contingency tables (χ^2_1), with factors in descending significance by *P* values. Other factors *not* associated with diagnostic stability included: (1) sex; (2) onset gradual versus acute or subacute; (3) months from initial symptoms to first syndromal illness; (4) specific types of Schneiderian first-rank symptoms other than hallucinations and feelings of influence; (5) visual, olfactory, gustatory, tactile, or somatosensory hallucinations; (6) Capgras misidentification features; (7) cycloid features; (8) other prepsychotic anxiety disorders or PTSD; (9) personality disorder or cluster type; (10) previous eating disorder; (11) significant medical, neurologic, or surgical comorbidity, including head injury, epilepsy, migraine, or allergy, during outpost or prodromal phases; (12) early learning disorder; or (13) study site. [b]All data are presented as percentages unless otherwise noted. [c]Data presented as mean ± SD. [d]Logistic regression model based on factors suggested in preliminary bivariate contrasts shown; factors favoring diagnostic change are ranked by descending significance.
Abbreviations: ANOVA = analysis of variance, PTSD = posttraumatic stress disorder.

Table 5. Comparisons of *ICD-10* and *DSM-IV* Diagnostic Stability (%) of Psychotic Disorders[a]

Category	*ICD-10*	*DSM-IV*	Ratio
Schizophrenia-like or schizophreniform	28.6	10.5	2.7
Psychosis NOS	66.7	51.5	1.3
Acute or brief	66.7	61.1	1.1
Major depression with psychosis	85.2	70.1	1.2
Delusional disorder	88.2	72.7	1.2
Schizophrenia	94.6	75.0	1.3
Bipolar disorder	96.5	96.5	1.0
Overall	90.4	77.6	1.2

[a]The diagnostic systems yield highly correlated stability estimates ($r = 0.97$ [7 diagnoses], $P = .0004$), but there is consistently higher stability (by 10%–270%) with *ICD-10* criteria (slope = 1.16 [95% CI, 0.90–1.67]), including the identical high values for bipolar disorder.
Abbreviation: NOS = not otherwise specified.

ICD-10 diagnoses was consistently higher than with *DSM-IV* criteria (Table 5). A noteworthy exception was bipolar disorder, which yielded the same highest stability of any diagnosis (96.5%). The greatest difference in diagnostic stability was found at the low end, between *ICD-10* schizophrenia-like disorders (28.6%) and *DSM-IV* schizophreniform disorders (10.5% stability), although these diagnoses may not be directly comparable.

DISCUSSION

Study Strengths and Limitations

Strengths of this study include its prospective and systematic follow-up of a large cohort of 500 first-episode patients assigned categorical, syndromal diagnoses using standardized and reliable methods with a broad range of both *ICD-10* affective and nonaffective psychotic disorders, on the basis of initial hospitalization and repeated, prospective, systematic, clinical, and rating scale–based assessments over 24 months of follow-up, evaluated with formal SCID-P assessments at baseline and 24 months. During follow-up, there was only a 3.3% loss due to consistent and intensive pursuit of all subjects. Study limitations include assignment of *ICD* diagnostic categories at baseline and 24 months by 1 expert diagnostician, using extensive, prospectively acquired data, held blind to consensus *DSM-IV* diagnoses and interpretations of SCID assessments, and considering cases in random order over many weeks. In addition, there were relatively small samples (n < 30) in several categories at intake (especially acute schizophrenia-like psychotic disorder, unspecified nonorganic psychosis, and APPD with and without schizophrenia-like symptoms), reflecting their limited prevalence. Such power limitations precluded statistical analysis of predictive factors for specific diagnostic changes, and the overall analyses reported may not apply to all disorders. Also, these findings for initially hospitalized patients in first psychotic episodes may not apply to samples obtained in other settings (outpatient clinics, community samples, or others).

