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CME Objective

After studying this article, you should be able to:

- Incorporate prospectively identified precursors of bipolar disorders into assessment of patients' risk factors to improve diagnostic accuracy

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This educational activity is eligible for *AMA PRA Category 1 Credit*[™] through May 31, 2017. The latest review of this material was April 2015.

Financial Disclosure

All individuals in a position to influence the content of this activity were asked to complete a statement regarding all relevant personal financial relationships between themselves or their spouse/partner and any commercial interest. The CME Institute has resolved any conflicts of interest that were identified. In the past year, Alan J. Gelenberg, MD, Editor in Chief, has been a consultant for Zynx Health and Bloom Burton, has received grant/research support from Pfizer, and has been a stock shareholder of Healthcare Technology Systems. No member of the CME Institute staff reported any relevant personal financial relationships. **Faculty financial disclosure appears at the end of the article.**

Precursors of Bipolar Disorders: A Systematic Literature Review of Prospective Studies

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ABSTRACT

Objective: To evaluate the presence of affective signs and symptoms as precursors of bipolar disorder in prospective studies, including assessment of their prevalence, duration, and predictive value.

Data Sources: We followed PRISMA guidelines to search PubMed, CINAHL, PsycINFO, EMBASE, SCOPUS, and ISI Web of Science databases to May 31, 2013, using the terms *bipolar disorder* AND (*antecedent** OR *predict** OR *prodrom** OR *prospect**) AND (*diagnosis* OR *development*). Hand searching of identified reports led to additional relevant references.

Study Selection: We included only English-language articles containing (1) prospective, longitudinal studies with at least 2 structured clinical assessments (intake and follow-up); (2) no previous *DSM-III* or *DSM-IV* diagnoses of bipolar I or bipolar II; and (3) diagnostic outcome of bipolar I or bipolar II. Studies of subjects at familial risk of bipolar disorder were excluded, as these have been reviewed elsewhere.

Data Extraction: We tabulated details of study design, outcomes, precursors, and predictive value. Only studies reporting a positive predictive association were included.

Results: In 26 published reports meeting selection criteria, methods varied widely in terms of design, duration of follow-up, ages, and populations investigated. Despite such heterogeneity in methods, findings were notably consistent. Precursors of bipolar disorder include mood lability, subsyndromal and major depression, subsyndromal hypomanic symptoms with or without major depression, cyclothymia and bipolar not otherwise specified, major depression with psychotic features, and other psychotic disorders. Bipolar disorder was also predicted by juvenile onset of major depression as well as frequency and loading of hypomanic or depressive symptoms.

Conclusions: Despite the limitations of published reports, prospectively identified precursors of bipolar disorder typically arose years prior to syndromal onset, often with significant early morbidity and disability. Prospectively identified precursors of bipolar disorder are generally consistent with findings in retrospective and family-risk studies. Combining precursors and other risk factors may increase predictive value, support earlier diagnosis, improve treatment, and limit disability in bipolar disorder.

J Clin Psychiatry 2015;76(5):614–624

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Submitted: November 22, 2013; *accepted* July 14, 2014 (doi:10.4088/JCP.13r08900).

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Bipolar disorder is a major psychiatric illness, with lifetime prevalence of approximately 1.0% for bipolar I, 1.1% for bipolar II, and 2.4% for bipolar not otherwise specified (NOS).¹ Bipolar disorder is strongly associated with family psychiatric history and early onset age (peaking at ages 15–25 years) and is often comorbid with substance abuse, anxiety, behavioral, and personality disorders, with high rates of suicide as well as excess mortality from medical disorders.² Diagnosis and treatment of bipolar disorder are typically delayed for 5–15 years from estimated onset, especially in adult cases involving young onset, particularly cases with initial depression.³

The transition from normality to illness occurs gradually in most psychiatric syndromes⁴ with the more or less subtle or gradual appearance of symptoms of varying degrees of severity, duration, co-occurrence, and associated disability. Although episodes of hypomania or mania can onset suddenly with little preceding psychopathology, many retrospective and family risk studies have detected attenuated symptoms before the syndromal onset of bipolar disorder,^{3,5–10} including mood-shifts, emotional lability, irritability, depressive and hypomanic symptoms, sleep disturbances, distractibility, hyperactivity, impulsivity, anxiety, and aggression; such symptoms have been identified 1.8–7.3 years before a first major mood episode and sometimes more than a decade earlier, especially in childhood or adolescence.^{1,3–7,10–15}

Little is known about the prevalence of acute versus gradual onset of mania, hypomania, mixed states, and depression. Most studies of bipolar I and first-episode mania recruited inpatients and reported a sudden onset, more males, and a younger age at onset of mania compared to depression.^{9,16} Studies of bipolar II and first-episode depression that recruited inpatients and outpatients described a sudden onset of depression, usually in females, with a younger age at onset of depression.^{17,18}

The relative frequency of prodromal manifestations is also unknown, and few studies report the onset type (ie, acute vs gradual), and the proportion of bipolar I and bipolar II cases is not always specified.^{3,5,8–10} Nevertheless, bipolar I or bipolar II usually onsets with depression, younger age at onset, more recurrences, and a more disabling course of illness.^{3,6,10,12,19} The early psychopathology of bipolar disorder may also alter normative developmental processes and further complicates the task of clarifying the development of the disorder in children, adolescents, and young adults.

The lack of accepted terms to define and study the onset of bipolar disorder has prompted the International Society for Bipolar Disorder to convene a task force to improve timely diagnosis and early intervention. Among those clinical symptoms or syndromes that precede the syndromal onset of bipolar disorder, we define *precursors*, *clinical risk factors*, and *environmental risk factors* (exposures) as prospectively identified variables that increase the risk of later bipolar disorder (Figure 1; also Supplementary eFigure 1 [available at Psychiatrist.com]), as suggested by Eaton⁴; precursors and clinical and environmental risk factors are collectively referred to as *clinical predictors*. Risk factors

- Precursors of bipolar disorder include mood lability, subsyndromal hypomanic symptoms, subsyndromal depression, cyclothymia and bipolar not otherwise specified (NOS), and major depression, especially with hypomanic or psychotic symptoms.
- Monotonically increasing rates of progression to bipolar disorder were found in cohorts and community samples with isolated hypomanic symptoms, cyclothymic disorder, and bipolar NOS.
- Young age at onset of depression, hypomanic symptoms, cyclothymic temperament, psychotic features, suicidal ideation, and family history of bipolar disorder were associated with unfavorable clinical outcomes.
- The loading and persistence of hypomanic symptoms and positive family history increased the rates of bipolar disorder.

can be environmental (prenatal and perinatal exposures, traumatic events, substances of abuse, effects of medicines) or personal (ie, clinical risk factors) and will be reviewed separately.

