Predicting Diagnostic Change Among Patients Diagnosed With First-Episode *DSM-IV-TR* Major Depressive Disorder With Psychotic Features

Paola Salvatore, MD; Ross J. Baldessarini, MD; Hari-Mandir K. Khalsa, MS; Mario Amore, MD; Cristina Di Vittorio, MD; Gabriella Ferraro, PhD; Carlo Maggini, MD; and Mauricio Tohen, MD, DrPH

ABSTRACT

Objective: Longitudinal studies beginning from onset of major depressive disorder (MDD) with psychotic features in young adults are rare; therefore, in this study, subjects across a wide age range were included. Since psychotic MDD may be unstable diagnostically, we systematically evaluated such patients prospectively from first episode to ascertain predictors of later diagnostic change.

Method: In this prospective naturalistic study, we recruited patients with *DSM-IV-TR* psychotic MDD from 1989 through 2003 at psychiatric inpatient units in Massachusetts and Italy and followed them from first hospitalization to compare demographic, antecedent, and first-episode clinical characteristics for associations with later changes of diagnosis based on interviews using the Structured Clinical Interview for *DSM-III-R*, Patient Version.

Results: Within a mean (SD) of 4.0 (2.7) years, diagnoses among 107 subjects aged 34.6 (16.2) years (range, 10–82 years) who were experiencing a first lifetime *DSM-IV-TR* psychotic MDD episode changed in 29.9% to *DSM-IV-TR* bipolar disorder (18.7%) or schizoaffective disorder (11.2%). Factors associated with stable diagnoses of psychotic MDD included ontological anguish ($\chi^2 = 13.8$, $P < .0001$), nihilistic delusions ($\chi^2 = 4.47$, $P = .034$), and weight loss ($\chi^2 = 4.69$, $P = .030$) at initial syndromal presentation. Factors preceding diagnoses of bipolar disorder included antecedent impulsivity ($\chi^2 = 9.10$, $P = .003$), *ICD-10* mixed states at intake ($\chi^2 = 19.4$, $P < .0001$), and previous hypomanic symptoms ($\chi^2 = 13.7$, $P = .002$). Factors predicting later schizoaffective diagnoses included mood-incongruent delusions ($\chi^2 = 9.17$, $P = .002$) and somatosensory hallucinations ($\chi^2 = 9.53$, $P = .033$) at intake, previous functional decline ($\chi^2 = 8.13$, $P = .008$), initial Schneiderian first-rank symptoms ($\chi^2 = 10.6$, $P = .005$), and meeting criteria for *ICD-10* schizoaffective disorder at intake ($\chi^2 = 24.9$, $P < .0001$).

Conclusions: Among patients who initially met *DSM-IV-TR* criteria for first-episode psychotic MDD, early indications of features typically associated with bipolar disorder or with nonaffective psychoses, respectively, strongly predicted later diagnostic change to bipolar disorder or schizoaffective disorders. The findings support the value of psychopathological details in improving diagnostic and prognostic criteria for complex illnesses.

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Psychotic depression, or major depressive disorder (MDD) with psychotic features, may constitute a distinct syndrome, despite presenting variable clinical and psychobiological features, treatment responses, longitudinal course, and outcomes.[1–12] Support for this disorder as a distinct phenotype requires at least longitudinal diagnostic stability. However, 25%–35% of diagnoses of patients initially considered to have psychotic MDD by standard diagnostic criteria are reported to change during long-term follow-up, most often to a bipolar or schizoaffective disorder.[9,13–16] Although it would be helpful to identify early characteristics that might either predict stability of initial psychotic MDD diagnoses or anticipate likely changes, studies of early predictors of later outcomes of illnesses presenting as psychotic MDD remain rare, particularly among young adults in first lifetime episodes.[16–18] Such studies should be useful for improving prognosis and planning appropriate long-term clinical management and treatment. Specific potential benefits might include limiting risks of excessive antidepressant treatment without an accompanying antipsychotic, which may induce mania or behavioral destabilization, particularly among patients later considered to have bipolar disorder, or worsening of psychosis in patients with schizoaffective disorders.[19–21]

Given a striking lack of information about predicting diagnostic stability or change during follow-up of patients who present in an initial episode of apparent psychotic MDD, we studied patient-subjects diagnosed with a first lifetime episode of psychotic MDD and evaluated them prospectively in the McLean-Harvard International First-Episode Project to ascertain predictive factors of long-term diagnostic outcomes on the basis of specific clinical features of the presenting illness episode or its antecedents.[9,13,21] We hypothesized that stable diagnoses would be predicted by psychopathological features including ontological anguish, or the excruciating experience of impending catastrophe to one's very existence, a proposed core characteristic of severe or melancholic unipolar MDD.[22–25] We also hypothesized that early mild hypomania-like features would predict later diagnoses of bipolar disorder and that initial psychotic phenomena typically associated with schizophrenia would suggest later diagnoses of schizoaffective or other primary psychotic disorders.