Stability of Specific Initial Diagnoses

Overall, diagnostic stability of first-episode *ICD-10* psychotic disorders in the first 2 years of follow-up from initial major episodes (90.4%) was significantly greater than previously reported for *DSM-IV* categories in the same patient sample (77.6%).[38] This superior stability was sustained for all 7 psychotic disorder diagnoses considered to be similar in both classification systems (Table 5). A second main finding was that all 48 initial *ICD-10* schizoaffective diagnoses remained stable for 2 years. In addition, mania with psychotic symptoms remained stable in 99.0% of 99 cases; only 1 case of mania with psychotic symptoms later changed to schizoaffective disorder, and 14 (14.1%) initially manic patients did not experience a major recurrence within 2 years. Of 156 cases diagnosed initially as mixed affective episode, 94.9% remained stable; all 8 changes (5.1%) involved later-emerging psychotic features, with new schizoaffective diagnoses. Another 14.1% had no further episodes within 24 months (Figure 1, Table 2). Previous studies have reported prevalence of single-episode manic or mixed states at 0%–55% of cases (usually ≤ 8%).[54,55] Schizophrenia was the fourth most stable diagnosis (94.6% of 56 unchanged); all changes (5.4%) involved new schizoaffective diagnoses, mostly from the paranoid subtype. Only 4 *ICD-10* psychotic disorder diagnoses (schizoaffective disorder, mania with psychotic symptoms, mixed affective episode, and schizophrenia) remained stable for 2 years in ≥ 94.6% of cases.

The uncommon *ICD-10* diagnosis delusional disorder (3.4%) remained stable in 88.2% of cases (Table 2). Such conditions often evolve into schizophrenia or schizoaffective diagnoses, with emergence of hallucinations or formal

thought disorder or of affective features,[29] although their relationship to schizophrenias and paraphrenias has been ambiguous for a century.[2] Severe depressive episode with psychotic symptoms (54 cases) was similarly stable (85.2%), shifting to bipolar affective disorder as later manic or mixed episodes arose (6/8 changes) or to 1 each of new schizoaffective or schizophrenia diagnoses. Also, among 46 subjects initially diagnosed with severe depressive episode with psychotic symptoms both at intake and 2 years later, 15 (32.6%) had only a single episode.

Of initial acute polymorphic psychotic disorder (APPD) diagnoses with and without symptoms of schizophrenia (n = 32 initially), 33.3% changed to other categories (Tables 1 and 2, Figure 1). Diagnostic instability was anticipated among psychotic disorders expected to be acute, time limited, and prognostically favorable, particularly acute schizophrenia-like psychotic disorder. Initially, this diagnosis was uncommon (n = 7 cases), and 71.4% changed to other diagnoses, particularly schizophrenia (Table 2). Diagnostic instability rates of *ICD-10* acute and transient psychotic disorders (ATPDs; n = 55 or 11.0%, including APPD [n = 48] and acute schizophrenia-like psychotic disorder [n = 7]) averaged 46.0% overall, and 33.3% of APPDs underwent diagnostic changes. These disorders, in the same patients, may compare best to *DSM-IV* categories of schizophreniform (89.5%) and brief psychotic disorders (38.9% involved changed diagnoses; 64.2% overall).[38] Accordingly, *ICD-10* diagnoses of ATPDs, particularly the APPD subtypes, may be somewhat more stable and potentially more reliable and valid constructs than *DSM-IV* schizophreniform and brief psychotic disorder. Several studies[21,25,39,41,43,44] investigated the incidence, characteristics, and diagnostic stability of *ICD-10* acute, transient psychoses, alone or within the broad range of first-episode functional psychoses, generally finding low to moderate overall stability rates (34.4%–57.9%), though relatively high positive predictive power was found among such diagnoses in developing countries (64.4%–73.3%),[28,40,42] particularly for the APPD subtypes.[40]