This review focuses on precursors of bipolar disorder, their characteristics and timing based on available prospective studies in which outcomes are bipolar I or bipolar II. Our emphasis on prospective studies reflects methodological concern to limit the effects of inaccurate or incomplete information (recall bias) and selection bias (diagnosed cases) associated with retrospective analyses.

Research addressed the following questions: (1) Is there evidence of a prodromal phase of bipolar disorder in prospective studies? (2) Are there specific premorbid affective signs and symptoms (precursors) that predict bipolar disorder? (3) What are the nature, timing, and duration of precursors? (4) How sensitive and specific are they in predicting later diagnosable bipolar disorder? and (5) Does the prodromal phase differ by bipolar subtype?

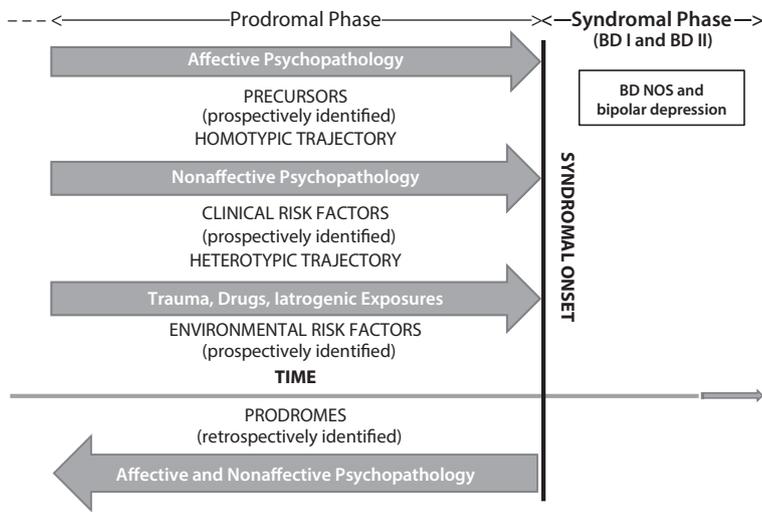
DATA SOURCES

We carried out a computerized search of PubMed, CINAHL, PsycINFO, EMBASE, SCOPUS, and ISI Web of Science databases from inception up to May 31, 2013, using the following search algorithm: (*bipolar disorder* AND [*antecedent** OR *predict** OR *prodrom** OR *prospect**] AND [*diagnosis* OR *development*]). Hand searching of references in identified reports led to additional relevant reports.

STUDY SELECTION AND DATA EXTRACTION

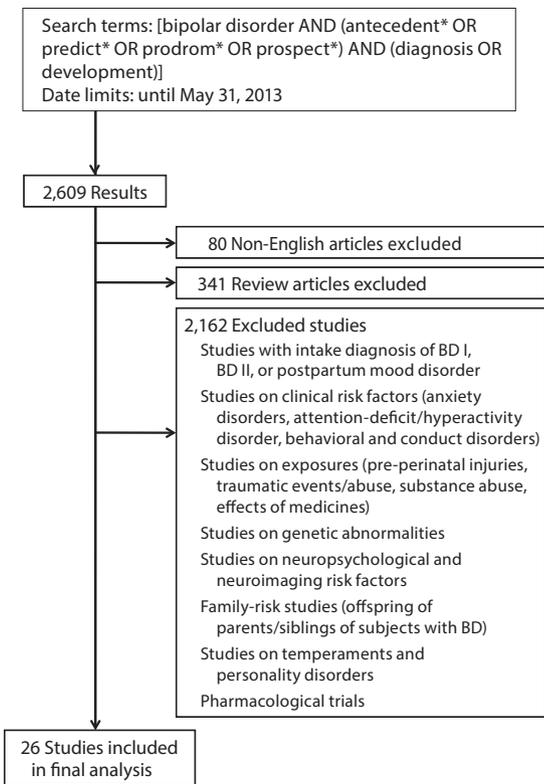
Articles selected were published in the English language and met the following inclusion criteria: (1) prospective, longitudinal studies with at least 2 structured clinical assessments (intake and follow-up); (2) diagnoses at intake that included *DSM-III* or *DSM-IV* major depressive episode (MDE) and major depressive disorder (MDD), dysthymia, cyclothymia, or bipolar NOS as well as subjects with subsyndromal affective disorders or symptoms; (3)

Figure 1. Predictors of Bipolar Disorder^a



^aRefer to Supplementary eFigure 1 for glossary of terms used in this figure.

Figure 2. Study Selection Flowchart



diagnostic outcome at follow-up of bipolar I or bipolar II. Exclusion criteria are detailed in Figure 2.

We identified a total of 26 reports meeting inclusion criteria. We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses: <http://www.prisma-statement.org>) guidelines, and for each article selected, we extracted the following information: number of subjects, initial diagnosis, age at intake, study design and assessment tool, duration of follow-up, percentage of subjects diagnosed

as bipolar I or bipolar II during follow-up, and clinical features predicting later bipolar diagnosis and their statistical power (odds ratio [OR] or adjusted odds ratio, hazard ratio, likelihood ratio, or Bayesian sensitivity, specificity, and positive or negative predictive value). Only studies reporting a positive predictive value were included in this review.

We excluded family-risk studies (offspring of parents/siblings of subjects diagnosed with bipolar disorder), as they have been reviewed elsewhere.²⁰ Also, while many affected patients have a positive family history for bipolar disorder, this is not true for all patients with bipolar disorder, because of misdiagnosis, undiagnosed illness, recurrent depression not meeting criteria for bipolar disorder, or the lack of family history. This suggests that there may be sporadic or nonfamilial forms of illness.