METHOD

Subjects and Assessments

Research methods employed were detailed previously.[9,13,21,26,27] Briefly, specially trained master's level evaluators with more than 5 years of experience recruited and assessed patient-subjects from psychiatric inpatient units at McLean Hospital, Belmont, Massachusetts, and the University of Parma Medical Center, Parma, Italy, within 72 hours of first lifetime psychiatric hospitalization for a first episode of any major psychiatric illness with psychotic features from 1989 through 2003. Subject recruitment occurred after initial and annual approval of study protocols by the Human Studies Review Committee of each institution, and participants

Clinical Points

- Psychotic major depressive disorder (MDD) occurs across a broad age range and is not limited to geriatric patients.
- *ICD-10* diagnostic criteria were more effective in identifying first-episode patients diagnosed by *DSM-IV-TR* criteria as having psychotic depression who later met *DSM-IV-TR* criteria for other disorders.
- Change of *DSM-IV-TR* diagnosis from psychotic MDD to bipolar disorder was predicted by affective features, and change from psychotic MDD to schizoaffective diagnoses was predicted by features associated with nonaffective psychotic disorders such as schizophrenia. Stable diagnoses of psychotic MDD were associated with initial existential anguish, nihilistic delusions, and weight loss.

provided written informed consent for study participation and for anonymous and aggregate reporting of clinical findings. All subjects underwent prospective, structured reassessments approximately weekly during the first hospitalization, at 6 and 12 months, and yearly thereafter for several years after initial hospitalization. Clinical, diagnostic, and research protocols were identical at both study sites. Diagnostic assessments included the Structured Clinical Interview for *DSM-III-R*, Patient Version (SCID-P)[28] at intake and at 2 years, followed by best-estimate diagnostic procedures based on the consensus of several clinically expert investigators (P.S., H.-M.K.K, C.D., G.F., M.T.), as well as consideration of all available information, with diagnoses updated to meet *DSM-IV-TR* criteria since 2000 and compared with *ICD-10* criteria.[13,21,29–31] Long-term diagnostic stability was assessed with blinding to initial SCID-P–based and best-estimate, investigator-consensus diagnoses.[9,13,26]

Exclusion criteria were (1) current intoxication, substance withdrawal, or delirium at intake; (2) documented Wechsler Adult Intelligence Scale intelligence quotient of < 70; (3) previous psychiatric hospitalization, unless for detoxification; (4) ill continuously for ≥ 12 months at any time before intake or for ≥ 6 months in the index episode; or (5) treatment ever with electroconvulsive therapy, or treatment with an antidepressant, mood stabilizer, or antipsychotic for a total of 3 months or more. Treatment was determined clinically by physicians not involved in the study or influenced by study protocol requirements.

Assessments of Antecedent and Index Episode Psychopathology

The first author (P.S.) carried out a comprehensive, retrospective review of all available clinical documents for each subject (2 SCID-P assessments, medical records, clinical narratives from interviews of family members and primary treating clinicians), aimed at describing and dating antecedents and first-episode psychotic psychopathology and identifying detailed clinical phenomena. For this purpose, information on primary diagnosis and type of first psychotic episode was removed from the material reviewed, and all 107 psychotic MDD study subjects were assessed,

randomly, among a total of over 500 subjects with a range of first-episode affective and nonaffective psychoses. These circumstances, based on a decade-long accumulation of subjects and records and on analyses carried out over 3 years (2010–2012), assured effective blinding with respect to first psychotic episode diagnoses. We also applied *ICD-10* diagnostic criteria to initial assessments of all 500 subjects with a first psychotic episode, again in random order and under blinded conditions.[13] Psychopathological details of index episodes and antecedents included affective, perceptual, psychomotor, cognitive, social, and behavioral dimensions. These assessments were guided by consideration of the 100-item *Manual for the Assessment and Documentation of Psychopathology* (AMDP system)[32] and the 66-item Bonn Scale for the Assessment of Basic Symptoms (BSABS)[33–35] to record clinical phenomena and develop comprehensive and systematic symptom inventories.[27]

Information concerning psychopathological features of antecedents and index episodes and their approximate timing was abstracted from all available sources and reported in a semistructured summary for each subject by the same expert rater (P.S.) under conditions of blindedness to diagnosis and without preconceptions about the nature or timing of premorbid phenomena in relation to type of presenting episode or final diagnoses after 2 years or more of prospective, structured follow-up. Identified features were ordered by approximate age at initial appearance, clinically assessed severity (mild, moderate, severe), and approximate duration prior to the index first lifetime psychiatric hospitalization. In addition, the prodromes of first psychotic episodes were rated as being *acute* (<1 month), *subacute* (1–6 months), or *gradual* (>6 months) in evolving from symptoms to syndrome. This information was used to produce a comprehensive research summary for each subject.[27]

Outcome Assessments

Following intake at the index hospitalization, follow-up information was gathered prospectively and systematically over 2 years or more by specially trained master's level evaluators with more than 5 years of experience who were blinded to baseline information and initial diagnoses. Diagnostic outcomes were based on SCID-P examinations at 24 months after initial hospitalization or on final follow-up assessments based on semistructured clinical evaluations— again assessed by the first author (P.S.), who was blinded to initial and 2-year SCID-P–based and best-estimate investigator-consensus diagnoses. The primary study outcome was the *DSM-IV-TR* primary consensus diagnosis at the final follow-up assessment.

Statistical Analyses

We analyzed associations of final *DSM-IV-TR* diagnoses with a range of independently ascertained demographic, antecedent, and first-episode clinical characteristics and compared subjects with stable MDD diagnoses versus those with changed diagnoses. Categorical variables were assessed with contingency tables (χ^2, with degrees of freedom [df] = 1, unless stated otherwise), and continuous variables were assessed with ANOVA methods (F statistic). Associations of factors with final diagnoses also were analyzed by Bayesian methods to estimate *sensitivity* (true positive cases of all patients in a diagnostic category), *specificity* (true negative cases of all persons not in a diagnostic category), and *positive predictive value* (true cases of all positive results), for which "true" indicated association with a diagnostic group (unchanged or changed), to evaluate the potential prognostic value of specific factors.[36] Measures with at least suggestive differences ($P \le .10$) in initial bivariate comparisons were entered stepwise into logistic, multivariate regression modeling to identify factors independently associated with diagnostic change, with reporting of odds ratios (ORs) with their 95% confidence intervals (CIs). Data are presented as means (standard deviations [SDs]) unless stated otherwise. Statistical analyses were performed using Stata software (StataCorp; College Station, Texas) and StatView software (SAS Institute Inc; Cary, North Carolina) for microcomputer.