The present and previous findings[38] indicate limitations of both *ICD-10* and *DSM-IV* diagnostic categories, particularly in attempting to account for acute, nonaffective, remitting psychoses.[56] Notably, several criteria—including 1–3 months' duration required for acute psychoses in both systems, the schizophrenia Criterion A required for *DSM-IV* schizophreniform disorder, and lack of negative symptoms for *DSM-IV* brief psychotic disorder—all seem limited and arbitrary and fail to capture the complexity of many psychotic disorders. As acute onset is not a criterion for *DSM-IV* brief psychotic or schizophreniform disorders, but *ICD-10* considers onset type to be crucial, remitting psychoses with nonacute onset and typical cases of schizophrenia and other persistent psychoses, as well as nonaffective acute remitting psychoses, may be misclassified, especially by *DSM-IV* criteria. As highlighted in *ICD-10*, initial acute versus nonacute onset and a remitting versus chronic course, as well as prolonged stability during follow-up, may be relatively robust criteria for differentiating psychotic disorder subtypes.[56] Also, the relatively high instability of undifferentiated/unspecified psychoses may reflect their possible status as prodromes of more stable conditions such as schizophrenia and schizoaffective disorder.[57]

The present finding of diagnostic stability of *ICD-10* APPD diagnoses with and without symptoms of schizophrenia (both 66.7%) might be related partly to the higher prevalence of cycloid features at presentation (64.3% and 66.7%) among longitudinally stable cases of APPD than for other categories (0%–50% stability; not shown), including schizophrenia (1.6%) and schizoaffective disorders (9.1%). Some recent reports comment on the presence of cycloid phenomena, including rapidly changing moods and activity levels, delusions, confusion or perplexity, and anxiety or ecstasy, not only to distinguish APPD from chronic psychotic illnesses but also to predict a more favorable course and outcome.[41,58–60]

Diagnostic Stability of Schizoaffective Disorder

Schizoaffective disorder is of particular interest owing to variance in both concepts and criteria. With *ICD-10* criteria, its prevalence increased from 9.6% to 13.2% within 2 years, and it accounted for 37.5% of new diagnoses; moreover, this diagnosis remained stable in 100.0% of the 48 patients initially so diagnosed, to represent the most stable *ICD-10* psychotic disorder diagnosis (Table 2). In contrast, based on *DSM-IV* criteria, schizoaffective disorder was rare initially.[38] Such striking differences probably reflect (1) allowance in *ICD-10* of broad temporal relations between schizophrenia-like (psychotic) and affective symptoms,[4] (2) narrow definitions of psychotic phenomena in *DSM-IV* Criterion B, and (3) the required meeting of criteria for a major mood episode in *DSM-IV*.[5] Kasanin's[61] concept of the schizoaffective syndrome as the acute admixture or rapid succession of schizophrenia-like and mood features anticipated the *ICD-10* concept,[4] whose essential criterion is prominence of both affective and psychotic symptoms in the same episode or within a few days. The more restrictive *DSM-IV*[5] Criterion B required for schizoaffective disorder ("during the same period of illness, there have been delusions or hallucinations for ≥ 2 weeks in the absence of prominent mood symptoms") extends the requirement of "an uninterrupted period of illness of at least 1 month, during which, at some time, there is a 1- to 2-week major mood episode as well as symptoms meeting *DSM-IV* Criterion A for schizophrenia" and narrowly limits potential psychotic phenomena to the occurrence of delusions or hallucinations alone.

