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Antecedents of Manic versus Other First-Psychotic Episodes in 263 Bipolar-I Disorder Patients

Paola Salvatore, M.D.^{a,b,c}, Ross J. Baldessarini, M.D.^{a,b}, Hari-Mandir K. Khalsa, M.S.^b, Gustavo Vázquez, M.D., Ph.D.^{b,d}, Jesus Perez, M.D., Ph.D.^{b,e}, Gianni L. Faedda, M.D.^{b,f,g}, Mario Amore, M.D.^h, Carlo Maggini, M.D.^{b,c}, and Mauricio Tohen, M.D. Dr.P.H.^{b,i}

^aDepartment of Psychiatry & Neuroscience Program, Harvard Medical School, Boston, MA 02115

^bInternational Consortium for Psychotic & Bipolar Disorders Research, Mailman Research Center, McLean Hospital, Belmont, MA 02478

^cSection of Psychiatry, Department of Neuroscience, University of Parma, 43100 Parma, Italy

^dDepartment of Neuroscience, University of Palermo, Buenos Aires, Capital Federal 1175, Argentina

^eCAMEO Early Intervention Services, Department of Psychiatry, University of Cambridge, Cambridge CB21-5EE, United Kingdom

^f‘Lucio Bini’ Mood Disorders Center, New York, NY 10022

^gDepartment of Child Psychiatry, New York University School of Medicine, New York, NY 10016

^hPsychiatric Clinic, Department of Neuroscience, Ophthalmology & Genetics, University of Genoa, 16132 Genoa, Italy

ⁱDepartment of Psychiatry, University of Texas Health Science Center, San Antonio, TX 48229

Abstract

Objective—Since initial episode-type can predict later morbidity in bipolar disorder, we tested the hypothesis that clinical antecedents might predict initial episode-types.

Method—We studied 263 first-episode, adult, DSM-IV-TR type-I bipolar disorder (BD-I) subjects within the McLean-Harvard-International First-Episode Project. Based on blinded assessments of antecedents from SCID examinations and clinical records, we compared first-lifetime *Manic* vs. *Other* (mixed, depressive, or nonaffective) major psychotic-episodes.

Results—We identified 32 antecedents arising at early, intermediate or later times, starting 12.3±10.7 years prior to first-lifetime major psychotic-episodes. Based on multivariate modeling, antecedents associated significantly and independently with *Other* (n=113) more than *Manic* (n=150) first-lifetime major psychotic-episodes ranked by Odds Ratio: more early attentional disturbances, more late depression, more early perplexity, more detoxification, more early unstable-mixed affects, more antidepressants, more early dysphoria, more intermediate depression,

Correspondence to: Dr. Paola Salvatore, International Consortium for Psychotic & Bipolar Disorders Research, Center Building-G-07B, McLean Hospital, 115 Mill Street, Belmont, MA 02478-9106 USA; Tel. 1-617-855-2780; Fax 1-617-855-3479; <psalvatore@mclean.harvard.edu>.

Declaration of interest

Coauthors Amore, Baldessarini, Faedda, Khalsa, Maggini, Perez, Salvatore and Vázquez, have no relevant disclosures; none is currently engaged in industry-supported research, participates in pharmaceutical speakers' bureaus, nor do they or any immediate family member hold equity positions in biomedical or pharmaceutical corporations. Dr. Tohen was an employee and a minor stockholder of Eli Lilly & Co. until 2008, as is his wife currently.

more early impulsivity, more late anhedonia, longer early-to-intermediate intervals, more intermediate substance abuse, more family history of major depression, and younger at earliest antecedents. Antecedents selectively preceding *Manic* more than *Other* first-psychotic episodes included more late behavioral problems and more risk of familial BD-I.

Conclusion—Clinical antecedents in adult, BD-I patients, beginning a decade before first major-episodes and progressing through **sequential** stages were dissimilar in *Manic* versus *Other* first-psychotic-episodes.

Keywords

antecedents; bipolar disorder; first-psychotic episodes; prodromes; psychopathology

Introduction

Reliable characterization of clinical antecedents of major psychiatric disorders might support earlier recognition of emerging, potentially disabling or life-threatening illnesses, encourage improved prognosis, and guide early interventions and long-term treatment-planning (2-4). Psychopathological antecedents are extensively described for schizophrenia, in which they often arise in stages including early phenomena, unfolding through discontinuous phases years before first-psychotic episodes (*Outpost syndromes*), and later *prodromes* that gradually evolve into first major-episodes (5). Several studies of precursors of first-psychotic episodes involve mixed diagnostic groups and do not clearly distinguish cases of bipolar disorder (**BD**) from schizophrenia or other nonaffective psychoses (2,6-12). Studies of antecedents of BD, specifically, remain rare. Most are based on relatively small, retrospective investigations of first-episode (13-17) or mid-course (18-19) patients, case series (20), or epidemiological surveys (21), supplemented with prospective, high-risk studies (22-25) of pre-adult offspring of parents diagnosed with BD, as well as retrospective parental reports (26,27) concerning children later diagnosed with the illness. In short, much less is known about the early evolution of BD than of schizophrenia.

