Schizophrenia Bulletin vol. 35 no. 5 pp. 894–908, 2009
doi:10.1093/schbul/sbp027
Advance Access publication on April 21, 2009

Validity of the Prodromal Risk Syndrome for First Psychosis: Findings From the North American Prodrome Longitudinal Study

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Treatment and prevention studies over the past decade have enrolled patients believed to be at risk for future psychosis. These patients were considered at risk for psychosis by virtue of meeting research criteria derived from retrospective accounts of the psychosis prodrome. This study evaluated the diagnostic validity of the prospective "prodromal risk syndrome" construct. Patients assessed by the Structured Interview for Prodromal Syndromes as meeting criteria of prodromal syndromes (n = 377) from the North American Prodrome Longitudinal Study were compared with normal comparison (NC, n = 196), help-seeking comparison (HSC, n = 198), familial high-risk (FHR, n = 40), and schizotypal personality disorder (SPD, n = 49) groups. Comparisons were made on variables from cross-sectional demographic, symptom, functional, comorbid diagnostic, and family history domains of assessment as well as on follow-up outcome. Prodromal risk syndrome patients as a group were robustly distinguished from NC subjects across all domains and distinguished from HSC subjects and from FHR subjects on most measures in many of these domains. Adolescent and young adult SPD patients, while distinct from prodromal patients on definitional grounds, were similar to prodromals on multiple measures, consistent with SPD in young patients possibly being an independent risk syndrome for psychosis. The strong evidence of diagnostic validity for the prodromal risk syndrome for first psychosis raises the question of its evaluation for inclusion in *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition).

Key words: prodrome/risk syndrome/psychosis/schizophrenia/schizotypy

A prodrome has been defined as "an early or premonitory manifestation of impending disease, before specific symptoms begin,"[1] and a prodrome of schizophrenia has been described since the time of Bleuler.[2] So defined, a prodrome for schizophrenia can be identified only in retrospect, after the disease has been diagnosed, when the opportunity for preventing onset is past.

"The prodromal risk syndrome for psychosis" is a term here applied to the condition studied using prospective methods by researchers interested in prevention[3–26] over the past decade or so. These researchers have consistently described a syndrome carrying a substantial risk of progression to full-blown psychosis in the near future that is characterized by evolving attenuated positive symptoms, negative symptoms, and functional impairment. Other terms used for this syndrome include "at-risk mental state," "ultra high risk," "clinical high risk," and "putative prodrome." Two comprehensive reviews of this literature have appeared fairly recently,[19,27] and the "prodromal" or clinical high-risk paradigm has become relatively well established alongside the familial high-risk (FHR) paradigm[28,29] for investigating onset of psychosis longitudinally. One structured interview for prospective diagnosis of the prodromal risk syndrome for psychosis has shown excellent diagnostic interrater reliability,[4,5,30] and 2 such interviews have shown excellent item severity reliability within the at-risk sample.[5,12,31]

Despite the general consistency of this work, limitations of published studies have thus far restrained confidence about the validity of the prodromal risk syndrome for psychosis as a diagnosis. These limitations have included relatively small sample sizes, absence of appropriate comparison groups, and restricted domains of assessment. In only half of available reports are sample

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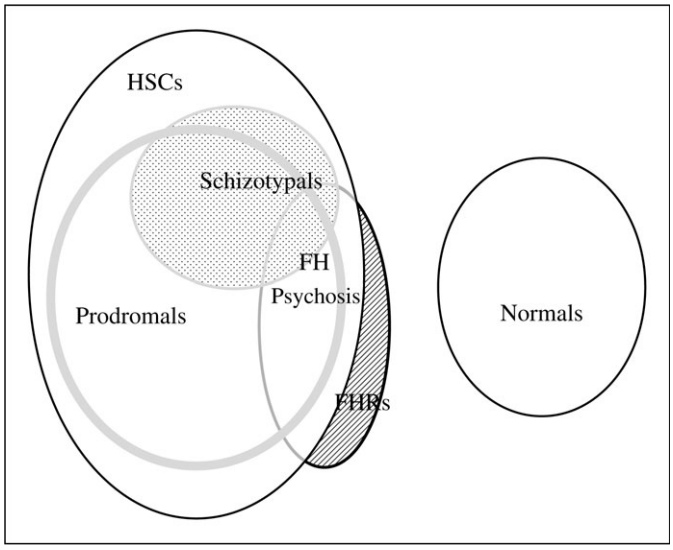