Later emergence of affective features led 5.6% of initial *ICD-10* nonaffective cases to be diagnosed later as schizoaffective, whereas 3.2% initially considered affective disorders later manifested sustained psychotic features, indicating that new affective features were the more likely route to *ICD-10* schizoaffective diagnoses (Table 3), similar to *DSM-IV* criteria.[38] In other studies, relative contributions of late affective versus psychotic features were not specified.[18,25–27,62] From a clinical and nosologic viewpoint, later emergence of affective components within initially psychotic conditions might

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reflect the phenomenological nature of acute psychoses in which affective expression is overwhelmed by pervasive positive psychotic symptoms, or affective features are quantitatively or temporally insufficient to meet diagnostic criteria for an affective psychotic disorder.[21,25,39–44] In addition, from the perspective of clinical psychopathology, as pointed out by Schneider,[53] subsequent appearance of affective components in initial nonaffective psychotic states might be triggered by the impact on the basic affective substratum of the profound existential catastrophe of first-rank symptoms (FRS), which are being experienced as a loss of unity of the self as the center of thought, perception, volition, bodily experience, and action.

Also, only 6.4% of initial *ICD-10* schizophrenia cases were later considered schizoaffective (Table 2), perhaps as a manifestation of early illness fluidity[7–11] and a need for 12 to 24 months of observation for confident diagnosis of schizophrenia.[63,64] In contrast, almost all *DSM-IV* schizoaffective cases were not diagnosed before 2 years of follow-up.[38] Indeed, schizoaffective disorder, as currently conceived in the United States, is similar to schizophrenia in severity, chronicity, and disability, high rates of comorbidity, and relatively young onset.[14,24] This concept differs sharply from Kasanin's[61] original concept of acute admixtures of features and other recent formulations that include both an episodic course[31] and a favorable long-term outcome.[22]

Comparisons With Earlier Studies

Several prospective studies considered stability of first-episode psychotic illness diagnoses, although studies including both large, broad samples followed up for a year or longer* and evaluations of factors associated with diagnostic stability are rare.[26,31,32,35,38] Several studies specifically considered longitudinal stability of individual, *ICD-10* acute psychotic disorder diagnoses,[39–44] schizophrenia,[45,46] mania with psychotic symptoms, or severe depression with psychotic features,[47–49] but only 2 considered diagnostic stability over time in a broad range of functional psychoses,[25,28] and neither explored factors predicting stability.[25,28]

These studies,[25,28] averaged with our findings (Table 2), indicated that *ICD-10* schizophrenia was a particularly stable initial diagnosis (mean ± SD = 92.2 ± 9.2%), mania with psychotic symptoms similarly stable (90.8 ± 8.4%), delusional disorder and severe depressive episode with psychotic features less stable (75.4 ± 21.2%), ATPD moderately unstable (63.7 ± 32.6%), and the pool of unspecified acute psychoses even less stable (40.1 ± 24.1% of cases remaining stable for at least 1 year). Compared with our findings of 100.0% longitudinal diagnostic stability among initial *ICD-10* schizoaffective cases (Table 2), one comparable study found that only 20.0% of cases initially considered schizoaffective (2.9%) remained so at 36 months,[25] and the other did not identify any subject as schizoaffective at baseline or at 12 months.[28]

*References 14, 18, 25, 26, 30–32, 34, 35, 38.

Predictive Factors

Factors associated with diagnostic instability included any type of Schneiderian FRS[53] at presentation and lack of previous substance use disorders (Table 4). Comparable studies are rare, and none used *ICD-10* criteria. Schwartz et al[26] found that diagnostic change between 6 and 24 months to *DSM-IV* schizophrenia or schizoaffective categories was associated with poor adolescent adjustment, lack of early substance abuse, psychosis lasting ≥ 3 months before hospitalization, more initial negative symptoms, prolonged hospitalization, and antipsychotic treatment at discharge. For Schimmelmann et al,[31] higher initial global impression (Clinical Global Impressions) and lower premorbid functional (Global Assessment of Functioning) scores predicted shifts from *DSM-IV* schizophreniform disorder to schizophrenia or schizoaffective diagnoses. Whitty et al[32] associated diagnostic change generally with less education, milder initial *DSM-IV* psychopathology, and comorbid substance abuse. Relationships of substance use disorders to risk or timing of new psychotic disorder diagnoses remain particularly unclear, as the evidence is inconsistent.[26,32,33,65]