Furthermore, most family risk studies focus on offspring of adults or siblings of subjects with bipolar I,² although there are exceptions.^{14,15}

RESULTS

Figure 2 shows a flowchart of the number of articles identified and their disposition; Table 1 summarizes the findings obtained.

Summary of Methods Used in the Studies

Sample characteristics. Six studies included child and/or adolescent subjects, 12 studies included adult subjects, and 8 studies included subjects spanning from childhood to adulthood. All studies included subjects of both sexes. The group sample sizes for the studies varied widely, with groups as small as 32 to as large as 5,501.

Diagnosis. Six studies included subjects with intake diagnosis of MDD or depression, 6 studies included samples with MDD with psychotic features, 3 studies included psychotic (non-MDD) patients, 3 studies included subjects diagnosed with cyclothymic disorder or bipolar NOS, 5 studies had subjects with subsyndromal depressive or hypomanic symptoms, and 6 community studies included subjects at risk (see Table 1). Diagnoses were obtained with structured interviews using *DSM-III*, *DSM-III-R*, or *DSM-IV* criteria in all studies selected except for Akiskal et al.²¹⁻²³ The assessment tools also included self-reports of hypomanic or temperamental features in patients with major and minor depression (see Table 1), but their validity, reliability, or predictive value was not always reported and could not be operationalized. We refer the reader to the original reports for details about the psychometric properties of instruments used.

Design. All studies included were longitudinal and prospective: 11 studies included inpatients, 5 studies followed outpatients, and 10 studies included a community sample. The duration of follow-up varied markedly, ranging from 6 months to 31 years.

Table 1. Precursors Identified in Prospective Studies as Significantly Predictive of Later Bipolar Disorder

Study	Diagnosis, N	Age, Range (mean), y	Design (cohort name)/ Assessment Tool	Follow-Up,		Outcome, n (%)	Notes ^a
				Range (mean), y	Range (mean), y		
Mood lability							
Akiskal et al, ²⁴ 1995	MDD, 559	> 17	Prospective, inpatients (NIMH-CDS)/SADS	2–11	BD I, 22 (3.9) BD II, 48 (8.6)	Mood-lability factor predicted BD II (specificity, 86%; sensitivity, 42%)	
Angst et al, ²⁵ 2003	Risk set, 591 ^b	(18.5)	Prospective, community (Zurich Cohort Study)/ SCL-90-R	15	BD II, 41 (7) BD I/NOS, 45 (7.6)	Self-reported "frequent ups and downs of mood" predicted BD spectrum (OR = 14.3) and BD II (OR = 20.6)	
Tohen et al, ²⁶ 2012	MDDP, 49	18–75 (36.3)	Prospective, inpatients (MCL-FEP)/SCID	0.5–9 (3.9)	BD I/NOS, 14 (28.6)	Past/current mood swings at intake predicted BD ($\chi^2 = 4.85$)	
Subsyndromal depression							
Akiskal et al, ²² 1978	Subsyndromal depression, 100	17–65	Prospective, outpatients/ clinical ^c	3–4	BD I, 4 (4) BD II, 14 (14)	Subsyndromal depression referred to as "situational, reactive or neurotic"	
Beesdo et al, ²⁷ 2009	MDE, 649 Subsyndromal depression, 327	14–24	Prospective, community (EDSP)/M-CIDI	7.3–10.6 (8.3)	MDE BD I, 15 (2.3) BD II, 11 (1.7)	MDE significantly associated with later BD I than with later BD II (OR = 5.20)	
Regeer et al, ²⁸ 2006	Risk set, 4,628 ^d	18–64 (41.2)	Prospective, community (NEMESIS)/CIDI	3	BD I/NOS, 14 (0.3)	Lifetime subsyndromal depression predicted BD (PP = 1.0, LR = 3.3)	
Subsyndromal hypomanic symptoms in major depression							
Akiskal et al, ²⁴ 1995	MDD, 559	> 17	Prospective, inpatients (NIMH-CDS)/SADS	2–11	BD I, 22 (3.9) BD II, 48 (8.6)	Hyperenergetic involvement in activities predicted BD; 36% of BD II patients had diagnosis later changed to BD I	
Tohen et al, ²⁶ 2012	MDDP, 49	18–75 (36.3)	Prospective, inpatients (MCL-FEP)/SCID	0.5–9 (3.9)	BD I/NOS, 14 (28.6)	Subsyndromal hypomania predicted BD ($\chi^2 = 4.76$)	
Fiedorowicz et al, ³⁴ 2011	MDD, 550	> 17	Prospective, inpatients (NIMH-CDS)/SADS	1–31 (17.5)	BD I, 41 (7.5) BD II, 67 (12.2)	Five combined manic symptoms significantly predicted BD (HR = 1.34), BD I (HR = 1.28), BD II (HR = 1.23)	
Zimmerman et al, ³⁵ 2009	Risk set, 2,210 ^e	14–24	Prospective, community (EDSP)/M-CIDI	7.3–10.6 (8.3)	BD I, 65 (3) BD II, 33 (1.4)	Mood disturbances/change in functioning observable by other significantly predicted BD (OR = 4.25) and BD I (OR = 8.32) in MDD subjects	
Nadkarni et al, ³⁶ 2010	DSD + TMS, 25 DSD, 8	8–11 (9.9)	Prospective, outpatients (MF-FEP)/ChIPS	1.5	BD, 12 (48) (from DSD + TMS) BD, 1 (12.5) (from DSD)	Transient hypomanic symptoms increase the risk of BD by 3.8 times (48% vs 12.5%)	
Subsyndromal hypomanic symptoms							
Regeer et al, ²⁸ 2006	Risk set, 4,628 ^d	18–64 (41.2)	Prospective, community (NEMESIS)/CIDI	3	BD I/NOS, 14 (0.3)	Lifetime subsyndromal hypomania predicted BD (PP = 7.1, LR = 25.4) and MDE (PP = 17.9, LR = 3.7)	
Kwapil et al, ²⁹ 2000	HYP+, 36 HC, 31	(31.8) HYP+ (33.6) HC	Prospective, community/ HPS	12–14 (13)	BD I, 2 (4.25) BD II, 7 (14.9)	Elevated score on HPS predicted BD; no conversions in HC	
Kaymaz et al, ³⁰ 2007	Risk set, 5,501 ^d	18–64 (41.2)	Prospective, community (NEMESIS)/CIDI	2	BD, 5 (0.09)	Baseline subclinical mania + psychosis predicted BD (PP = 9.5) compared to subclinical mania alone (PP = 3.0)	
Homish et al, ³² 2013	Elation and/or irritability, 2,755 ^f	> 18	Prospective, community (NESARC)/ AUDADIS-IV	3	BD, 201 (8) (from patients with elation or irritability) BD, 32 (13) (from patients with elation and irritability)	Elation or irritability alone (both OR = 2.8) or in combination (OR = 4.6) significantly predicted BD, also in association with lifetime MDD (OR = 2.2)	