Fig. 1. Description of Subject Groupings. Sample sizes and overlaps are approximately proportional to oval areas. Subjects within the largest oval were clinically referred because of psychotic like symptoms. Within this large group ($n = 624$), subjects who met prodrome criteria ($n = 377$) are shown inside the widely outlined oval, and subjects who met schizotypal personality disorder (SPD) criteria are shown inside the lightly hatched oval ($n = 147$). Among the 147 schizotypal patients, 98 also met prodrome criteria (67% of schizotypals and 26% of prodromals). The remaining clinically referred subjects who met neither prodrome nor schizotypal criteria are labeled help-seeking comparison (HSC) subjects ($n = 198$). The crosshatched oval containing subjects with a definite first-degree family history of psychosis ($n = 125$) includes 40 subjects who were not clinically referred (familial high risk subjects, FHR, darkly hatched region). A total of 19% of prodromals, 11% of HSC subjects, and 5% of the SPD analysis group had a definite first-degree family history of psychosis (table 6). All subjects meeting prodromal criteria were retained in the prodromal analysis group, regardless of schizotypal comorbidity or family history. The SPD analysis group was restricted to schizotypal patients who did not meet prodrome criteria, without regard to family history ($n = 49$). All HSC subjects were retained in the HSC analysis group, without regard to family history. In addition to these subjects, 196 subjects referred as healthy volunteers and who had no first-degree family history of psychosis defined the normal comparison group.

sizes of prodromal patients larger than 50.[6–11,13,15,21–26] Of these, only 4 reports feature nonprodromal comparison groups,[6,23,24,26] and only 2 reports included more than one domain of assessment.[6,23]

As a result of these limitations, the prospective diagnosis of patients as being in a prodromal risk syndrome for psychosis has yet to be accepted by psychiatric professional societies, the Food and Drug Administration, or US insurance companies. The absence of these operational hallmarks of clinical validity has in turn slowed the development of a treatment research evidence base that could benefit these impaired, symptomatic, at-risk patients and their families.

The purpose of the present study was to evaluate the construct validity of the prodromal risk syndrome for first psychosis (hereafter also referred to as "the prodromal patient" or simply as "the prodrome"). An approach for establishing the diagnostic validity of psychiatric syndromes in general was outlined in a seminal 1970 article by Robins and Guze.[32] Our North American Prodrome Longitudinal Study (NAPLS) collaboration[30] permitted application of this method to the prodromal risk syndrome for psychosis in a large sample with multiple comparison groups and cross-sectional demographic, symptom, functional, comorbid diagnostic, and family history domains of assessment as well as follow-up outcome.

Method

The construction of the database has been described previously.[30] Briefly, 7 projects with broadly similar goals that focused on prospectively determining the outcomes of a prodromal diagnosis and improving prediction were funded by National Institute of Mental Health (NIMH) between 2000 and 2003. An eighth NIMH-funded project was collecting a sample of well-characterized FHR subjects for the analysis of psychosis risk factors. These projects were granted supplements to create a federated database to increase sample size and statistical power and became known collectively as NAPLS. Each site utilized the Structured Interview for Prodromal Syndromes (SIPS) to evaluate and monitor prodromal symptoms. Detailed descriptions of SIPS symptom severity scales, prodromal diagnostic criteria, and psychometric properties are available.[4,5,33,34] Diagnostic agreement with gold standard SIPS diagnoses was in the excellent range ($\kappa > 0.80$) at each center.[30] Other assessment methods varied across site, because the projects had been conceived independently, although there was considerable overlap as well.[30] Each site obtained institutional review board approval to contribute anonymous data.