RESULTS

Diagnostic Outcomes

The 107 subjects included 57 women and 50 men with a mean (SD) age of 34.6 (16.2) years at intake (median age = 29 years; interquartile range, 22–43 years; range, 10–82 years). Estimated mean age at first antecedent morbidity was 19.8 (15.7) years, or approximately 15 years prior to first lifetime psychiatric hospitalization. Initial *DSM-IV-TR* diagnoses of psychotic MDD were sustained in 75 of 107 subjects (70.1%), and diagnoses for 32 of 107 subjects (29.9%) changed to other disorders over a mean of 4.0 (2.7) years of follow-up. Changed diagnoses were entirely accounted for by bipolar disorder in 18.7% of all subjects (20 of 107), based on later emergence of *DSM-IV-TR* mania or mixed states (20 cases of 32 changed diagnoses, including 10 to bipolar I and 10 to bipolar not otherwise specified), or by a schizoaffective disorder in 11.2% of all subjects (12 of 107), due to the presence of sustained nonaffective psychotic phases (12 cases of 32 changed diagnoses, including depressive types [10 of 12] and bipolar types [2 of 12]). Neither sex (percentage of women: bipolar disorder, 70.0%; MDD, 52.0%; schizoaffective disorder, 33.3%) nor intake age (bipolar disorder, 33.4 [13.1] years; MDD, 36.2 [17.6] years; schizoaffective disorder, 27.0 [8.45] years) differed significantly among final diagnoses. Follow-up duration was somewhat longer with schizoaffective than with bipolar or MDD final diagnoses (5.52 [2.31] years >3.74 [1.20] years ≥3.41 [2.08] years, respectively; $t = 2.34$, overall $P = .004$; Bonferroni-adjusted post hoc tests: schizoaffective disorder >bipolar disorder, $P = .04$; schizoaffective disorder >MDD, $P = .002$).

Factors Associated With Any Diagnostic Change

Characteristics associated with *any* diagnostic change ranked as follows: (1) initially meeting *ICD-10* criteria

Table 1. Factors Associated With Diagnostic Change Versus Stability in Patients Initially Diagnosed With First-Episode *DSM-IV-TR* Major Depressive Disorder With Psychotic Features (N = 107)

Factor	Diagnosis (%)		Relative Risk[a]	χ² or F[b]	P Value[c]	Bayesian Characteristics (%)[d]		
	Changed	Stable				Sensitivity	Specificity	PPV
New diagnosis: bipolar disorder[b]								
ICD-10 mixed-state diagnosis at intake	50.0	9.20	5.43	19.4	<.0001	50.0	90.8	55.6
Antecedent hypomanic symptoms	25.0	2.30	10.9	13.7	.002	25.0	97.7	71.4
Antecedent impulsivity	70.0	33.3	2.10	9.10	.003	70.0	33.3	32.6
Hypomanic symptoms at onset	55.0	26.4	2.08	6.12	.013	55.0	73.6	32.4
Lack of ontological anguish at onset	50.0	26.4	1.90	4.23	.040	50.0	73.6	30.3
Affective-psychomotor instability at onset	75.0	51.7	1.45	3.58	.05	75.0	48.3	25.0
New diagnosis: schizoaffective disorder[b]								
ICD-10 schizoaffective diagnosis at intake	33.3	1.05	31.7	24.9	<.0001	33.3	98.9	80.0
Mood-incongruent psychosis at onset	91.7	45.3	2.02	9.17	.002	91.7	54.7	20.4
FRS of thought passivity at onset	50.0	12.6	3.97	10.6	.005	50.0	87.4	33.3
Antecedent functional decline	66.7	26.3	2.51	8.13	.008	66.7	73.7	24.2
Lack of ontological anguish at onset	66.7	26.3	2.51	8.13	.008	66.7	73.7	24.2
Somatic delusions at onset	50.0	20.0	2.50	5.36	.031	50.0	80.0	24.0
Somatosensory hallucinations at onset	16.7	1.05	15.9	9.53	.033	16.7	98.9	66.7
Antecedent *DSM-IV-TR* PTSD	41.7	14.7	2.84	5.29	.037	41.7	73.7	24.2
FRS of delusional perception at onset	58.3	28.4	2.05	4.40	.049	58.3	71.6	20.6
Any new diagnosis during follow-up[b]								
Ontological anguish at onset	43.7	80.0	0.55	13.8	<.0001	56.3	80.0	54.5
Antecedent impulsivity	65.6	29.3	2.24	12.3	<.0001	65.6	70.7	48.8
ICD-10 mixed-state diagnosis at intake	34.4	9.33	3.69	10.1	.003	34.4	90.6	61.1
Mood-incongruent psychosis at onset	71.9	41.3	1.74	8.37	.004	71.9	58.7	42.6
FRS of thought passivity at onset	31.3	10.7	2.93	6.79	.021	31.3	89.3	55.6
Age in years at initial antecedent morbidity[e]	14.5 ± 7.98	22.0 ± 17.6	0.66	5.36	.023	NA	NA	NA
Antecedent hypomanic symptoms	15.6	2.67	5.84	6.16	.024	15.6	97.3	71.4
ICD-10 schizoaffective diagnosis at intake	12.5	1.33	9.40	6.28	.027	12.5	98.7	80.0
FRS of delusional perception at onset	46.9	25.3	1.85	4.80	.028	46.9	74.7	44.1
Weight loss at onset	21.9	44.0	0.50	4.69	.030	78.1	44.0	37.3
Nihilistic delusions at onset	9.38	28.0	0.34	4.47	.034	90.6	28.0	34.9