(continued)

Table 1 (continued). Precursors Identified in Prospective Studies as Significantly Predictive of Later Bipolar Disorder

Study	Diagnosis, N	Age, Range (mean), y	Design (cohort name)/ Assessment Tool	Follow-Up, Range (mean), y		Outcome, n (%)	Notes ^a
				inpatients/K-SADS, GHT	outpatients/clinical ^c (EDSP)/M-CIDI		
Cyclothymic disorder and bipolar NOS							
Kochman et al, ¹⁸ 2005	MDD, 80	7-17 (12.7)	Prospective, inpatients/K-SADS, GHT	2-4 (2.2)	BD, 35 (43)		Cyclothymic temperament significantly predicts BD, suicidal ideation, and attempts
Cyclothymia							
Akiskal et al, ²¹ 1977	Cyclothymia, 46	15-45	Prospective, outpatients/clinical ^c	2-3	BD I, 3 (7) BD II, 13 (28)		
Beesdo et al, ²⁷ 2009	Hypomanic, 91 Manic, 63	14-24	Prospective, community (EDSP)/M-CIDI	7.3-10.6 (8.3)	BD II, 15 (16.5) BD I, 30 (47.6)		
Axelsson et al, ³⁷ 2011	BD NOS, 140	7-17	Prospective, outpatients (COBY)/K-SADS-PL, PSR, LIFE	0.5-8.3 (5.4)	BD I, 32 (23) BD II, 31 (22)		Intake ratings of hypomanic symptoms (HR = 1.03)
Alloy et al, ³⁸ 2012	Cyclothymia or BD NOS, 57	18-24	Prospective, community (LIBS)/exp-SADS-L, GBI	(4.5)	BD I, 6 (10.5) BD II, 24 (42.1)		High BAS sensitivity and fun seeking moderately predicted BD II (OR = 1.4)
Psychotic symptoms in major depression							
Strober et al, ¹⁷ 1993	MDD, 40 MDDP, 18	13-17 (15.3)	Prospective, inpatients/SADS, PSR, LIFE	2	BD I/II, 5 (8.6)		Psychotic symptoms predicted conversion to BD (all converted cases were in MDDP group)
Kochman et al, ¹⁸ 2005	MDD, 80	7-17 (12.7)	Prospective, inpatients/K-SADS, GHT	2-4 (2.2)	BD, 35 (43)		Cyclothymic temperament with psychotic symptoms significantly predicted BD (57.4% vs 6.10%)
Fiedorowicz et al, ³⁴ 2011	MDD, 550	> 17	Prospective, inpatients (NIMH-CDS)/SADS	1-31 (17.5)	BD I, 41 (7.5) BD II, 67 (12.2)		Severity of psychotic symptoms at intake predicts BD I (HR = 3.54) and BD II (HR = 1.97)
DelBello et al, ³⁹ 2003	MDDP, 157	15-75 (33)	Prospective, inpatients (UC-FHS; McL-FEP; SC-MHP)/SCID	1-2	BD I, 14 (9) BD II, 7 (4)		
Salvatore et al, ⁴⁰ 2009	MDDP, 77 Psychosis, 121 ^g	(31.7)	Prospective, inpatients (McL-FEP)/SCID	2	BD I, 29 (14.6)		Percentage of conversion doubled in MDDP vs psychosis (20.7% vs 10.7%) group
Bromet et al, ⁴¹ 2011	MDDP, 80	15-60	Prospective, inpatients (SC-MHP)/SCID	10	BD, 11 (14.3)		Decrease in psychotic and negative symptoms predicted BD
Salvatore et al, ⁴² 2013	MDDP, 107	10-82 (34.6)	Prospective, inpatients (McL-FEP)/SCID	4	BD I, 10 (9.35) BD NOS, 10 (9.35)		ICD-10 mixed states at intake, previous hypomanic symptoms, and impulsive behavior preceded BD
Psychotic disorder							
Salvatore et al, ⁴⁰ 2009	MDDP, 77 Psychosis, 121 ^g	(31.7)	Prospective, inpatients (McL-FEP)/SCID	2	BD I, 29 (14.6)		Percentage of conversion doubled in MDDP vs psychosis (20.7% vs 10.7%) group
Gogtay et al, ⁴³ 2007	Psychosis NOS, 32	10-12 (11)	Prospective, inpatients/K-SADS	4-8	BD I, 12 (38)		
Castro-Fornieles et al, ⁴⁴ 2011	Psychosis, 70 ^h	9-17 (15.5)	Prospective, inpatients (CAFEPS)/K-SADS-PL	2	BD, 7 (10)		
Rössler et al, ⁴⁵ 2011	Risk set, 335 ^b	(18.5)	Prospective, community (Zurich Cohort Study)/SCL-90-R, SPIKE	27	BD, 56 (16.7)		Schizotypal features moderately predicted BD (AOR = 1.57) but lacked specificity; schizophrenia nuclear symptoms were associated with lifetime BD

(continued)

Table 1 (continued). Precursors Identified in Prospective Studies as Significantly Predictive of Later Bipolar Disorder