Subjects

The 8 sites contributed data for 860 nonpsychotic subjects enrolled between 1998 and 2005. These subjects were categorized into 5 nonoverlapping groups as described in figure 1. Briefly, prodromal patients met the criteria for prodromal syndromes outlined in the SIPS after clinical referral. One or more of 3 criteria had to be met: (1) new onset or recent worsening of subsyndromal ("attenuated") positive psychotic symptoms, (2) very brief periods of fully psychotic positive symptoms, or (3) deterioration in functioning within the last year and schizotypal personality disorder (SPD) or a having first-degree relative with psychosis. Detailed research definitions of the 3 prodromal syndromes have been published previously.[4,5] Patients meeting prodrome criteria ($n = 377$) were classified for the present analysis in the prodromal analysis group without regard to whether they also had a family history of psychosis or whether

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Table 1. Numbers of Subjects by Site and Baseline Diagnosis

Baseline	UNC	Emory	Harvard	ZHH	Toronto	UCLA	UCSD	Yale	Total
Prodrome	51	11	0	45	39	46	59	126	377
NC subjects	36	30	54	23	0	5	48	0	196
HSC subjects	7	58	0	57	11	0	2	63	198
FHR subjects	0	0	38	2	0	0	0	0	40
SPD subjects	0	27	0	3	0	0	3	16	49
Total	94	126	92	130	50	51	112	205	860

Note: UNC, University of North Carolina; ZHH, Zucker Hillside Hospital; UCLA, University of California, Los Angeles; UCSD, University of California, San Diego; NC, normal comparison; HSC, help-seeking comparison; FHR, familial high risk; SPD, schizotypal personality disorder.

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they also met SPD criteria. Prodromal patients were excluded from the defined nonoverlapping FHR and SPD analysis groups (see below). Seven sites recruited prodromal patients (table 1). Normal comparison (NC) subjects ($n = 196$) were recruited as healthy volunteers by 6 sites (table 1). Recruitment practices for NC subjects differed somewhat across site: 5 sites used advertisements,[28,35–37] 2 sites Web sites,[28,35] and 1 site a university registry.[38] Four sites sought NC subjects with no history of psychiatric illness; these sites excluded subjects with any current or lifetime *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) diagnosis. Two sites sought NC subjects with no history of psychosis[28]; these sites permitted nonpsychotic Axis I current or lifetime *DSM* diagnoses. All sites excluded subjects with first-degree family histories of psychosis, but 4 sites permitted second-degree family histories of psychosis,[35,36,38] and 2 excluded those with second-degree histories.[28,37] Help-seeking comparison (HSC) subjects ($n = 198$) are included from 6 sites. These subjects had been clinically referred for evaluation of symptoms that appeared potentially to qualify as prodromal on initial telephone contact. Then, on formal SIPS interview, these subjects did not meet prodrome (or SPD) criteria. Usually, these subjects did not meet prodrome criteria on interview because attenuated positive symptoms had not begun or worsened in the past year, although in some cases the attenuated positive symptoms were too mild or too infrequent. Usually, the HSC subjects did not meet SPD criteria because they did not have symptoms in at least 5 of the 9 areas required. FHR subjects ($n = 40$, from 2 sites) were nonclinical recruits from 2 sites with a first-degree family history of psychosis; and patients in the SPD group ($n = 49$, from 4 sites) met *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*) schizotypal (but not prodrome) criteria as determined by SIPS interview.

Assessments

Subjects underwent baseline interviews at each site. Positive, negative, disorganized, and general symptoms (table 4) were rated using the Scale of Prodromal Symptoms (SOPS) contained within the SIPS[4,5,20,33,34] for nearly all subjects. SOPS are scaled 0–6, with extensive anchors for each scale point for each symptom. For positive symptoms, the anchor title for a rating of zero is ''none'' and for a rating of six is ''psychotic.'' SOPS scores for some positive items were estimated from other available instruments in 38 FHR subjects (details on request). Functional status was assessed with a modified Global Assessment of Functioning (GAF) Scale,[39] the Cannon-Spoor Premorbid Adjustment Scale,[40,41] and with new measures of social functioning and instrumental role performance.[42] Axis I diagnoses were established by structured interview, conducted by a trained interviewer who met local reliability standards, usually at the masters or doctoral level. Sites consistently employed versions of the Structured Clinical Interview for *DSM-IV* (SCID-IV)[43] and/or the Schedule for Affective Disorder and Schizophrenia for School-Aged Children (K-SADS).[44] The Comprehensive Assessment of Symptoms and History (CASH)[45] was used by 3 sites for some subjects. Some sites obtained substance diagnoses from Drake's Alcohol and Drug Use Scales.[46] Axis II diagnoses were established using the Structured Interview for *DSM-IV* Personality Disorders,[47] Diagnostic Interview for *DSM-IV* Personality Disorders,[48] or the SCID-IV Axis II personality disorders.[49] Family psychiatric history was determined using the Family History-Research Diagnostic Criteria data sheet,[50] the Family Interview for Genetic Studies,[51] or local structured measures.