[a]Ratio of prevalence of each factor with a new diagnosis present or absent (bivariate analysis). [b]Subjects whose diagnoses changed to bipolar disorder (n = 20) or schizoaffective disorder (n = 12) or both combined (n = 32) are compared to all others (n = 87, n = 95, or n = 75, respectively); subjects with a sustained MDD diagnosis (n = 75) are compared to those with any diagnostic change (n = 32). [c]Data are ranked by between-diagnosis P value within diagnostic groups. [d]Bayesian analyses of sensitivity, specificity, and positive predictive value are for associations of each factor with an indicated new or stable diagnosis. [e]Ages are shown as mean ± SD.
Abbreviations: FRS = Schneiderian first-rank symptom, NA = not applicable, PPV = positive predictive value, PTSD = posttraumatic stress disorder.

for a schizoaffective disorder; (2) antecedent hypomanic symptoms; (3) initially meeting *ICD-10* criteria for a mixed episode; (4) initial Schneiderian first-rank symptoms of thought passivity and alienation, including thought insertion, withdrawal, diffusion, or broadcasting, and any other form of thought interference; (5) lack of initial ontological anguish; (6) evidence of antecedent impulsive behavior; (7) initial first-rank symptoms of delusional perception or abnormal attribution of meaning; (8) initial mood-incongruent psychotic features; (9) lack of initial weight loss; (10) lack of initial nihilistic delusions; and (11) relatively young age at first antecedent psychopathological symptoms in childhood or early adolescence.

Factors Associated With Specific Diagnostic Outcomes

Several features significantly differentiated subgroups defined by final *DSM-IV-TR* diagnoses (Table 1). For subjects finally diagnosed with bipolar disorder, distinctive features ranked (by statistical significance) as follows: (1) initially meeting *ICD-10* (but not *DSM-IV-TR*) criteria for a mixed manic-depressive state; (2) indications of antecedent mild mood elevations that did not meet *DSM-IV-TR* criteria for hypomania, or suggestions of hyperthymia; (3) evidence of antecedent impulsive behavior; (4) lack of initial

ontological anguish characteristic of patients who retained MDD diagnosis; and (5) younger age at first antecedent symptoms.

Features differentiating subjects whose diagnosis changed to a schizoaffective disorder ranked as follows: (1) initially meeting *ICD-10* (but not *DSM-IV-TR*) diagnostic criteria for schizoaffective disorder; (2) initial mood-incongruent psychotic features; (3) initial first-rank symptoms of passivity, external control, or alienation of thoughts; (4) antecedent functional decline; (5) lack of initial ontological anguish; (6) initial somatic delusions; (7) initial somatosensory hallucinations (including tactile bodily sensations or gustatory and olfactory phenomena); (8) antecedent posttraumatic stress disorder; (9) initial first-rank symptom of delusional perception; and (10) relatively young age at first antecedent symptoms (see Table 1).

Features that distinguished subjects with sustained diagnoses of psychotic MDD from those with changed diagnoses ranked as follows: (1) initial ontological anguish; (2) lack of antecedent impulsivity; (3) not meeting *ICD-10* (or *DSM-IV-TR*) criteria for a mixed manic-depressive state at intake; (4) lack of initial mood-incongruent psychotic features; (5) lack of initial first-rank symptom of thought passivity; (6) oldest age at first antecedent symptoms;

(7) lack of antecedent hypomanic symptoms; (8) not meeting *ICD-10* (or *DSM-IV-TR*) diagnostic criteria for a schizoaffective disorder at intake; (9) lack of initial first-rank symptom of delusional perception; (10) initial weight loss; and (11) initial nihilistic delusions.

Additional factors not associated with diagnostic change (data not shown) included hypersexuality at onset, antecedent epileptic seizures, sex, affective or psychomotor instability at onset, formal thought disorder at onset, motor retardation at onset, guilty or hypochondriacal delusions at onset, antecedent eating disorder, antecedent substance abuse, command as well as commenting auditory hallucinations or visual hallucinations at onset, catatonic features at onset, antecedent head trauma, antecedent learning disability, earlier nonpsychotic depression, suicide attempt at first episode or earlier, preceding anxiety or panic, or Capgras syndrome at onset.

Bayesian Analyses

Bayesian analyses of the prognostic value of features just summarized indicated only moderate sensitivity, specificity, and predictive value (see Table 1). The highest sensitivity (70%–75%) in predicting a diagnostic change to bipolar disorder was associated with antecedent impulsive behavior as well as initial affective and psychomotor instability in an episode of *DSM-IV-TR* psychotic MDD. The highest specificity (91%–98%) was associated with previous hypomanic symptoms and with meeting *ICD-10* criteria for diagnosis of a mixed state at intake. The highest positive predictive value (71%) was associated with previous subsyndromal hypomanic symptoms.

For diagnostic change to schizoaffective disorder, the highest sensitivity (91%) was associated with initial mood-incongruent psychotic symptoms. The highest specificity (87%–99%) was associated with initial somatosensory hallucinations, meeting *ICD-10* diagnosis of schizoaffective disorder at intake, and initial first-rank symptoms of thought passivity and alienation. The highest positive predictive value (80%) was associated with meeting *ICD-10* diagnostic criteria for schizoaffective disorder at intake.

Sustained diagnoses of psychotic MDD were predicted by nihilistic delusions, ontological anguish, and weight loss at initial syndromal presentation.

Antecedent or presenting features that significantly distinguished specific diagnostic outcomes are summarized in Figure 1, which indicates rates for specific features associated with retaining the diagnosis of psychotic MDD and with changing to a bipolar or schizoaffective disorder. Factors most strongly associated with each outcome are shown.