Study	Diagnosis, N	Age, Range (mean), y	Design (cohort name)/ Assessment Tool	Follow-Up, Range (mean), y	Outcome, n (%)	Notes ^a
Age at onset of major depression						
Akiskal et al, ²³ 1983	Depression, 206	Adults	Prospective, outpatients/ clinical ^c	1–9 (3)	BD I, 41 (20)	Early onset (<25 y) MDE/MDD predicted BD I (sensitivity, 71%; specificity, 68%; positive predictive value, 69%)
Akiskal et al, ²⁴ 1995	MDD, 559	> 17	Prospective, inpatients (NIMH-CDS)/SADS	2–11	BD I, 22 (3.9) BD II, 48 (8.6)	Early onset MDE/MDD predicted BD II ($t = 2.79$)
Beesdo et al, ²⁷ 2009	MDE, 649 Subsyndromal depression, 327	14–24	Prospective, community (EDSP)/ M-CIDI	7.3–10.6 (8.3)	MDE BD I, 15 (2.3) BD II, 11 (1.7) Subsyndromal depression BD I, 4 (1.2) BD II, 5 (1.5)	9% Conversion risk from MDD to BD in early onset depression (<17 y)
Homish et al, ³² 2013	Elation and/or irritability, 2,755 ^e	> 18	Prospective, community (NESARC)/ AUDADIS-IV	3	BD, 201 (8) (from patients with elation or irritability); BD, 32 (13) (from patients with elation and irritability)	
Frequency and loading of affective symptoms						
Regeer et al, ²⁸ 2006	Risk set, 4,628 ^d	18–64 (41.2)	Prospective, community (NEMESIS)/CIDI	3	BD I/NOS, 14 (0.3)	Loading of lifetime MDE (PP = 14.3–50, LR = 2.7–16.4) and hypomanic symptoms (PP = 25–50, LR = 5.5–16.4) predicted BD
Tijssen et al, ³¹ 2010	Risk set, 1,902 ^e	14–24 (18.3)	Prospective, community (EDSP)/M-CIDI	7.3–10.6 (8.3)	BD, 21 (1.1)	Loading of depressive symptoms, duration of MDE, and recurrence rates increased risk of BD

^aUnless specified otherwise, all statistical measures reported were below the threshold of significance ($P < .05$).

^bRisk set consisted of a sample of subjects selected for interview, with two-thirds consisting of high scorers (defined by the 85th percentile or higher of SCL-90-R) and a random sample with scores below the 85th percentile.

^cAssessment tools with diagnostic criteria other than DSM-III.

^dRisk set consisted of (1) all individuals who at baseline had never had any diagnosis of major depression, bipolar disorder, or psychotic disorder and (2) all individuals who had had at least 1 postbaseline CIDI interview (first or second follow-up).

^eIncludes schizophrenia disorder (n = 19), brief psychotic disorder (n = 36), and psychotic disorder NOS (n = 66).

^fRisk set consisted of a sample of randomly selected civilian, noninstitutionalized adults representative of the US population.

^gIncludes schizophrenia disorder (n = 5), schizoaffective disorder (n = 5), and psychotic disorder NOS (n = 66).

Abbreviations: AOR = adjusted odds ratio; AUDADIS-IV = Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV; BAS = Behavioral Approach System Scale; BD = bipolar disorder; CAPEPS = Child and Adolescent First-Episode Psychosis Study; CHIPS = Children's Interview for Psychiatric Syndromes; CHT = Cyclothymic-Hyper-sensitive Temperament Questionnaire; CIDI = Composite International Diagnostic Interview; COBY = Course and Outcome of Bipolar Youth study; DSD = depressive spectrum disorder; EDSP = Early Developmental Stages of Psychopathology; exp-SADS-L = expanded version of SADS, lifetime assessment; GBI = General Behavior Inventory; HC = healthy controls; HPS = Hypomanic Personality Scale; HR = hazard ratio; HYP+ = hypomanic personality (as assessed with HPS); K-SADS = Schedule for Affective Disorders and Schizophrenia for School Aged Children; K-SADS-PL = Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version; LIBS = Longitudinal Investigation of Bipolar Spectrum Disorders Project; LIFE = Longitudinal Interval Follow-up Evaluation; LR = likelihood ratio; M-CIDI = computer-assisted Munich-Composite International Diagnostic Interview; McL-FEP = McLean First Episode Psychosis study; MDD = major depressive disorder; MDDP = major depressive disorder with psychotic symptoms; MDE = major depressive episode; MF-PEP = Multi-Family Psychoeducational Psychotherapy study; NEMESIS = Netherlands Mental Health Survey and Incidence Study; NESARC = National Epidemiologic Survey on Alcohol and Related Conditions study; NIMH-CDS = National Institute of Mental Health Collaborative Depression Study; NOS = not otherwise specified; OR = odds ratio; PP = positive predictive value; PSR = Psychiatric Status Rating scales; SADS = Schedule for Affective Disorders and Schizophrenia; SCID = Structured Clinical Interview for DSM; SCL-90-R = Symptom Checklist-90-Revised; SC-MHP = Suffolk County Mental Health Project; SPIKE = Structured Psychopathological Interview and Rating of the Social Consequences of Psychological Disturbances for Epidemiology; TMS = transient manic symptoms; UC-FHS = University of Cincinnati First Hospitalization Study.