The SIPS was readministered at 6-month intervals up to 30 months. The primary course variable was time from baseline to conversion to psychosis. Conversion to psychosis was defined according to criteria operationalized in the SIPS. These criteria define frank psychosis as the presence of positive symptoms of sufficient intensity that are either seriously disorganizing or dangerous or that have been present for a month, at least half the days, at least an hour per day.[4,5] In addition to the SIPS, another

diagnostic interview (SCID-IV, K-SADS, or CASH) was used to determine *DSM-IV* psychotic syndrome diagnoses for interviewed converting cases. When possibly converting subjects could not be interviewed in person, sites established best estimates of conversion to psychosis based on review of hospital and other medical records and telephone interviews with subjects, family members, and members of the treatment team. When conversion to psychosis was established with these methods, the *DSM-IV* diagnosis was considered missing. The database was closed to inclusion of follow-up information after September 30, 2006.

Statistical Methods

Available data for the 5 subject groups were compared for each measure. Because initial findings suggested demographic differences in age, gender, and race across groups, subsequent analyses employed these demographic variables as covariates. General linear models were used for continuous measures, logistic regression for categorical measures, and proportional hazards models for time-to-event measures. Post hoc testing utilized the same models and was restricted by design to the 4 pairwise comparisons of the prodromal group to the 4 comparison groups. When there were 0 cases in a cell, 2 × 2 Fisher exact tests were substituted for logistic regression. Alpha for post hoc testing was set at a Bonferroni-corrected .0125, 2 tailed.

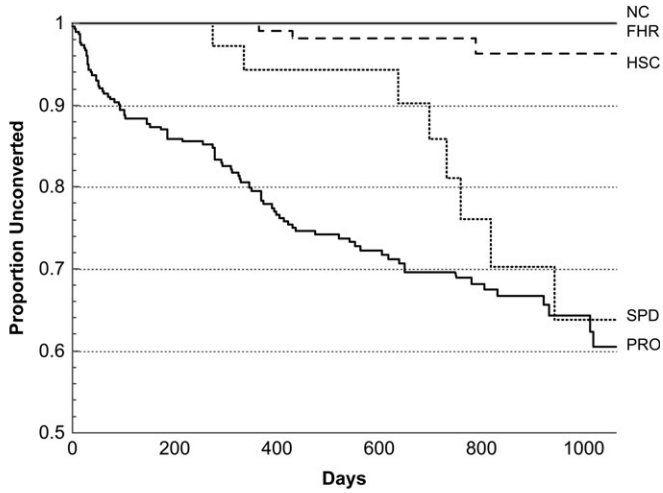
Previous Reports

To date there are 2 previous NAPLS publications which use data from the same subject group. The first article,[30] while largely a description of methodology, reports demographic and diagnostic data, in less detail than the current table 3 and Supplementary Table S2 and for the prodromal group in comparison to 2 comparison groups reported here but not in comparison to SPD or FHR groups. The second article focuses on improving the positive predictive value of conversion to psychosis within the prodromal group,[52] a topic not addressed in the present report. The second article also presents a figure comparing conversion rates in prodromals and NC subjects, similar to the current figure 2 but without findings on the SPD, FHR, and HSC groups. Otherwise there is no overlap among the articles. Several of the subject counts differ slightly between the first 2 articles and the current one, as a result of identification and correction of internal inconsistencies in the database.