Multivariate Modeling

We analyzed factors associated significantly and independently with changed diagnoses using multivariate logistic regression modeling that controlled for age and sex to distinguish subjects with a stable long-term diagnosis of psychotic MDD from those with any longitudinal diagnostic change (Table 2). On the basis of their statistical significance, 4 factors associated with diagnostic change ranked as follows: (1) disagreement between *DSM-IV-TR* and *ICD-10* diagnoses at intake (usually involving a bipolar or schizoaffective disorder detected by *ICD-10* criteria); (2) evidence of antecedent impulsive behavior; (3) any first-rank symptom detected at initial, first-episode onset; and (4) lack of initial ontological anguish, which was strongly associated with stable diagnoses of *DSM-IV-TR* psychotic MDD.
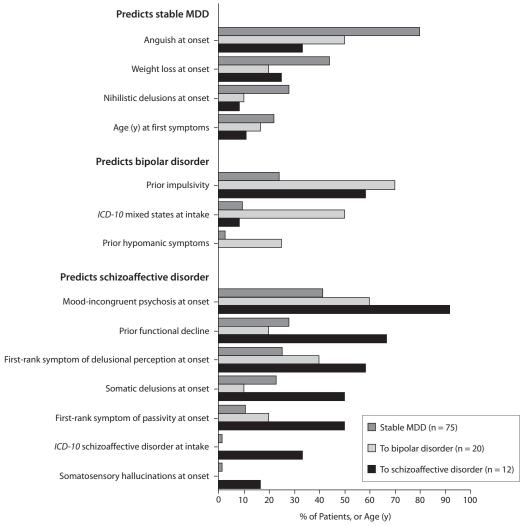
DISCUSSION

The present findings are based on 107 patients with a first lifetime episode of psychotic MDD. Despite substantial study,[1–12] this disorder continues to require investigation as to its validity as an independent diagnostic entity, particularly prospectively from onset in broad samples of subjects across a wide age range who are experiencing both affective and nonaffective first psychotic episodes, as well as versus nonpsychotic bipolar and unipolar depressive illnesses. We found that 70.1% of initial *DSM-IV-TR* diagnoses of psychotic MDD remained stable over an average of 4 years of systematic follow-up and that 29.9% changed to either a *DSM-IV-TR* bipolar disorder (18.7%) or a depressive type or bipolar type of schizoaffective disorder (11.2%). This heterogeneity of long-term diagnostic outcomes suggests that *DSM-IV-TR* psychotic MDD is a complex nosologic construct that clinically overlaps bipolar disorder and schizoaffective disorder, although evidently not schizophrenia. This impression is in accord with a recent study[37] of familial risk factors of psychotic MDD that found excess parental bipolar disorder but not schizophrenia. The present findings also support our previous study[13] with a broad range of first-episode psychotic disorders, which found that *ICD-10* diagnostic criteria were effective in identifying patients in first psychotic episodes who eventually were rediagnosed with a bipolar or schizoaffective disorder on the basis of *DSM-IV-TR* criteria. Recent proposals for redefining psychotic MDD in *ICD-11* include its definition as an independent "meta-syndrome" with both bipolar and unipolar presentations and courses, again emphasizing its relationship with bipolar and schizoaffective disorders.[38] In addition, the *DSM-5* Task Force would remove the label "severe" from the "with psychotic features" subtype.[38] These proposals highlight the probable validity of psychotic MDD as a distinct syndrome but also recognize its susceptibility to follow different diagnostic trajectories over time. Previous studies of psychotic MDD have often emphasized the association of the disorder with relatively late onset, often in geriatric samples. It remains to be clarified whether psychotic MDD that arises in late juvenile or young adult years differs from seemingly similar syndromes that present in later life.

It is not surprising that suggestions of hypomania-like features before first major episodes of psychotic MDD predicted later bipolar diagnoses, as occurs with nonpsychotic mood disorders initially presenting as depressive.[9,20] Observed hypomanic features included elevation of mood or psychomotor activity and behavior not meeting

Figure 1. Summary of Distribution of Factors (from Table 1) Identified as Preceding Stable Diagnosis of Major Depressive Disorder (MDD) or Change in Diagnosis to Bipolar Disorder or Schizoaffective Disorder (N = 107)[a]

[a]Indicates how each factor was associated with each of the 3 diagnostic outcomes. Data are all percentages (prevalence of antecedent and onset factors within type of diagnostic outcome) except for age (in years) at first symptoms.

DSM-IV-TR diagnostic criteria for hypomania, or indications of hyperthymia or impulsivity—all prior to the index major depressive episode. Such antecedents were found as early as approximately 15 years (mean age, 19.8 years) prior to the initial episode of psychotic MDD leading to the first lifetime psychiatric hospitalization at an average age of 34.6 years. It is also noteworthy that patients eventually diagnosed with a *DSM-IV-TR* bipolar disorder met *ICD-10* criteria for a mixed manic-depressive episode at intake and so would have been diagnosed with bipolar disorder initially. This finding agrees with findings of a Danish register-based study[39] that pointed to a significant reciprocal association between psychotic MDD or psychotic mania and mixed manic-depressive states. In contrast to later rediagnoses of bipolar disorder, future schizoaffective diagnoses were anticipated by initial psychotic features considered mood-incongruent and commonly associated with schizophrenia and other

nonaffective psychoses. These included first-rank symptoms of thought passivity, alienation, abnormal attribution of meaning, and hallucinations with predominantly tactile or abnormal bodily sensations and rare olfactory or gustatory phenomena.