Summary of Results

Mood lability. We found that mood lability predicted bipolar II (but not bipolar I) in adult inpatients with MDD,²⁴ whereas it predicted bipolar II and bipolar spectrum disorders (MDD and subsyndromal hypomania) in young adults in a community risk set.²⁵ Past or current mood lability at intake predicted a change of diagnosis to bipolar I or bipolar NOS in adults hospitalized for MDD with psychotic features.²⁶

Subsyndromal depression. An 18% rate of later diagnoses of bipolar disorder, especially bipolar II, was reported among adult outpatients with mild depressive episodes (defined as situational, reactive, or neurotic)²²; lower rates were reported in community studies of young adults (1.5% bipolar II, 1.2% bipolar I)²⁷ and adults (0.3% for bipolar disorder).²⁸

Subsyndromal hypomanic symptoms. Elevated scores on the Hypomanic Personality Scale significantly predicted later bipolar disorder, especially bipolar II,²⁹ in a cohort of college students compared to healthy controls. Also, lifetime subsyndromal hypomanic symptoms predicted bipolar I, bipolar NOS, and a major depressive episode in a Dutch community sample of adults,²⁸ and the combination of subclinical mania with subclinical psychosis at baseline predicted 3 times more new diagnoses of bipolar disorder as compared to those with subclinical mania only.³⁰ In the Early Developmental Stages of Psychopathology (EDSP) community study, the majority of youths experiencing an episode of hypomania or mania experienced isolated hypomanic and/or depressive symptoms; number and persistence of symptoms increased monotonically during prospective follow-up before criteria for bipolar disorder were met.³¹ In a community study, symptoms of elation or irritability, and especially their combination, predicted later hypomania or mania independent of major depression in 3 years of follow-up.³²

Major depression. We recently reviewed studies (both prospective and retrospective) on rates of conversion from MDD to bipolar I or bipolar II, differentiating cases of spontaneous conversion from those emerging with antidepressant use.³³ The rate of spontaneous hypomania or mania was 3.3% (0.36% per year) and similar in prospective and retrospective studies but much lower than the 8.2% (4.1% per year) risk of mania or hypomania associated with antidepressant treatment; moreover, changes of diagnosis to bipolar disorder were 4.5 times higher among juveniles than adults.³³

Subsyndromal hypomanic symptoms in major depression. In adults with current MDD,²⁴ the presence of the hypomanic symptom hyperenergetic involvement in activities predicted diagnostic switch to bipolar disorder, with more cases involving later hypomanic than manic episodes; however, more than one-third of those diagnosed with bipolar II later developed mania, suggesting a progression of intensity of mood elevation. In the same cohort, but with longer follow-up,³⁴ the sum of ratings of 5 hypomanic symptoms moderately but significantly predicted bipolar disorder, with a similar relationship to later mania or hypomania; in bivariate analyses, decreased need for sleep, unusually high energy, and

increased goal-directed activity significantly predicted both hypomania and mania, whereas grandiosity predicted only mania. The presence of at least 3 hypomanic symptoms was fairly specific in predicting bipolar disorder.³⁴

The presence of subsyndromal hypomania at baseline in a cohort of community at-risk adolescents and young adults with lifetime MDD significantly increased the likelihood of a later diagnosis of bipolar and bipolar I (compared to those without); in particular, "mood disturbances or change in functioning observable by others" (*DSM-IV* manic episode, criterion D) was a strong predictor of change of diagnosis from MDD to bipolar disorder and especially to bipolar I.³⁵ Similarly, the presence of current subsyndromal hypomanic symptoms significantly predicted bipolar I and bipolar NOS in psychotic MDD adults.²⁶ Additionally, among children with depressive spectrum disorders (MDD and/or dysthymia), the presence of transient manic symptoms was associated with almost 4 times increase in bipolar spectrum disorders (bipolar I, bipolar II, or bipolar NOS) after 18 months of follow-up.³⁶

Cyclothymic disorder and bipolar NOS. Among adolescent and adult outpatients diagnosed with cyclothymic disorder, 35% developed bipolar disorder within 3 years,²¹ while in children and adolescents hospitalized with MDD, high scores on the Cyclothymic-Hypersensitive Temperament Rating Scale significantly predicted diagnoses of bipolar disorder.¹⁸

Among youths with hypomania but without a lifetime history of major depression, 16.5% developed an MDE and were re-diagnosed as bipolar II, while the rest continued to experience hypomania alone.²⁷ Higher rates of conversion from bipolar NOS to bipolar disorder were also reported in the Course and Outcome of Bipolar Youth study³⁷: over 5 years, 23% were re-diagnosed with bipolar I (following hypomania in 61% of cases) and 22% with bipolar II; elevated intake ratings of hypomanic symptoms predicted conversion. Of 119 subjects without a lifetime history of hypomania at intake, later bipolar disorder occurred in 44% (24% bipolar I, 20% bipolar II), particularly in those with a family history of mania or hypomania.³⁷

A similar pattern of results in adults with bipolar NOS or cyclothymic disorder were reported by Alloy,³⁸ who found that more than half developed bipolar disorder over 4.5 years, especially bipolar II; higher levels of interpersonal sensitivity and fun seeking predicted conversion.³⁸

Psychotic symptoms in major depression. Psychotic features predicted conversion to bipolar disorder in a cohort of adolescents hospitalized for MDD (compared to those without psychotic features),¹⁷ a finding replicated by Kochman¹⁸: depressed youths with psychotic features and cyclothymic temperament were 9.40 times more likely to be diagnosed with bipolar disorder compared to those without.

Several prospective studies reported further evidence of diagnostic instability of psychotic MDD and its conversion to bipolar disorder, both in adolescents and adults.^{34,39-42}

Psychotic disorders. In children hospitalized and initially diagnosed with psychosis NOS, 38% met criteria for bipolar I within 8 years,⁴³ while another group reported a lower rate of conversion but with a shorter follow-up duration.⁴⁴ Finally, in

a 27-year follow-up of a community group of at-risk subjects, schizotypal features moderately predicted later bipolar disorder but lacked specificity⁴⁵; similarly, schizophrenia nuclear symptoms (assessed with the Symptom Checklist-90-Revised) were associated with a lifetime diagnosis of bipolar disorder but also with phobias.⁴⁵

Age at onset of major depression. Akiskal et al²³ found that early onset of depression (age < 25 years) predicted later bipolar disorder; several other prospective studies^{24,27,32} had similar findings.