A widely held view is that schizophrenia is often preceded by cognitive, neuromotor, behavioral, and social-developmental dysfunctions, and that major mood disorders are most often preceded by disturbances of affect and arousal (7,8,11,28). However, such generalizations are not based on prospective analyses using modern assessment techniques in large samples diagnosed with a range of affective and nonaffective psychoses, and studied over several years preceding and following a first-lifetime major-episode of functional psychosis. Also, most studies indicate that evolution of major psychiatric disorders is a complex process, and consensus about features that can reliably differentiate later psychotic-affective from schizophrenia-like syndromes, or subtypes within major diagnostic groups, is notably lacking (2,15,20,29). Even after initial major-episodes, many forms of psychosis, and especially nonaffective disorders, continue to evolve over years, and may meet different diagnostic criteria with follow-up (30-32). Moreover, there are virtually no studies of antecedents among various diagnostic subtypes of BD (I, II, unspecified, or those presenting in mania or mixed-states) in adults, and they are rare in juveniles (33,34).

Aims of the study

The McLean-Harvard International First-Episode Psychosis Project has studied a large sample of over 500 patients reliably diagnosed by DSM-IV-TR criteria with a range of affective and nonaffective psychoses, and systematically followed-up prospectively for several years following a first-lifetime hospitalization. We used this sample to investigate antecedents of 263 DSM-IV-TR type-**I bipolar disorder (BD-I)** subjects, aiming to test the hypothesis that antecedent symptoms, interventions, their timing, and family history factors

will differ between patients later presenting in *Manic* versus *Other* (mixed, depressive, or apparently nonaffective) first-lifetime episodes with psychotic features.

Material and methods

Subjects and assessments

We studied 517 initially hospitalized, first-episode patients with DSM-IV-TR psychotic-disorders in the McLean-Harvard-International First-Episode Psychosis Project based at McLean Hospital and University of Parma, with enrollment in 1989-2003. Project protocols were reviewed annually and approved by the McLean Hospital Internal Review Board and the Ethical Committee of the University of Parma Medical Center, through 2012, and are in full accordance with the Helsinki Declaration of 1975. For inclusion, all subjects presented in a first-lifetime psychotic-episode of major affective (manic, mixed, or depressive), nonaffective (schizophrenia, unspecified psychosis [NOS], schizophreniform, brief-psychotic, and delusional disorders), or schizoaffective disorders, and gave written informed consent for participation and anonymous, aggregate reporting of findings. Exclusion criteria were: [a] acute alcohol or drug intoxication or withdrawal, or any delirium; [b] previous psychiatric hospitalization, unless for detoxification or a nonpsychotic syndrome; [c] documented mental retardation (WAIS-tested IQ <70) or other organic mental disorder; [d] index syndrome present >6 months; [e] any previous psychotic syndrome; or [f] prior total treatment with an antipsychotic for 4 weeks, or an antidepressant or mood-stabilizer for 3 months.

Comprehensive review of all available documents retrieving, describing, defining, scoring and dating antecedents, first-presentation features and follow-up clinical phenomena was conducted in random-order by the first-author (P.S.) for all 517 first-episode psychotic subjects, while held blind to initial and later diagnoses. This report considers the 263 subjects diagnosed consistently with DSM-IV-TR BD-I within two years of intake. Diagnoses were based on baseline and 2-year SCID-P assessments, followed by best-estimate, investigator-consensus, based on all available information, with diagnoses updated to meet DSM-IV-TR criteria in 2011-2012 (35). Assessments of antecedents, first-episode features and follow-up clinical phenomena also involved best-estimate procedures based on all available information from the SCID-P assessments (with diagnoses removed), medical records, and clinical narratives from interviews of family members and primary treating clinicians.

Moreover, to guide detailed and thorough recording of antecedents, first-presentation features and follow-up clinical phenomena, we considered the Manual for Assessment & Documentation of Psychopathology (AMDP-system [36]) and the *Bonn Scale for the Assessment of Basic Symptoms* (BSABS [37]) as descriptive psychopathology frames of reference to develop comprehensive and systematic symptom inventories in reviewing each case-history. These broad assessment schemes include affective, thought, linguistic, perceptual, psychomotor, and psychotic disturbances as well as behavioral and social dimensions of psychopathology. The AMDP-system includes definitions and operationalized criteria for 100 psychopathological phenomena derived from classic psychopathology studies and scored for severity (0-3: absent, mild, moderate, and severe). The 66-item English-language version of the BSABS employed includes operationalized definitions and examples of patients' statements about subjective experiences of psychopathology, scored as present/absent, and for severity as for the AMDP (38). These assessments were made without preconceptions about the nature or timing of antecedents and other clinical phenomena in relation to type of presenting episode. Information concerning antecedents, first-episode features and follow-up clinical phenomena was abstracted from the available clinical documents into a written semi-structured log for each

of the 517 subjects evaluated in random-order over a three-year period, so as to leave the rater blinded to diagnosis and presenting syndromal-type.

Preliminary review of data obtained from the first 50 of all 517 psychotic-subject records indicated that most had antecedents clustered in phases following a sequencing pattern marked by two discrete (early and intermediate) periods with complete remissions, typically several years apart and several years before first-psychotic episodes, as well as later prodromes that progressed continuously without remission into first-psychotic episodes. This experimental observation kept being replicated in the whole sample of 517 affective and non-affective first-psychotic episodes.