Bayesian analyses of the prognostic value of features associated selectively with rediagnoses to bipolar or schizo-affective disorders indicated moderate sensitivity, specificity, and predictive power and so may serve to guide future studies. Diagnostic change to bipolar disorder was most sensitively predicted by antecedent impulsivity, as well as affective and psychomotor instability at presentation in a first lifetime episode of *DSM-IV-TR* psychotic MDD, with high specificity associated with meeting initial *ICD-10* diagnostic criteria for a mixed state, and moderate predictive power associated with previous subsyndromal hypomanic symptoms. Diagnostic change to schizoaffective disorder was most sensitively

Table 2. Multivariate Logistic Regression Model for Factors Associated With Later Change in Diagnosis From First-Episode Major Depressive Disorder With Psychotic Features[a,b]

Factor	Odds Ratio (95% CI)	χ^2	P Value
ICD-10 diagnosis disagrees at first psychotic episode	6.89 (1.95–24.3)	9.00	.003
More antecedent impulsivity before first psychotic episode	4.67 (1.62–13.5)	8.17	.004
Any first-rank symptom at first psychotic episode	5.70 (1.46–22.3)	6.28	.01
Lack of ontological anguish at first psychotic episode	3.25 (1.07–9.91)	4.29	.03

[a]The outcome is diagnostic change; factors are ranked by P value.
[b]Factors not associated with diagnostic change included antecedent posttraumatic reactions or asocial tendencies with introversion and, at first psychotic episode, mood-incongruence of delusions, mood and behavioral instability, formal thought disorder, guilty or nihilistic delusions, and hypochondriasis.

predicted by mood-incongruent psychotic symptoms at initial presentation, with high specificity associated with initial somatosensory hallucinations, meeting ICD-10 diagnosis of schizoaffective disorder at intake, and first-rank symptoms of thought passivity and alienation. Sustained diagnoses of unipolar psychotic MDD over several years of follow-up were predicted best by ontological anguish, nihilistic delusions, weight loss, not meeting ICD-10 criteria for a mixed state or a schizoaffective disorder, and lack of Schneiderian psychotic features at initial presentation as DSM-IV-TR psychotic MDD. The observed inconsistency between ICD-10 and DSM-IV-TR diagnoses underscores continuing differences in their conceptualizations and criteria for mixed states and schizoaffective disorders. These differences may hinder development of reliable and valid definitions of such complex illness constructs.[13,40] These implications are especially relevant in light of the DSM-5 initiative of discarding the diagnosis of mixed episode in favor of a mixed features specifier. However, ongoing efforts to redefine mixed affective episodes and their relevant subtypes for ICD-11 might help preserve mixed states as a distinct diagnostic entity and encourage further research on this construct.[40]

Anguish and nihilism have been reported repeatedly to be characteristic of severe, melancholic depression, often with psychotic features.[22–25,32–35,41] In such forms of depression, mood often appears not to be sorrowful or anhedonic but to represent a hard-to-communicate experience of enduring catastrophic threat to one's very existence. We propose that such features can support the presumed validity and stability of initial diagnoses of psychotic MDD. In addition, initial weight loss predicted a unipolar depressive course, perhaps in accord with the concept that bipolar depression is often characterized by "atypical" somatic features including hyperphagia, weight gain, hypersomnia, and psychomotor retardation.[42–44]

Previous impulsivity, subsyndromal hypomanic excitability, affective psychomotor instability, and meeting initial ICD-10 criteria for a mixed manic-depressive episode (rather than more narrowly defined DSM-IV-TR mixed state) were selectively associated with change of diagnosis to bipolar disorder. Change of diagnosis to a schizoaffective disorder was predicted by initial mood-incongruent psychotic features, early functional decline, initial first-rank symptoms of delusional perception or thought passivity and alienation as well as abnormal self-awareness and attribution of meaning, initial somatic delusions, meeting ICD-10 criteria for a schizoaffective disorder at intake, and initial somatosensory hallucinations. Taken together, these several associations support the diagnostic value of traditional psychopathological concepts.[45]

Also, the finding that diagnoses for more women with initial psychotic MDD converted to bipolar disorder than to schizoaffective disorder (70.0% vs 33.3%), although not statistically significant, may be important. Perhaps affective instability and manic or mixed episodes preceding new diagnoses of bipolar disorder are more likely among women.[46] On the other hand, emergence of schizophrenia-like psychotic phenomena, negative symptoms, and functional decline preceding new schizoaffective diagnoses may be more common among male patients.[47]

Limitations of this study include ascertainment of antecedent and initial psychopathological features based on retrospective reviews of medical records and histories gathered from the participants and family members over prolonged periods of follow-up. These assessments also were carried out by 1 investigator without independent corroboration, although under conditions of blindness with respect to initial and final diagnoses so as to assure comparable assessments across final diagnoses. Also, although studies of psychotic MDD have often considered geriatric samples, this study involved young adult as well as older subjects, consistent with their first-episode status. Moreover, the present findings suggest an association between psychotic MDD and bipolar disorder that may be more likely among younger patients.[48,49] It is unclear to what extent patients considered to have a schizoaffective disorder may include those with psychotic MDD that has not been adequately treated, particularly with antipsychotic medicines.[50] If such treatment deficiencies occurred, they may have been less likely if ICD-10 diagnostic criteria had supported early recognition of schizoaffective disorders. Finally, the relatively small numbers of patients with different outcomes limited statistical power for identifying predictive factors.

In conclusion, this study supports the value of evaluating specific and detailed clinical and psychopathological features early in the evolution of complex disorders like psychotic MDD. It also underscores the need for continued refinements of standard diagnostic criteria, particularly those of DSM-IV-TR pertaining to major affective and psychotic disorders, and the need for further comparisons of cases of psychotic MDD with relatively young versus older ages at onset. Earlier and more accurate diagnoses can serve to guide prognosis and appropriate counseling of patients and their families and help in planning of treatment and other aspects of appropriate long-term clinical management.