Frequency and loading of affective symptoms. The risk of bipolar disorder increased with the number of lifetime depressive episodes and with the number of hypomanic symptoms.²⁸ Longer episodes of depression, greater loading of depressive symptoms, and higher recurrence rates predicted increased risk of later diagnoses of bipolar disorder.³¹

DISCUSSION

We found evidence of a prodromal phase of bipolar disorder, characterized by several precursors. Precursors of bipolar disorder had significant time depth, anticipating syndromal onset by years. Manic and depressive symptoms appeared early and increased in number, duration, and secondary impairment, following a chronic rather than episodic course over several years. Hypomanic and depressive symptoms increased the risk of their own recurrence and of the occurrence of episodes of opposite polarity. Monotonically increasing rates of progression to bipolar disorder were found in cohorts and community samples with isolated hypomanic symptoms,^{27–30,32,34,36} cyclothymic disorder,^{18,21,38} and bipolar NOS as well as those prospectively diagnosed with bipolar II and bipolar I.^{27,37,38} In spite of the relative frequency of unipolar hypomanic presentations, there was little or no evidence of a progression to mania as a necessary outcome, with significant numbers of those diagnosed with cyclothymic disorder or bipolar NOS never progressing to mania or those meeting criteria for bipolar II never experiencing mania.^{18,27,37,38}

Some precursors were selective for bipolar I or bipolar II, but data on phenomenological differences by subtype in the prodromal features observed are insufficient.

While acute onset of mania or depression is often reported in retrospective studies,^{3,5,12} the presence of chronic and gradually worsening symptoms was found in most cases.

We also found a good deal of consistency between the present findings and those identified with retrospective studies.

Affective lability or mood swings before the diagnosis of bipolar disorder have been described in retrospective analyses of both youths and adults,^{5,8,10,46–48} although these symptoms were observed in only a significant minority of adults: 30% of bipolar I,²¹ 33% of bipolar II,⁴⁹ and 17% of first-episode bipolar I patients with psychotic features.⁴⁸ We found that mood lability and cyclothymic features preceding depressive episodes were associated mainly with bipolar

II^{18,21,24,25} and predicted bipolar II in 2 juvenile cohorts,^{18,38} confirming the presence of a homotypic trajectory of illness' development.

A depressive onset is common in all subtypes of bipolar and cyclothymic disorder both in retrospective^{3,5,6,8,12,50} and prospective studies^{17,18,24,27,34,36–38} as well as family risk studies.^{15,20} Minor depression with subsyndromal hypomania in children predicted bipolar I and bipolar II,^{27,36} while in bipolar I adults presenting with euphoria and grandiosity, cross-sectional ORs were elevated for both dysthymia (OR = 13.6) and MDD (OR = 18.4).⁵¹ Young age at onset of depression, hypomanic symptoms (such as brief mood-elevation, irritability, increased energy, restlessness, or agitation), cyclothymic temperament, psychotic features, suicidal ideation, and a family history of bipolar disorder were associated with change in diagnosis to later bipolar disorder,^{18,24,27,30,31,34,45} a finding confirmed in retrospective studies.^{5,19,52–54} When minor or major depression occurred in the absence of putative markers of bipolar disorder (ie, hypomanic features, young onset age, or family history), the risk of progression to bipolar disorder was not increased.^{27,36} While the diagnoses of bipolar disorder are highly stable and reliable,⁴⁰ variable proportions of subjects initially diagnosed with major depression were later re-diagnosed as bipolar. Such outcome has been described in a substantial proportion of patients, especially in youth and early adulthood^{5,6,8,10,14,15,27} and often in response to antidepressant treatment.⁵⁵ It is therefore a priority to identify those forms that tend to recur or develop into hypomania or mania, as this knowledge might have important diagnostic and prognostic value.

High scores in ratings of hypomanic personality traits and hypomanic symptoms in young depressed patients as well as early onset hypomania have predicted bipolar disorder in only a minority of subjects over relatively short periods of follow-up.^{27,28,32,36–38} Youths diagnosed with bipolar NOS at intake have later met criteria for bipolar I or II in less than half of cases within 5 years of follow-up, suggesting a developmental continuum of manic severity.^{27,37} Nevertheless, some cases of cyclothymic disorder, bipolar NOS, and bipolar II remain stable and do not develop into mania.^{27,37,38,56} In the Course and Outcome of Bipolar Youth study,³⁷ at 2, 4, and 5 years of follow-up, 25%, 38%, and 45% of bipolar-NOS patients met criteria for bipolar I or II, and 28% followed a progression from bipolar NOS to bipolar II before experiencing mania, whereas 24% did not have another mood episode within 5 years. These findings suggest that the predictive power and diagnostic specificity of hypomanic symptoms and attenuated syndromes (cyclothymic disorder and bipolar NOS) for mania may be limited or that these syndromes themselves might represent stable outcomes. It is also clear, however, that in some adolescents, persistence (rather than the sole presence) of hypomanic or manic symptoms increases the risk of a progression to diagnosable bipolar disorder.³¹

Recurrent unipolar hypomania was found in 42% of the youths with bipolar disorder in the EDSP study.²⁷ It

is possible that such frequent occurrence of hypomanic symptoms in youth might represent developmental variations or self-limiting delays in mood regulation. Similarly, in the Longitudinal Assessment of Manic Symptoms study, Findling et al⁵⁷ reported that only 15% of youths with high scores on the Parent-General Behavior Inventory (scores >12) developed bipolar disorder; most of those went through an attenuated bipolar syndrome with most hypomanic symptoms either remitting with development or failing to progress to a bipolar syndrome. Consistent with the EDSP findings,^{27,56} hypomanic or manic symptoms might increase the risk of bipolar disorder only if recurrent, persistent or both, and especially when associated with other precursors (depressive symptoms^{31,36}) and risk factors.^{27,36,56} Therefore, while hypomanic or manic symptoms were sensitive, they were not necessarily specific; they helped identify the subjects whose symptoms loading or persistence increased the risk for bipolar disorder.