Accordingly, we organized individual, written semi-structured logs or research summaries to include the timing of distinct clinical antecedent phenomena of at least a moderate severity by AMDP-system scoring (38), as regards their stage of emergence in either early, intermediate or late (prodromal) antecedent phases. We recorded starting ages and approximate durations of antecedent phenomena, intervals between apparent early, intermediate, and late (prodromal) antecedent phases (time between end date of preceding phase and start date of following phase), as well as evolution of earliest presentations of symptoms to syndromes of first-psychotic episodes. Also, the onset of first-psychotic episodes was rated as being *acute* (<1 month), *sub-acute* (1-6 months) or *gradual* (>6 months) in evolving from symptoms to syndromes.

Data analyses

We compared subjects with DSM-IV-TR diagnoses of BD-I with first-lifetime major-episodes considered *Manic* versus *Other* (depressed, mixed, psychotic apparently nonaffective) at first-lifetime hospitalization for a major illness-episode with psychotic features. Statistical comparisons used ANOVA (*F*) methods for continuous variables, and contingency tables (χ^2 or Fisher exact-*p*) for categorical factors. Significance was set at two-tailed $p < 0.05$. Measures with at least suggestive differences ($p < 0.10$) in initial bivariate comparisons were entered, stepwise, into logistic regression modeling to identify factors independently associated with *Manic* versus *Other* initial presentation, based on Odds Ratios (ORs) with 95% confidence intervals (CI). Averages are means with standard deviations ($\pm$ SD) unless stated otherwise. Analyses are based on commercial statistical programs (Stata-9®, Stata Corp., College Station, TX; Statview-5®, SAS Institute, Cary, NC).

Results

Sample and antecedents characteristics

We analyzed antecedents among 263 adults meeting DSM-IV-TR criteria for BD-I, established by consensus after two years of follow-up from hospitalization for a first-lifetime psychotic episode. The sample included 141 (53.6%) men and 122 (46.4%) women, of average age 30.8 ± 12.8 years at intake. Only 32 (12.2%) of subjects would be considered at-risk by having at least one first-degree relative affected by BD-I. First-psychotic episode diagnoses included: mania ($n=150$; 57.0%), mixed-state ($n=84$; 31.9%), major depression (MDE, $n=16$; 6.1%), unspecified psychosis (NOS, $n=6$; 2.3%), brief psychotic disorder ($n=5$; 1.9%) and schizophreniform disorder ($n=2$; 0.8%), but all cases met DSM-IV-TR diagnostic criteria for BD-I by 24 months of follow-up. Through follow-up averaging 5.8 ± 3.2 years, no new BPD-I diagnosis was found that was not present by 24 months.

Almost all subjects (92.4% [243/263]) had findings of one or more of a total of 32 distinguishable types of antecedent phenomena, starting as early as 9.6 ± 4.8 years of age, and averaging 12.3 ± 10.7 years before diagnosis for a first-lifetime psychotic episode (Table 1).

Prior to first-psychotic episodes, 186 of the 243 subjects (76.5%) presented an earlier major but nonpsychotic episode of either depression ($n=142$, 58.4%; at average age 21.3 ± 9.7 years), or mania ($n=44$, 18.1%; at average age 23.4 ± 11.7 years).

These antecedents clustered in early, intermediate, and late (prodromal) phases, starting at mean age 18.5 ± 10.4 years (median=16, IQR=13-21), 23.3 ± 11.3 years (median= 19, IQR=16-27), and 29.7 ± 12.7 years (median= 26, IQR= 20-37), respectively, without significant sex-differences. Study subjects with identifiable antecedent phases (92.4% [243/263]) included 64.6% (157/243) with early, intermediate and late (prodromal) antecedents, 20.6% (50/243) with both early and late (prodromal) antecedents; and 14.8% (36/243) with only early (16/243) or intermediate antecedents (20/243). Mean latency between early and intermediate antecedent phases was 4.7 ± 6.9 years; between intermediate and late (prodromal) antecedent phases, 6.4 ± 8.5 years; between late (prodromal) antecedent phases and first-psychotic syndrome onset, 17.5 ± 37.0 weeks; and between first-episode symptoms and syndrome, 8.4 ± 14.4 weeks. Notably, there were significant differences between *Manic* and *Other* first-psychotic presentations as regards the interval between the end date of early- and the start date of intermediate-antecedent phases as well as time from first-episode symptoms to syndromes (Table 2).

Types of antecedent phenomena

In initial overall blinded analyses of all 517 cases of first-lifetime psychotic episodes, we identified a total of 40 distinct antecedent phenomena, and 32 of these (30 symptoms, plus suicide attempts and evidence of sexual abuse) were identified among the 263 cases of BD-I (Table 1). As expected, age at first antecedent phenomena in BD-I patients was negatively correlated with latency to first-psychotic episodes ($r_s = -0.472$, $p=0.001$).

Antecedent phenomena found as early as childhood or early adolescence included mild mental retardation, learning difficulties or dyslexia, attentional disturbances, behavioral dysfunctions, head trauma, epilepsy, anxious-depressive, schizoid-obsessive, odd-eccentric, or sensitive-suspicious tendencies associated with shyness, as well as obsessive-compulsive manifestations, perceptual disturbances or perplexity, dissociation, and indications of sexual abuse (Table 1). Features identified during mid-to-late adolescence in at least 10% of subjects (Table 1) included: [a] nonpsychotic depression (32.0%) > [b] substance-abuse (27.4%) > [c] generalized anxiety, somatization, or hypochondriasis (20.5%) > [d] mood-lability or cyclothymia (17.1%) > [e] impulsivity (14.1%) > [f] dysphoria (11.8%). Identified suicidal behaviors were infrequent during adolescence (4.6% of subjects). Features first emerging in early adulthood included attenuated psychotic experiences or thought-disorder, as well as hypomanic symptoms and aggressive tendencies, vital-drive disturbances or anhedonia, and eating disorders (Table 1).