REFERENCES

1. Coryell W, Keller M, Lavori P, et al. Affective syndromes, psychotic features, and prognosis, pt 2: mania. *Arch Gen Psychiatry*. 1990;47(7):658–662.
2. Schatzberg AF, Rothschild AJ. Psychotic (delusional) major depression: should it be included as a distinct syndrome in *DSM-IV*? *Am J Psychiatry*. 1992;149(6):733–745.
3. Serretti A, Lattuada E, Cusin C, et al. Clinical and demographic features of psychotic and nonpsychotic depression. *Compr Psychiatry*. 1999;40(5):358–362.
4. Petrides G, Fink M, Husain MM, et al. ECT remission rates in psychotic versus nonpsychotic depressed patients: a report from CORE. *J ECT*. 2001;17(4):244–253.
5. Vythilingam M, Chen J, Bremner JD, et al. Psychotic depression and mortality. *Am J Psychiatry*. 2003;160(3):574–576.
6. Birkenhager TK, van den Broek WW, Mulder PG, et al. Efficacy of imipramine in psychotic versus nonpsychotic depression. *J Clin Psychopharmacol*. 2008;28(2):166–170.
7. Rothschild AJ, Winer J, Flint AJ, et al; Study of Pharmacotherapy of Psychotic Depression (STOP-PD) Collaborative Study Group. Missed diagnosis of psychotic depression at 4 academic medical centers. *J Clin Psychiatry*. 2008;69(8):1293–1296.
8. Gaudiano BA, Dalrymple KL, Zimmerman M. Prevalence and clinical characteristics of psychotic versus nonpsychotic major depression in a general psychiatric outpatient clinic. *Depress Anxiety*. 2009;26(1):54–64.
9. Salvatore P, Baldessarini RJ, Tohen M, et al. McLean-Harvard International First-Episode Project: two-year stability of *DSM-IV* diagnoses in 500 first-episode psychotic disorder patients. *J Clin Psychiatry*. 2009;70(4):458–466.
10. Østergaard SD, Bille J, Søltoft-Jensen H, et al. The validity of the severity-psychosis hypothesis in depression. *J Affect Disord*. 2012;140(1):48–56.
11. Farahani A, Correll CU. Are antipsychotics or antidepressants needed for psychotic depression? a systematic review and meta-analysis of trials comparing antidepressant or antipsychotic monotherapy with combination treatment. *J Clin Psychiatry*. 2012;73(4):486–496.
12. Ostergaard SD, Petrides G, Dinesen PT, et al. The association between physical morbidity and subtypes of severe depression. *Psychother Psychosom*. 2013;82(1):45–52.
13. Salvatore P, Baldessarini RJ, Tohen M, et al. McLean-Harvard International First-Episode Project: two-year stability of *ICD-10* diagnoses in 500 first-episode psychotic disorder patients. *J Clin Psychiatry*. 2011;72(2):183–193.
14. Bromet EJ, Kotov R, Fochtmann LJ, et al. Diagnostic shifts during the decade following first admission for psychosis. *Am J Psychiatry*. 2011;168(11):1186–1194.
15. Ruggero CJ, Kotov R, Carlson GA, et al. Diagnostic consistency of major depression with psychosis across 10 years. *J Clin Psychiatry*. 2011;72(9):1207–1213.
16. Fennig S, Bromet EJ, Karant MT, et al. Mood-congruent versus mood-incongruent psychotic symptoms in first-admission patients with affective disorder. *J Affect Disord*. 1996;37(1):23–29.
17. Jager M, Bottlender R, Strauss A, et al. Fifteen-year follow-up of *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition depressive disorders: the prognostic significance of psychotic features. *Compr Psychiatry*. 2005;46:322–327.
18. Baldessarini RJ, Willmuth RL. Psychotic reactions during amitriptyline therapy. *Can Psychiatr Assoc J*. 1968;13(6):571–573.
19. Kantrowitz JT, Tampi RR. Risk of psychosis exacerbation by tricyclic antidepressants in unipolar major depressive disorder with psychotic features. *J Affect Disord*. 2008;106(3):279–284.
20. Tondo L, Vázquez G, Baldessarini RJ. Mania associated with antidepressant treatment: comprehensive meta-analytic review. *Acta Psychiatr Scand*. 2010;121(6):404–414.
21. Tohen M, Zarate CA Jr, Hennen J, et al. The McLean-Harvard First-Episode Mania Study: prediction of recovery and first recurrence. *Am J Psychiatry*. 2003;160(12):2099–2107.
22. Schneider K. *Clinical Psychopathology*. New York, NY: Grune and Stratton; 1959.
23. Binswanger L. *Melancholie und Manie: Phanomenologische Studien*. Pfullingen, Germany: Günther Neske Verlag; 1960.
24. Tellenbach H. *Melancholie*. Berlin, Germany: Springer Verlag; 1961.
25. Tatossian A. *La Phenomenologie des Psychoses*. Paris, France: Masson e Cie; 1979.
26. Salvatore P, Tohen M, Khalsa HM, et al. Longitudinal research on bipolar disorders. *Epidemiol Psichiatr Soc*. 2007;16(2):109–117.
27. Salvatore P, Khalsa HM, Hennen J, et al. Psychopathology factors in first-episode affective and non-affective psychotic disorders. *J Psychiatr Res*. 2007;41(9):724–736.
28. Spitzer RL, Williams JBW, Gibbon M, et al. *Structured Clinical Interview for* DSM-III-R, *Patient Edition (SCID-P)*. Washington, DC: American Psychiatric Press; 1990.
29. Leckman JF, Sholomskas D, Thompson WD, et al. Best estimate of lifetime psychiatric diagnosis: a methodological study. *Arch Gen Psychiatry*. 1982; 39(8):879–883.
30. American Psychiatric Association . *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
31. World Health Organization. *International Classification of Diseases, 10th Edition*. Geneva, Switzerland: World Health Organization; 1992.
32. Guy W, Ban TA. The AMDP and NCDEU/BLIPS systems: similarities and differences. *Mod Probl Pharmacopsychiatry*. 1983;20:185–192.
33. Gross G, Huber G, Klosterkötter J, et al. *Bonner Skala für die Beurteilung von Basissymptomen (BSABS; Bonn Scale for the Assessment of Basic Symptoms)*. Berlin, Germany: Springer Verlag; 1987.
34. Ebel H, Gross G, Klosterkötter J, et al. Basic symptoms in schizophrenic and affective psychoses. *Psychopathology*. 1989;22(4):224–232.
35. Klosterkötter J, Hellmich M, Steinmeyer EM, et al. Diagnosing schizophrenia in the initial prodromal phase. *Arch Gen Psychiatry*. 2001; 58(2):158–164.
36. Baldessarini RJ, Finklestein S, Arana GW. The predictive power of diagnostic tests and the effect of prevalence of illness. *Arch Gen Psychiatry*. 1983;40(5):569–573.
37. Ostergaard SD, Waltoft BL, Mortensen PB, et al. Environmental and familial risk factors for psychotic and non-psychotic severe depression [Epub ahead of print December 7, 2012]. *J Affect Disord*. 2012.
38. Ostergaard SD, Rothschild AJ, Uggerby P, et al. Considerations on the *ICD-11* classification of psychotic depression. *Psychother Psychosom*. 2012;81(3):135–144.
39. Ostergaard SD, Bertelsen A, Nielsen J, et al. The association between psychotic mania, psychotic depression and mixed affective episodes among 14,529 patients with bipolar disorder [Epub ahead of print October 30, 2012]. *J Affect Disord*. 2012.
40. Ostergaard SD, Rothschild AJ, Bertelsen A, et al. Rethinking the classification of mixed affective episodes in *ICD-11*. *J Affect Disord*. 2012;138(1–2):170–172.
41. Maggini C, Lattanzi L, Sbrana S. Nosografia della depressione psicotica. *Psichiatr Psicoter Anal*. 1991;10:223–239.
42. Kupfer DJ, Weiss BL, Foster G, et al. Psychomotor activity in affective states.