Results

Demographics

Sites contributed between 50 and 205 subjects each (table 1). Most subjects were followed at least 6 months (638/860, 74%). The large majority of prodromal patients qualified



		0	200	400	600	800	1000
PRO	Con	0	42	67	77	84	88
	AR	303	238	188	139	88	33
NC	Con	0	0	0	0	0	0
	AR	136	131	108	68	41	21
HSC	Con	0	0	1	2	3	3
	AR	135	127	107	83	54	32
FHR	Con	0	0	0	0	0	0
	AR	26	24	20	18	15	8
SPD	Con	0	0	2	2	6	8
	AR	38	37	29	23	13	8

Fig. 2. Time to Conversion to Psychosis Among Subjects in the 5 Groups. Solid black line—prodromal patients ($n = 303$, 89 converters). One patient in the prodromal group converted at 1006 days. Thin black line—normal comparison subjects (136, 0 converters, $P < .001$ vs prodromals). Dashed black line—help-seeking comparison subjects ($n = 135$, 3 converters, $P < .001$ vs prodromals). Solid gray line—familial high-risk subjects ($n = 26$, 0 converters, $P < .001$ vs prodromals). Dotted line—schizotypal personality disorders ($n = 38$, 8 converters, $P = .230$ vs prodromals). PRO—prodromals, NC—normal comparison subjects, HSC—help-seeking comparison subjects, FHR—familial high-risk subjects, SPD—schizotypal personality disorder patients, Con—cumulative number of converters, AR—number of at-risk subjects remaining.

for the diagnosis because of attenuated positive symptoms (96%, table 2, first column, bottom row). Usually, this was the sole prodromal syndrome diagnosed, although Genetic Risk and Functional Decline Prodromal Syndrome (GRD) was comorbid in a minority. Roughly 4% of the prodromal sample met brief intermittent psychosis criteria. GRD criteria were satisfied in 12%, with this syndrome usually comorbid with Attenuated Positive Symptom Prodromal Syndrome. Only 6 patients (1.7%) met criteria for GRD alone. Table 3 shows some small group differences on gender, age, and race. Analyses adjusting for these variables revealed no significant differences between prodromal patients and comparison groups on education or employment measures except that the prodromal patients had completed slightly less schooling than NC subjects and that the FHR subjects were less likely to be employed than prodromal patients.

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Table 2. Distribution of Prodromal Syndromes, *n* (%)

Syndrome	Any APS	Any BIPS	Any GRD
Patients with complete data			
One syndrome only	304/344 (88.4)	8/12 (66.7)	6/45 (13.3)
+APS only	—	2/12 (16.7)	37/45 (82.2)
+BIPS only	2/344 (0.6)	—	1/45 (2.2)
+GRD only	37/344 (10.8)	1/12 (8.3)	—
+APS and BIPS	—	—	1/45 (2.2)
+APS and GRD	—	1/12 (8.3)	—
+BIPS and GRD	1/344 (0.3)	—	—
Total complete data	344/359 (98.5)	12/359 (3.3)	45/359 (12.5)
Patients with missing data			
Missing APS only	—	0/14 (0.0)	0/45 (0.0)
Missing BIPS only	0/360 (0.0)	—	0/45 (0.0)
Missing GRD only	16/360 (4.4)	2/14 (14.3)	—
Missing both others	0/360 (0.0)	0/14 (0.0)	0/45 (0.0)
Total	360/377 (95.5)	14/377 (3.7)	45/377 (11.9)

Note: APS, Attenuated Positive Symptom Prodromal Syndrome; BIPS, Brief Intermittent Psychosis Prodromal Syndrome; GRD, Genetic Risk and Functional Decline Prodromal Syndrome.

Symptoms

Prodromal patients were distinguished from NC subjects on the SOPS total score, every SOPS subscale, and every SOPS item (table 4 and Supplementary Table S1). NC group means were close to the SOPS minimum possible score. HSC subjects had somewhat higher severity scores on the SOPS, but the prodrome group was distinguished from the HSC on the SOPS total score, all subscales, and all but 3 individual items. Prodromal patients were distinguished from FHR subjects on available positive symptom SOPS items; data were otherwise sparse. The SPD-alone group received SOPS totals scores and 3 subscale scores that were similar to those from the prodrome group. Many of the individual SOPS item scores were also similar, but the schizotypal group was rated more severe than the prodrome group on several items (disorganized speech, social anhedonia, emotional expression, odd behavior, and personal hygiene,