Only two early antecedents were associated with relatively older age at first-psychotic episodes: [a] hypomania (38.7 ± 16.6 vs. 30.3 ± 12.4 years) and [b] panic-agoraphobia (37.3 ± 15.1 vs. 30.3 ± 12.5 years). Only early, unspecified behavioral dysfunctions were associated with younger age at first-psychotic episode (24.3 ± 6.0 vs. 31.2 ± 13.0 years). All of these differences were statistically significant (all $F \geq 3.9$, all $p \leq 0.05$; not shown).

Moreover, five features were identified at more than twice (2-9-times) greater prevalence among patients later presenting in non-manic (*Other*) first-psychotic episodes of BD-I (Table 1). These included: [a] perceptual disturbances or perplexity, [b] attentional disturbances, [c] unstable-mixed affects, [d] impulsivity, and [e] dysphoria (all $\chi^2 \geq 5.8$, all $p \leq 0.03$). Additional differences between the first-psychotic episode presentation-types were a 1.6-times longer interval between early and intermediate antecedent phases (6.0 vs. 3.8 years) in the *Other first-psychotic episodes*, and a 3-times longer evolution from prodromal

symptoms to *Other* first-episodes (13.2 vs. 4.4 weeks). Only late (prodromal) behavioral dysfunctions anticipated later *Mania* (22.0% vs. 10.6%; $\chi^2 = 5.9$, $p=0.01$; Table 2).

Early treatment

We identified 28 apparent indications for a total of 16 types of early clinical interventions (pharmacological or psychosocial). Ages and indications for first treatments ranged from 8.8 years for learning disability or dyslexia, to 34.5 years for epilepsy (Table 3). Two circumstances were more prevalent before *Other* vs. *Manic* first-psychotic episodes: treatment of substance-abuse (17.7% vs. 6.0%), and depression (45.2% vs. 27.3%). Only treatment of attenuated psychotic symptoms anticipated later *Manic* vs. *Other* first-psychotic episodes (44.7% vs. 26.6%). All three differences were highly significant (all $\chi^2 \geq 8.9$, all $p \leq 0.003$).

We also compared onset-age of first-psychotic episodes among BD-I subjects who did or did not receive at least one of the 16 identified early treatments. Age at first-psychotic episodes was older following treatment with modern antidepressants (35.0 ± 13.8 vs. 29.5 ± 12.2 years) or benzodiazepines (39.6 ± 17.8 vs. 30.2 ± 12.2 years), and younger after psychotherapy (28.2 ± 9.9 vs. 31.8 ± 13.7 years; all $F \geq 4.3$, all $p \leq 0.04$). Only antidepressants and detoxification for substance-abuse were significantly associated with *Other* more than *Manic* first-psychotic episodes (Table 2).

Family-history factors

High-risk for BD-I or having at least one first-degree relative diagnosed with BD-I was significantly higher among cases with *Manic* vs. *Other* first-psychotic episodes (16.7% vs. 6.2%; $\chi^2 = 6.6$, $p=0.01$). High-risk for major depressive disorder (MDD) or having at least one first-degree relative with MDD was nonsignificantly more prevalent among subjects with *Other* vs. *Manic* first-psychotic episodes (26.6% vs. 18.7%; $\chi^2 = 2.3$, $p=0.13$); however, any family history of MDD was significantly more likely among *Other* vs. *Manic* first-episode patients (37.2% vs. 24.7%; $\chi^2 = 4.8$, $p=0.03$). Family risk for psychosis, anxiety and substance abuse disorders did not differ between the onset-subgroups (not shown).

Factors associated with first-psychotic episode type

We first considered antecedent phenomena or treatments appearing at early, intermediate, or late (prodromal) times, as well as family-history factors that differed at least suggestively ($\geq 10\%$) between subjects presenting later in *Manic* versus *Other* first-psychotic episodes of BD-I. Factors more associated with later *Other* than *Manic* first-psychotic episodes included: [a] more intermediate and late (prodromal) depression, [b] more exposure to modern antidepressants, [c] longer intervals from late (prodromal) symptoms to first-psychotic episodes, and [d] greater risk of substance-abuse (all with Bonferroni-adjusted significance of $p < 0.005$; Table 2).

Factors with at least suggestive ($p \leq 0.10$) differences between those presenting later in *Other* versus *Manic* first-psychotic episodes of BD-I were entered, stepwise, into multivariate, logistic regression modeling. Among factors (ranked by ORs; Table 4; Figure), 14 were significantly more likely to precede non-manic (*Other*) first-psychotic episodes. They were: [a] more early attentional disturbances, [b] more late (prodromal) depression, [c] more early perceptual perplexity, [d] more detoxification, [e] more early unstable-mixed affects, [f] more antidepressants, [g] more early dysphoria, [h] more intermediate depression, [i] more early impulsivity, [j] more late (prodromal) anhedonia or vital-drive disturbances, [k] longer interval between early and intermediate antecedent phases, [l] more intermediate substance-abuse, [m] more family history of MDD, and [n] younger at earliest antecedents. Two other

factors were less associated with *Other* than *Manic* first-psychotic episodes: familial BD-I and late prodromal behavioral problems.