Arch Gen Psychiatry. 1974;30(6):765–768.
43. Kupfer DJ, Foster FG, Detre TP, et al. Sleep EEG and motor activity as indicators in affective states. *Neuropsychobiology*. 1975;1(5):296–303.
44. Foster FG, Kupfer DJ. Psychomotor activity as a correlate of depression and sleep in acutely disturbed psychiatric inpatients. *Am J Psychiatry*. 1975;132(9):928–931.
45. Jaspers K. *General Psychopathology (1913)*. Hoenig J, Hamilton MW (trans). Baltimore, MD: Johns Hopkins University Press; 1997.
46. Akiskal HS, Hantouche EG, Bourgeois ML, et al. Gender, temperament, and the clinical picture in dysphoric mixed mania: findings from a French national study (EPIMAN). *J Affect Disord*. 1998;50(2–3):175–186.
47. Aleman A, Kahn RS, Selten JP. Sex differences in the risk of schizophrenia: evidence from meta-analysis. *Arch Gen Psychiatry*. 2003;60(6):565–571.
48. Strober M, Carlson G. Bipolar illness in adolescents with major depression: clinical, genetic, and psychopharmacologic predictors in a three- to four-year prospective follow-up investigation. *Arch Gen Psychiatry*. 1982;39(5):549–555.
49. Akiskal HS, Walker P, Puzantian VR, et al. Bipolar outcome in the course of depressive illness: phenomenologic, familial, and pharmacologic predictors. *J Affect Disord*. 1983;5(2):115–128.
50. Andreescu C, Mulsant BH, Peasley-Miklus C, et al; STOP-PD Study Group. Persisting low use of antipsychotics in the treatment of major depressive disorder with psychotic features. *J Clin Psychiatry*. 2007;68(2):194–200.

CME INSTITUTE™ POSTTEST

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1. **In this study, patients hospitalized with a *DSM-IV-TR* diagnosis of first-episode major depressive disorder (MDD) with psychotic features were followed for a mean of 4 years. How stable was the diagnosis?**
   a. Initial diagnoses of psychotic MDD were sustained in 30% of patients
   b. Initial diagnoses of psychotic MDD were changed to bipolar disorder or schizoaffective disorder in 70% of patients
   c. Initial diagnoses of psychotic MDD were changed to bipolar disorder or schizoaffective disorder in 30% of patients
   d. Initial diagnoses of psychotic MDD were sustained in 95% of patients

2. **Ms K has been admitted for first-episode MDD with psychotic features. Her symptom profile met *ICD-10* criteria but not *DSM-IV-TR* criteria for a mixed manic-depressive state. Which of the following additional features would suggest that her diagnosis may need to be changed to bipolar disorder?**
   a. Initial ontological anguish
   b. Lack of evidence of antecedent impulsive behavior
   c. Initial first-rank symptom of passivity, external control, or alienation of thoughts
   d. Antecedent mild mood elevations that did not meet *DSM-IV-TR* criteria for hypomania

3. **Mr L has been admitted for first-episode MDD with psychotic features. His symptom profile met *ICD-10* criteria but not *DSM-IV-TR* criteria for schizoaffective disorder. Which of the following features *most* suggests that his diagnosis may need to be changed to schizoaffective disorder?**
   a. Initial mood-incongruent psychotic features
   b. Antecedent functional decline
   c. Initial somatic delusions
   d. Initial olfactory hallucinations

4. **Ms M has been admitted for first-episode MDD with psychotic features. Which of the following features *most* suggests that you should not change her diagnosis?**
   a. Initial weight loss
   b. Initial ontological anguish
   c. Initial nihilistic delusions
   d. Lack of initial first-rank symptom of delusional perception