Table 3. Group Comparisons on Demographic Measures

Dependent Measures	Prodromal $n = 377$[a]	Comparison Group				Overall F, χ^2, or Wald (P)
		NC $n = 196$[a]	HSC $n = 198$[a]	FHR $n = 40$[a]	SPD $n = 49$[a]	
Gender, (%) males	62.1	*45.9*	63.6	42.5	67.3	23.3[b] (<.001)
Mean age (y)	18.2	18.7	*16.1*	19.4	*16.1*	13.8[c] (<.001)
Race, nonwhite (%)	22.0	36.2	29.3	42.5	28.6	17.5[b] (.002)
Mean highest grade	10.3	11.2	8.9	11.2	8.8	8.8[d] (<.001)
Current FT/PT school (%)	69.6	70.6	86.4	51.4	87.8	8.3[e] (.080)
Current FT/PT work (%)	21.6	22.8	14.1	*0.0*	6.1	13.8[e] (.008)
Parent college grade (%)	66.2	75.0	63.2	59.5	67.4	6.7[e] (.154)

Note: FT/PT, full-time or part-time.
[a]Data are complete for gender, age, and race. Due to missing data, the actual sample size for other measures varied: 302–375 for prodromal patients, 167–193 for normal comparison (NC) subjects, 182–198 for help-seeking comparison (HSC) subjects, 21–37 for familial high-risk (FHR) subjects, and 46–49 for schizotypal personality disorder (SPD) patients. Italicized values are significantly lower than for the prodromal group; underlined values are significantly higher than for the prodromal group; values neither italicized nor underlined are not significantly different from the prodromal group.
[b]Indicates that statistic value is χ^2.
[c]Indicates that statistic value is F from analysis of variance.
[d]Indicates that statistic value is F from analysis of covariance, adjusting for gender, age, and race.
[e]Indicates that statistic value is Wald from logistic regression, adjusting for gender, age, and race.

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Table 4. Group Comparisons on the SOPS Symptom Measures

Dependent Measures	Prodromal $n = 377$[a]	Comparison Group				Overall F (P)
		NC $n = 118$[a]	HSC $n = 198$[a]	FHR $n = 2$	SPD $n = 49$[a]	
SOPS total	38.4	*2.1*	*23.5*	*0.5*	39.2	206.8 (<.001)
SOPS positive	11.9	*0.7*	*4.6*	*0.0*	10.7	277.9 (<.001)
SOPS negative	12.1	*0.6*	*9.9*	*0.5*	13.7	79.5 (<.001)
SOPS disorganization	6.5	*0.3*	*3.5*	*0.0*	7.9	92.9 (<.001)
SOPS general	8.0	*0.4*	*5.5*	*0.0*	6.6	83.0 (<.001)

Note: General linear models adjusted for age, gender, and race. Post hoc contrast findings are illustrated as for table 3. SOPS, Scale of Prodromal Symptoms.
[a]Due to missing data, the range of actual sample sizes for each group is prodromal 360–377, normal comparison (NC) subjects 117–118, help-seeking comparison (HSC) subjects 189–198, and schizotypal personality disorder (SPD) subjects 48–49.

Supplementary Table S1) and the disorganization subscale (table 4).

Functional Status

Prodromal patients were impaired relative to normal and FHR groups on all measures of current functioning (table 5). The mean GAF score was 46. HSC subjects were less impaired than prodromal patients on some measures of current functioning, whereas schizotypals were as impaired as prodromal patients on 3 measures and more impaired on social functioning.

Premorbid Adjustment Scale scores distinguished prodromal patients from NC subjects but not from HSC or FHR subjects. Schizotypal patients showed poorer premorbid adjustment than prodromal patients, beginning in early adolescence.

Diagnostic Comorbidity

DSM-IV diagnostic comorbidity with the prodrome at baseline was common: 69% had one or more mood/anxiety diagnoses, 25% had one or more substance abuse or dependence diagnoses, and 44% had one or more Axis II