Discussion

The main finding of this study is that antecedent psychopathological, behavioral, or neurological abnormalities, as well as early treatment-interventions and family-history factors, could be identified among 263 patients later presenting in first-lifetime episodes of psychotic illnesses diagnosed as BD-I, based on DSM-IV-TR criteria, and that many of them predicted non-manic versus manic first-psychotic episodes (Tables 1-3). It is important to emphasize that BD-I diagnosis was established within 24 months of intake in all subjects, and that no further diagnoses were found up to a total of 5.8 ± 3.2 years of systematic follow-up.

Features preceding first-lifetime major psychotic-episodes of BD-I appeared to arise sequentially, in early, intermediate, and late (prodromal) phases, similar to descriptions of symptoms preceding syndromal schizophrenia (5). Of all antecedent phenomena, early treatment-interventions and family-history factors identified, multivariate regression modeling indicated that 12 were significantly and independently associated more with non-manic (*Other*) first-episodes that included mainly mixed-states, fewer episodes of major depression (both with psychotic features), or illnesses that appeared initially as nonaffective psychoses (Table 4 and Figure). These 12 features included more early attentional disturbances and perplexity as well as unstable-mixed affects, dysphoria, and impulsivity; more intermediate depression and substance abuse with associated antidepressant treatments and detoxification; more late (prodromal) depression and anhedonia; and more family history of major depressive disorder (MDD). Moreover, subjects with *Other* first-psychotic episodes had initial antecedents at younger ages, with longer intervals between early and intermediate antecedent phases. Two other features were significantly associated with *Manic* first-psychotic episodes, including having a first-degree relative diagnosed with BD-I and presenting with late prodromal behavioral problems leading to a first-psychotic episode. This finding may indicate that high familial and possibly genetic vulnerability to adult BD-I is most associated with a classic manic phenotype with its core phenomena of extreme psychomotor excitement and disorganized behavior. In contrast, the non-manic (*Other*) first-psychotic episode phenotype appeared to be associated with more complex psychopathology, along with familial loading for MDD and low familial risk of BD-I. A further possibility is that such psychopathological, clinical and family-history differences between *Other* vs. *Manic* first-psychotic episodes in BD-I may support early diagnostic recognition and timely treatment planning of BD-I illnesses with different courses and outcomes as well as different longitudinal morbidity and mortality rates, especially regarding suicide (34,35).

The early and timely detection of a BD-I diagnostic and prognostic trajectory can be particularly challenging when first-psychotic episodes do not involve pure mania but present as mixed states, psychotic depression, or acute, transient, unspecified forms of apparently non-affective psychosis to support their inclusion in the non-manic (*Other*) onset-type subgroup. As Weygandt (1) noted as early as 1899, a deeper understanding of bipolarity should overcome the narrow limits of a mood-centric frame of reference and rather focus on polymorphism, instability and susceptibility to synchronic and diachronic changes of psychopathological phenomena. The present findings indicate further that such phenomena can present long before more typical, syndromal illness, in some cases up to 28 years before first major psychotic episodes, and at ages below 10 years (Table 1).

Antecedents of non-manic (*Other*) first-psychotic episodes included dysfunctional social-competence, temperamental traits including interpersonal sensitivity and shyness, and disturbances of affect or drive, as well as impulsivity. Also found **was** evidence of cognitive, perceptual, or attentional disturbances, as well as depression, somatic anxiety, unstable-mixed affects, and lability or cyclothymia. These findings may suggest that non-manic (*Other*) first-psychotic episodes of BD-I might share with schizophrenia-like disorders a psychopathological vulnerability core characterized by cognitive deficits, affective disturbances, social isolation and school failures emerging several years before the onset of a psychotic syndrome (39). Overall, the psychopathological antecedents identified indicate that BD-I evolved over years before fully expressed adult syndromes were diagnosed (3,14,18,24,26). Neurodevelopmental mechanisms may be involved, or antecedents of evolving BD-I may reflect decreased stress-tolerance and dysfunctional reactions to traumatic or even ordinary life-events in early years (3,40,41).

It is particularly noteworthy that patients later presenting in *Other* (mixed, depressive, nonaffective) first-psychotic episodes were more likely to show evidence of early perceptual disturbances, perplexity, depersonalization or derealization, and apparent *delusional atmosphere* (37), as well as attentional disturbances—all compared to patients later presenting in *Mania*. Such early cognitive-perceptual and interpersonal sensitivity features have been found to predict Schneiderian first-rank symptoms and more severe deficits in social interactions later in cases of schizophrenia (5,37,42). Nevertheless, their early association with a potential subtype of BD-I is consistent with findings that Schneiderian symptoms are not unique to schizophrenia (43,44), and may arise in cases initially presenting with apparent first-lifetime non-affective psychotic episodes that later meet diagnostic criteria for BD-I (45). As all of the present subjects met diagnostic criteria for psychosis at their index first-episodes, more speculatively, such features may suggest that BD-I with prominent mixed manic-depressive states with psychotic features may not only differ from cases involving manic-onset (34), but also more closely resemble schizophrenia or schizoaffective disorders (45). Future studies that are beyond the scope of this report, need to consider early features that differentiate subjects who eventually present with non-affective psychoses from those who meet diagnostic criteria for BD-I, major depression with psychotic features, or schizoaffective disorders.