Subramaniam and colleagues[35] found duration of untreated psychosis to be the only significant predictor of diagnostic shifts toward a *DSM-IV* "schizophrenia spectrum." Fraguas et al[36] reported that diagnostic concordance of 54.2% between baseline and 1-year diagnoses rose to 95.7% by 2 years, highlighting the importance of prolonged follow-up to stable diagnosis. Our previous study[38] with the same 500-patient sample diagnosed by *DSM-IV* criteria found that diagnostic instability was predicted by initial nonaffective diagnoses and auditory hallucinations, younger age at syndromal onset, male sex, and gradual onset.

The finding that Schneiderian FRS predicted diagnostic instability while also representing important anchors for the relatively stable *ICD-10* diagnosis of schizophrenia seems paradoxical. It may be that FRS are also core descriptive features for ATPD, especially its highly unstable subtypes, namely acute schizophrenia-like and APPD with schizophrenia symptoms. Berner[66] hypothesized that FRS emerging during acute psychosis may represent continuously fluctuating impulses, drives, emotions, feelings, and mood states (the so-called "dynamic instability") that disrupt basic, innate behavioral schemes, ideas, mental images, and personal values ("structural components"). Because specific interactions between dynamic and structural components might facilitate emergence of mainly affective, nonaffective, or schizoaffective psychoses, FRS might well be associated with diagnostic changes that reflect the premorbid psychobiological substratum from which psychotic illnesses develop.

Associations of early features with later diagnoses encourage further study of the potential predictive value of early phenomenology,[21] to guide earlier diagnosis and therapeutic interventions aimed at limiting morbidity and disability, as well as to limit adverse effects and costs of unnecessary treatments.[67,68] However, challenges of evaluating early or premorbid phenomena are great, especially in young patients. Early symptoms can obscure or delay diagnosis of psychotic

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disorders, particularly when prominent nonspecific features suggest neurotic, personality, conduct, cognitive, or substance use disorders.†

CONCLUSIONS

Our findings underscore the wide diversity of diagnostic stability among initial *ICD-10* psychotic disorder diagnoses, based on 2 years of observation from onset. They suggest 4 major nodes of stability: (1) very high stability (94.6%–100.0%) in *ICD-10* schizoaffective disorder, mania with psychotic symptoms, mixed affective episode, and schizophrenia > (2) moderately high stability (85.2%–88.2%) in delusional disorder and severe depressive episode with psychotic symptoms > (3) limited stability (66.7%) in APPD and unspecified nonorganic psychosis >> (4) low stability (28.6%) in acute schizophrenia-like psychotic disorder. *ICD-10* schizoaffective disorder and mania with psychotic symptoms were particularly stable diagnoses and somewhat more robust as initial diagnoses than mixed affective episode, 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, including their timing and plasticity over time.

Most diagnostic changes were to schizoaffective diagnoses, usually anticipated by initial mixed affective episodes or later-emerging affective components of initially nonaffective psychotic illnesses and typically with unfavorable outcomes. This category challenges the standard psychotic versus affective Kraepelinian dichotomy underlying both *DSM-IV* and *ICD-10* and requires further study. Despite the higher sensitivity and stability of an *ICD-10* schizoaffective diagnosis than the corresponding *DSM-IV* category in this same cohort of 500 patients,[38] the diagnosis of schizoaffective disorders in general may require more than 12 months of follow-up and may include acute and episodic as well as chronic forms.

In light of the high diagnostic stability of *ICD-10* ATPD and its polymorphic subtypes, we also recommend critical reevaluation of the *DSM-IV* categories of "schizophreniform," "brief psychotic disorders," and related concepts. Developing improved diagnostic criteria for such supposedly good-prognosis and time-limited disorders may require integrating categorical and dimensional approaches, with consideration of early features and type of onset, as well as long-term outcomes.[1,76–80] 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.[67,81]

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