Table 5. Group Comparisons on the Functioning Measures

Dependent Measures	Prodromal $n = 377$[a]	Comparison Group				Overall F (P)
		NC $n = 139$[a]	HSC $n = 198$[a]	FHR $n = 38$[a]	SPD $n = 49$[a]	
Social function	6.2	*8.6*	6.0	*7.0*	5.3	102.4 (<.001)
Role performance	6.1	*8.7*	6.2	*6.9*	6.0	70.9 (<.001)
Psychological function	5.7	*9.0*	*6.3*	*7.0*	5.8	316.4 (<.001)
Global function current	46.4	*87.0*	*53.6*	*71.1*	47.5	162.7 (<.001)
PAS–child	0.75	*0.87*	0.72	0.76	0.62	13.4 (<.001)
PAS–early adolescent	0.66	*0.84*	0.62	0.70	0.50	30.9 (<.001)
PAS–late adolescent	0.64	*0.88*	0.62	0.73	0.51	21.5 (<.001)
PAS–adult	0.65	*0.96*	0.65	0.80	0.28	16.2 (<.001)
PAS–total	0.68	*0.85*	0.63	0.73	0.53	41.2 (<.001)

Note: General linear models adjusted for age, gender, and race. Post hoc contrast findings are illustrated as follows: values significantly more impaired than the prodromal group are underlined, values significantly less impaired than the prodromal group are italicized. Social, role, and psychological functioning scales ranged from 0 to 10 (highest).[42] Global functioning ranged from 0–100 (highest).[39] Premorbid Adjustment Scale (PAS) values reflect the proportion of optimal adjustment, ranging from 0.00 to 1.00 (highest).[40,41]
[a]Due to missing data, the range of actual sample sizes for each group is social, role, and psychological functioning 371–377 for prodromal patients, 137–139 for normal comparison (NC) subjects, 196–198 for help-seeking comparison (HSC) subjects, and no missing data for familial high-risk (FHR) subjects or schizotypal personality disorder (SPD) subjects; for Global Assessment of Functioning Scale 368 for prodromal patients, 57 for NC, 167 for HSC, no missing data for FHR, and 47 for SPD; for PAS across subscales 101–326 for prodromal patients, 34–120 for NC, 14–147 for HSC, 18–37 for FHR, and 4–37 for SPD.

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Table 6. Group Comparisons on Family History Measures

Dependent Measures	Prodromal $n = 344$[a]	Comparison Group				Overall χ^2 or F (P)
		NC $n = 190$[a]	HSC $n = 176$[a]	FHR $n = 40$[a]	SPD $n = 43$[a]	
Family history of psychotic illness						
Definite in FDR (%)[b]	18.6	*0.0*	10.8	100	4.7	220.9 (<.001)
Definite in FDR or SDR (%)[b]	33.0	*1.8*	26.2	100	*10.5*	197.7 (<.001)
Proportion FDR definite[b]	7.0	*0.0*	*3.8*	27.2	*1.2*	36.2 (<.001)
Family history of nonpsychotic psychiatric illness						
Definite in FDR (%)[b]	48.0	*15.3*	40.8	*22.5*	38.5	56.1 (<.001)
Definite in FDR or SDR (%)[b]	66.1	*37.2*	64.1	90.9	75.0	32.9 (<.001)
Proportion FDR definite[b]	23.0	*6.3*	*17.0*	*5.3*	19.2	11.1 (<.001)

Note: P values and statistic values are adjusted for gender, age, and race. Statistic value is F for diagnostic group term from general linear models for continuous measures and χ^2 from logistic regression for categorical measures. Post hoc test results are illustrated as for table 3.

[a]Sample size shown is for definite psychosis in first-degree relatives (FDRs). Sample size across other measures was 303–333 for prodromals, 121–189 for normal comparison (NC) subjects, 164–174 for help-seeking comparison (HSC) subjects, 11–40 for familial high-risk (FHR) subjects, and 36–42 for schizotypal personality disorder (SPD) subjects. SDR indicates second-degree relatives.

[b]"%"—The number of subjects with one or more relatives qualifying; "proportion"—mean density of illness, the average of the proportion of each subject's relatives who qualify.

diagnoses (Supplementary Table S2). Diagnostic comorbidity rates for many disorders distinguished prodromal patients from normals. Lifetime major depression and dysthymia rates were higher among prodromal patients than among HSC subjects, and anxiety disorder and social phobia rates were higher among prodromal patients than among schizotypals. Lifetime substance abuse diagnoses did not distinguish prodromal patients from FHR, SPD, or HSC groups. There were higher proportions of paranoid, schizoid, and avoidant personality disorders among schizotypals than among prodromal patients. HSC group membership excluded subjects with SPD by definition (figure 1).