As noted above, studies of antecedents in BD-I are far fewer than in other psychotic disorders, particularly schizophrenia (5,17,29). The hypothesis that BD-I, like schizophrenia, might evolve in predictable clinical sequences has been tested mainly with probands considered to be at high-risk for BD by having at least one parent diagnosed with the disorder, or in comparisons of juveniles who did or did not later meet diagnostic criteria for BD-I (22-27,33,40). However, assessments of high-risk juveniles have not all continued into adulthood so as to assure clinical outcomes, and findings from these same high-risk studies may only pertain to a minority of adult, BD-I cases. Moreover, high-risk for BD-I based on family history was present in only 12.2% of the present, large sample of BD-I patients. The apparent ability of antecedents to distinguish patients later presenting in *Manic* versus *Other* types of psychotic first-episodes of BD-I is striking, and may have even longer-term predictive value since first-episode polarity itself has been found to be strongly predictive of later morbidity in the same subject-sample (34).

Limitations of this study include ascertainment of antecedent psychopathological features by retrospective analyses of medical records and psychiatric interviews of patients and family members by a single investigator, albeit under conditions of virtual blindness to final diagnoses among a larger cohort of 517 subjects with a range of first-episode, psychotic disorders. Identification of precursors dating from childhood or early adolescence is particularly likely to be unreliable or incomplete when assessed in adults. Nevertheless, the

first-episode diagnostic types, final diagnoses, and long-term clinical outcomes of the present adult, DSM-IV-TR BD-I cases were determined rigorously and prospectively. It is also important to point out that all subjects presented with psychotic features in their first-episodes, so that their findings may not generalize to other BD-I patients lacking psychotic features, although such features are commonly found in acute mania and mixed-states. Also, psychopathological antecedents are not necessarily manifestations of evolving BD-I, and such an assumption requires verification, aside from its potential, empirical, prognostic significance (34) or possible value in planning therapeutic interventions (2-4). All such extrapolations remain to be tested empirically for their clinical value, ethical acceptability, feasibility, and cost-effectiveness when applied early and prospectively to potential cases of BD-I.

In conclusion, the present findings indicate that antecedent psychopathological phenomena and interventions among persons later diagnosed reliably with adult, DSM-IV-TR, BD-I were quite common, sometimes preceding first-psychotic episodes by more than a decade and including childhood and adolescent years. Particularly striking early illness-manifestations involved depression, dysthymia, and antidepressant treatment. Also, especially among those later presenting in non-manic first-episodes (mainly mixed-states, with fewer apparently psychotic-non-affective or psychotic-depressive illnesses), antecedents included prominent attentional disturbances, pre-psychotic perplexity, unstable-mixed affects, dysphoria, impulsivity, substance-abuse, and suggestions of anhedonia or vital-drive impairment. Several specific features significantly differentiated cases later presenting in manic versus non-manic first lifetime major episodes. Overall, the present findings suggest prognostic value in identifying clinical antecedents. Their potential value as leads to further clinical and psychobiological research remains to be demonstrated.

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Significant Outcomes

- A range of psychopathological and other clinical antecedents were identified in adult type-I bipolar disorder [BD-I] patients, beginning at least a decade prior to first-lifetime major-episodes with psychotic features.
- Such antecedents arose at early, intermediate and later times, progressing through distinct stages.
- Dissimilar antecedents predicted later *Manic* vs. *Other* (mixed, depressive, or nonaffective) first-lifetime major psychotic-episodes.

Limitations

- Ascertainment of sometimes distant clinical antecedents was based on retrospective analyses of medical records and psychiatric interviews of patients and family members, but was carried out by a single, expert investigator under conditions of virtual blindness to final diagnoses.
- The present findings may not generalize to BD-I patients lacking psychotic features at first-episodes.

Figureyy.

Antecedent features that significantly ($p=0.04-0.0001$) distinguish *Manic* ($n=150$) versus *Other* (mainly mixed, some depressive or initially apparently nonaffective; $n=113$) first major episodes with psychotic features among 263 type-I bipolar disorder patients, ranked in descending order of *Relative Risk* (ratio of magnitudes) among later *Other versus Manic* subjects (from Table 2). Striped bars represent *Relative Risk* for the first-episode type. Note that 18/22 factors were more likely to precede *Other* onsets (above horizontal dotted line). Onset-age averaged 31 years in both groups. Family history of BD-I (mania), late-antecedent (prodromal) behavioral dysfunction, as well as earlier identification of first-

psychotic episode symptoms and their treatment ranked as significantly greater among later *Manic* cases (below dotted horizontal line).