Early onset of bipolar disorder was associated with greater familial risk of mood disorders^{17,21,37,39} as well as with suicidal risk, psychotic features, mixed episodes, substance abuse, panic disorder, attention-deficit/hyperactivity disorder, early sexual or physical abuse, neuropsychological dysfunction, poor response to lithium treatment, or unfavorable clinical outcomes.^{3,20,24,34,35,54,57} The presence of additional risk factors like a family history of bipolar disorder^{36–38} or the co-occurrence (loading) and persistence of hypomanic symptoms was correlated with increased rates of transition to bipolar disorder.³¹

From a prevention–early identification perspective, the predictive value of precursors is lower than it is for risk factors, as the definition of the outcome includes such signs and symptoms. To increase predictive power and accurately identify populations with different types and levels of risk, it is often necessary to combine different, ideally independent risk markers. Populations with 1 or more of the known precursors (eg, hypomania, mood swings), risk factors (socioeconomic, family history of bipolar disorder, an anxiety disorder), and exposures (cannabis abuse, trauma) should then be monitored to assess the variable's predictive value.^{17,18,32,35–38,54,57}

In a prevention model, a different threshold besides the syndromal one can be useful. For instance, different thresholds could be used based on symptoms progression, associated disability, and developmental delays: a monitoring threshold, an intervention's threshold, and a treatment threshold might be helpful in establishing monitoring and treatment guidelines.

Limitations of this review are substantial. Heterogeneity of studies and samples precluded pooling of data that might clarify the timing and duration of such precursors. Similarly, only few studies provided data on sensitivity, specificity, and predictive value of reported precursors. Notably, the prevalence, sequence, and timing of psychopathology predictive of bipolar disorder remain understudied, lacking sensitivity and specificity. The assessment tools, their validity, reliability, or predictive value could not be operationalized in

a review of published reports. While these are objective and not methodological limitations, a cautious interpretation of the findings as to their generalizability is necessary. Specifically, it prevents the use of the data summarized in efforts to define stages of illness other than the obvious presyndromal and postsyndromal phases. Family risk studies were not reviewed here, as they have been reviewed elsewhere.^{14,15,20} Finally, this review focused on the putative presence of a progression of affective psychopathology and did not address clinical risk factors, exposures (Figure 1), or the interaction of precursors, clinical risk factors, exposures, and other risk factors like family history of bipolar disorder or recurrent depression.

Drug names: lithium (Lithobid and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.

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Financial disclosure: Drs Faedda, Marangoni, Serra, Salvatore, Sani, Vázquez, Tondo, Girardi, Baldessarini, and Koukopoulos have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.

Funding/support: This study was supported by a NIMH award R01 MH089743 to Martin H. Teicher, PhD, MD (with Dr Faedda); National Institutes of Health grants MH-47370 and MH-73049; a grant from the Aretæus Association and Lucio Bini Private Donors Research Fund (Dr Tondo); a NARSAD Young Investigator Award to Dr Salvatore; and a grant from the Bruce J. Anderson Foundation and the McLean Private Donors Research Fund (to Dr Baldessarini).

Role of the sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Previous presentations: Findings from this review were presented as a poster at the International Society for Bipolar Disorders Meeting in Miami (June 13–16, 2013) and were Drs Faedda, Baldessarini, and Salvatore's contribution to the “ISBD's Task Force on Prodromes of Bipolar Disorder,” co-chaired by Drs Christoph Correll and Faedda.

Supplementary material: Available at PSYCHIATRIST.COM

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POSTTEST

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- 1. According to published reports, prospectively identified precursors of bipolar disorder typically arise ___ prior to syndromal onset.**
 - a. Hours
 - b. Days
 - c. Months
 - d. Years
- 2. All of the following patients have a precursor of bipolar disorder for which prospective studies showed at least a 14% rate of later bipolar II diagnosis *except*:**
 - a. Mr A, who is a young adult outpatient with mood lability
 - b. Mr B, who is an adult outpatient with a situational mild (subsyndromal) depressive episode
 - c. Mr C, who is a college student with subsyndromal hypomanic symptoms
 - d. Mr D, who is an adult outpatient with cyclothymic disorder
- 3. Psychotic symptoms have been found to be a precursor of bipolar disorders in ___ of patients with major depression.**
 - a. 3%
 - b. Up to 23%
 - c. Up to 43%
 - d. Up to 63%
- 4. Which types of studies have found that a depressive onset is common in bipolar disorders?**
 - a. Retrospective
 - b. Prospective
 - c. Family risk
 - d. All of the above



THE JOURNAL OF
CLINICAL PSYCHIATRY
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Supplementary Material

Article Title: Precursors of Bipolar Disorders: A Systematic Literature Review of Prospective Studies

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DOI Number: 10.4088/JCP.13r08900

List of Supplementary Material for the article

1. [eFigure 1](#) Glossary of terms

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eFigure 1: Glossary of terms.

Clinical predictors: prospectively identified variables that increase the risk of later bipolar disorder diagnosis including precursors, clinical risk factors and environmental risk factors.

Prodromal Phase: the phase of illness preceding the syndromal onset of bipolar disorder, with *prospectively identified* signs, symptoms, deficits or a departure from normative development, and an observable change from a premorbid asymptomatic state (when present). The prodromal phase includes:

- Precursors: affective psychopathology preceding the full syndrome (i.e. subthreshold hypomania to mania, sadness before a major depressive episode).
- Clinical Risk Factors: non-affective psychopathology preceding the full syndrome (i.e. anxiety symptoms or disorder before mania). Clinical risk factors are phenomenologically distinct from the diagnostic outcome.
- Environmental Risk Factors: exposure to traumatic events, drugs of abuse, iatrogenic factors.

Syndromal Phase: the phase of illness after the diagnostic criteria for bipolar disorder (i.e. mania, hypomania, or mixed state) are met*.

Prodromes: *retrospectively identified* signs, symptoms or subthreshold conditions occurring before diagnostic criteria for bipolar disorder are met.

Homotypic illness' trajectory: a transition from affective psychopathology (i.e. syndromal or sub-syndromal depression or mania) to bipolar disorder.

Heterotypic illness' trajectory: a transition from non-affective psychopathology (i.e. syndromal or sub-syndromal anxiety or conduct disorders) to bipolar disorder.

*The diagnostic status of Major depression occurring before the onset of (hypo)mania remains controversial, as it is a syndromal onset before the diagnosis of bipolar disorder can be made according to current diagnostic criteria. Similarly, when diagnostic criteria

for bipolar disorder are not fully satisfied, the term bipolar-NOS is used, indicating an attenuated syndrome.