Table 1
Antecedent clinical phenomena: age at first appearance and prevalence among 263 patients with type-I bipolar disorder later presenting in first-lifetime psychotic major episodes of *Mania* versus *Other* syndromes

Antecedent Phenomena	Age at First Appearance	Duration (mos)	Years Before First-Episode	Prevalence (%) versus First-Episode Type		
				Mania (n=150)	Other (n=113)	Ratio
Behavioral dysfunction	9.6±4.8	12	14.7	7.3	2.7	0.4
Learning disability/dyslexia	9.9±3.8	72	20.1	7.3	8.0	1.1
Head trauma (lost consciousness)	10.3±7.5	1	23.7	0.7	2.7	3.9
Anxious-depressed + shyness-introversion	11.9±3.6	60	18.9	4.7	7.1	1.5
Schizoid-obsessive + shyness-introversion	12.7±3.7	60	14.8	0.7	4.4	6.3
OCD-spectrum disturbance	12.9±3.0	60	15.6	4.0	3.5	0.9
Early sexual abuse	—	—	—	2.0	6.2	3.1
Eccentric-odd + shyness-introversion	13.0±1.4	60	9.5	0.7	0.9	1.3
PTSD-dissociation	14.0±3.3	4	10.0	0.7	4.4	6.3
Mild mental retardation	14.5±9.2	72	27.5	1.3	0.0	<0.8
Epilepsy	14.6±7.6	60	13.1	5.3	9.7	1.8
Perceptual disturbance, perplexity, depersonalization, derealization, delusional atmosphere	14.6±12.0	2	10.2	1.3	7.1	5.5*
Attentional disturbance	15.1±13.2	36	8.2	0.7	6.2	8.9*
Sensitive-suspicious + shyness-introversion	15.2±3.8	60	12.7	4.7	2.7	0.6
Generalized anxiety, somatization, hypochondriasis	16.5±10.1	3	14.8	22.7	17.7	0.8
Panic, agoraphobia	16.5±11.5	3	20.8	6.7	8.9	1.3
Unstable-mixed affects	16.9±4.9	6	12.4	2.7	9.7	3.6*
Impulsivity	17.0±6.1	18	14.1	9.3	20.4	2.2*
Lability, cyclothymia	17.4±10.1	6	14.5	17.3	16.8	0.9
Sleep disturbance	18.0±0.0	6	16.5	1.3	0.0	<0.8
Self-referential thinking	18.5±8.8	2	12.4	5.3	7.1	1.3
Dysphoria	18.5±10.4	4	10.8	7.3	17.7	2.4*

Antecedent Phenomena	Age at First Appearance	Duration (mos)	Years Before First-Episode	Prevalence (%) versus First-Episode Type		
				Mania (n=150)	Other (n=113)	Ratio
Depression (not psychotic)	18.6±10.1	3	11.9	34.7	28.3	0.8
Functional decline	18.7±5.5	12	7.4	10.0	7.1	0.7
Substance-abuse	18.8±5.8	18	11.2	24.7	31.0	1.3
Suicidal attempt	19.6±8.6	—	16.4	3.3	6.2	1.9
Anhedonia, impaired vital drive	19.6±9.1	3	8.2	6.0	4.4	0.7
Mild psychotic thought content	20.1±9.1	2	7.0	4.7	4.4	0.9
Aggressive-homicidal behavior	21.3±11.9	—	13.4	0.7	1.8	2.6
Eating disturbance	21.6±10.3	12	7.4	4.0	4.4	1.1
Hypomania	23.1±13.5	2	15.6	5.3	6.2	1.2
Thought disturbance-disorganization	24.5±15.2	2	4.0	2.0	0.9	0.5

Clinical features (32 types) identified before *Manic* or *Other* first-lifetime psychotic major episodes, ranked by approximate age at first-appearance, with prevalence (%) by first-episode type. Prevalence ratios are for *Other/Manic* first-psychotic episodes

* indicates significant differences in prevalence by first-psychotic episode type. *Other* = mixed-states or major depression with psychotic features, or apparent nonaffective psychoses.

Table 2
Clinical features preceding *Manic* vs. *Other* first-lifetime psychotic major episodes in DSM-IV type-I bipolar disorder patients

Measures	First Episode Type		F or χ^2	p-value
	Manic (n=150)	Other (n=113)		
Early Antecedents				
Dysphoria (%)	7.3	17.7	6.7	0.01
Impulsivity (%)	9.3	20.4	6.5	0.01
Attentional disturbance (%)	0.7	6.2	6.7	0.02
Perceptual disturbance (%)	1.3	7.1	5.8	0.02
Unstable-mixed affects (%)	2.7	9.7	6.0	0.03
Early symptoms onset-age	19.7±11.8	17.0±8.1	4.5	0.04
Intermediate Antecedents				
Depression (not psychotic) (%)	19.3	38.1	11.4	0.001
Years: early-to-intermediate	3.8±6.5	6.0±7.2	6.5	0.01
Substance-abuse (%)	20.0	31.9	4.8	0.03
No antecedents (%)	38.7	26.6	4.2	0.04
Intermediate symptoms onset-age	23.5±12.8	22.9±8.9	0.2	0.67
Late or Prodromal Features				
Depression (not psychotic) (%)	12.7	51.3	46.5	0.001
Vital-drive impairment (%)	18.7	31.9	6.1	0.01
Functional decline (%)	18.0	30.1	5.3	0.02
Behavioral dysfunction (%)	22.0	10.6	5.9	0.02
Eating disturbance (%)	14.0	24.8	4.9	0.03
Late symptoms onset-age	30.1±13.7	29.2±11.3	0.3	0.56
First-Psychotic Episodes				
Weeks: prodrome to first episode	4.4±6.4	13.2±19.6	24.0	<0.0001
First-episode onset-age	31.0±13.6	30.6±11.7	0.1	0.83
Antecedent Treatments				
Antidepressants (%)	8.0	20.4	8.5	0.004
Psychiatric follow-up (%)	6.7	15.9	5.8	0.02
Detoxification (%)	1.3	6.2	4.6	0.04
Age at first-treatment	27.3±14.0	26.2±10.7	0.5	0.50
Antecedent Treatment Indications				
Substance-abuse (%)	6.0	17.7	9.0	0.003
Nonpsychotic depression (%)	27.3	45.1	9.0	0.003
First-psychotic episode symptoms (%)	44.7	26.6	9.1	0.003
Family History				
High-risk for BD-I (%)	16.7	6.2	6.6	0.01

Measures	First Episode Type		<i>F</i> or χ^2	<i>p</i> -value
	Manic (n=150)	Other (n=113)		
Risk for MDD (%)	24.7	37.2	4.8	0.03

Antidepressants mainly are modern selective serotonin- or serotonin+norepinephrine-reuptake inhibitors (SRIs and SNRIs).

Table 3
Indications and ages of first treatments and prevalence among type-I bipolar disorder patients later presenting in *Mania* or *Other* first-lifetime psychotic episodes

Indication for First Treatment	Age at First Treatment	Prevalence (%) by First Psychotic Episode Type		
		Mania	Other	Ratio
Learning disability-dyslexia	8.8±1.5	2.7	3.5	1.3
Schizoid-obsessive shy-introverted	15.9±6.1	3.3	3.5	1.1
Attentional disturbance	17.3±14.0	2.0	4.4	2.2
Sensitive-paranoid shy-introverted	18.0±2.8	1.3	0.0	<0.8
Suicidal attempt	19.3±2.4	1.3	1.8	1.4
Impulsivity	19.7±6.8	7.3	11.5	1.6
Behavioral dysfunction	20.5±10.1	2.0	2.7	1.3
PTSD-dissociation	21.3±10.6	2.0	2.7	1.3
Aggression	22.1±13.3	2.7	5.3	1.9
Eating disturbance	23.0±11.0	2.0	3.5	1.7
Dysphoria	23.5±12.4	5.3	8.0	1.5
Substance abuse	23.6±7.6	6.0	17.7	2.9*
Functional decline	23.7±14.3	7.3	11.5	1.6
Lability-cyclothymia	23.7±12.0	4.7	7.1	1.5
GAD-somatization-hypochondriasis	24.7±11.4	14.0	15.0	1.1
Sleep disturbance	24.8±17.6	1.3	1.8	1.4
Panic-agoraphobia	25.3±14.7	2.7	2.7	1.0
Hypomania-mania (not psychotic)	25.8±10.0	4.0	6.2	1.5
Thought disturbance-disorganization	26.7±13.1	2.7	1.8	0.7
Depression (not psychotic)	27.1±12.8	27.3	45.2	1.7*
Self-referential thinking	28.5±13.4	4.7	9.7	2.1
First-psychotic episode symptoms	29.2±12.9	44.7	26.6	0.6*
Psychomotor agitation	30.1±19.4	2.7	5.3	1.9
OCD-spectrum disturbance	30.8±16.6	2.7	1.8	0.7
Perceptual disturbance-perplexity	31.4±12.6	2.0	5.3	1.9
Unstable-mixed affects	31.6±16.3	4.0	6.2	1.5
Anhedonia-impaired vital drive	32.9±16.3	4.0	6.2	1.5
Epilepsy	34.5±2.1	0.7	0.9	1.3

Ranked by age at first treatment averaged for all subjects. Risk ratios are for *Other/Mania*

* indicates significantly different risks preceding *Manic* vs. *Other* first-lifetime psychotic episodes, based on Bonferroni-corrected significance criterion ($p < 0.05/28 [0.002]$; $\chi^2 = 8.98$): more treatment for early substance-abuse, and depression preceding *Other* presentations, but more early treatment for prodromal symptoms preceding *Manic* first episodes.

Table 4
Multivariate logistic regression model: Clinical features preceding *Other* versus *Manic* first-lifetime psychotic major episodes in 263 type-I bipolar disorder patients

Factors	OR [95% CI]	z-score	p-value
More early attentional disturbance	9.8 [1.2–81.1]	2.1	0.03
More late (prodromal) depression (not psychotic)	7.3 [3.9–13.3]	6.4	<0.001
More early perceptual perplexity	5.6 [1.2–27.1]	2.2	0.03
More detoxification	4.9 [1.0–23.9]	1.9	0.05
More early unstable-mixed affects	3.9 [1.2–12.7]	2.3	0.02
More antidepressant treatment	2.9 [1.4–6.2]	2.8	0.005
More early dysphoria	2.7 [1.2–5.9]	2.5	0.01
More intermediate depression (not psychotic)	2.6 [1.5–4.5]	3.3	0.001
More early impulsivity	2.5 [1.2–5.1]	2.5	0.01
More late (prodromal) anhedonia or impaired vital drive	2.0 [1.1–3.6]	2.4	0.01
Longer early-to-intermediate interval	1.9 [1.1–3.3]	2.5	0.01
More intermediate substance abuse	1.9 [1.1–3.3]	2.2	0.03
More MDD family-history	1.8 [1.1–3.1]	2.2	0/03
Younger at early-antecedents	1.7 [1.0–2.8]	2.1	0.04
Lower late behavioral problems	0.4 [0.2–0.9]	–2.4	0.02
Lower high-risk for BD	0.3 [0.1–0.8]	–2.5	0.01

The 16 factors are ranked by Odds Ratio (OR).