Family History

Family history of psychosis distinguished the prodromal group from the HSC group for illness density and from the schizotypal group on 2 measures (table 6). Family history of nonpsychotic psychiatric illness distinguished the prodromal group from the NC subjects on all measures and from the HSC group on illness density (table 6). The FHR group was defined by first-degree family history of psychosis and the NC group by its absence.

Course of Illness

Time-to-event curves for conversion to psychosis are shown in figure 2. Kaplan-Meier analyses show that 40% of prodromal patients converted to fully psychotic illness during 2.5 years of follow-up. Corresponding rates for NC, HSC, FHR, and SPD subjects were 0%, 4%, 0%, and 36%, respectively. Cox regression comparing groups with nonzero conversion rates distinguished prodromal patients from HSC subjects ($P < .001$) but not from SPD subjects ($P = .230$). Fisher exact tests showed that prodromals converted significantly more often than FHR subjects and NC subjects (both $P < .001$). Pooling all the nonprodromal subjects into a single comparison group, the sensitivity of a baseline prodromal diagnosis for conversion to psychosis was 89.0% (89/100), and the specificity was 60.2% (324/538).

DSM-IV diagnoses of converting patients are shown in table 7 by baseline status. A third of these diagnoses are missing, in cases where the site learned of conversion through telephone or collateral sources, and the subject could not be scheduled for structured interview. Conversion diagnoses in the former prodromal patients were schizophrenia-spectrum psychoses in 56%, affective psychoses in 10%, and other psychoses, principally psychosis not otherwise specified (NOS), in 34%. The diagnostic distribution of the small number of converters from outside the prodromal group does not differ conspicuously from the diagnostic distribution of the prodromal converters.

Discussion

The principal finding of the present study is that the SIPS structured interview identifies a prodromal risk syndrome that is generally distinct from NC, HSC, and FHR groups across symptom, functioning, comorbidity, family history, and course of illness domains (table 8).

Clear and compelling differences between a prodrome sample and NC subjects are certainly necessary to establish the validity of a prodromal diagnosis. Relatively few prior studies of prodromal patients in the past decade

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Table 7. *DSM-IV* Diagnoses of Converters by Baseline Diagnosis

	Baseline Diagnosis		
DSM-IV diagnosis at conversion	Prodromal	SPD	HSC
295.10 schizophrenia, undifferentiated	3 (5.1%)		
295.30 schizophrenia, paranoid	4 (6.8%)		
295.90 schizophrenia, undifferentiated	8 (13.6%)	4 (57.1%)	
295.70 schizoaffective disorder	6 (10.2%)	2 (28.6%)	
295.40 schizophreniform disorder	12 (20.3%)		
Subtotal schizophrenia-spectrum psychoses	33 (55.9%)	6 (85.7%)	
296.04 bipolar I, single mania, with psychosis			1 (50.0%)
296.44 bipolar I, MRE manic, with psychosis	5 (8.5%)		
296.64 bipolar I, MRE mixed, with psychosis	1 (1.7%)		
296.34 recurrent depression, with psychosis		1 (14.3%)	
Subtotal affective psychoses	6 (10.2%)	1 (14.3%)	1 (50.0%)
297.1 delusional disorder	2 (3.4%)		
298.8 brief psychotic disorder	2 (3.4%)		
298.9 psychosis NOS	16 (10.2%)		1 (50.0%)
Subtotal other psychoses	20 (33.9%)		1 (50.0%)
Total conversion with *DSM-IV* diagnoses	59 (100.0%)	7 (100.0%)	2 (100.0%)
Missing *DSM-IV* diagnoses	30 (33.7%)	1 (12.5%)	1 (33.3%)
Total conversions to psychosis	89 (100.0%)	8 (100.0%)	3 (100.0%)

Note: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition); SPD, schizotypal personality disorder; HSC, help-seeking comparison; MRE, most recent episode.

have taken this necessary step in any domain.[12,16,24] Historically, attempts to identify prodromal patients using the *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition Revised) checklist foundered on the inability of the checklist to distinguish patients from nonpatients.[53] Our findings based on current methods of prodromal diagnosis establish the distinction from NC subjects convincingly.

Although distinction from a NC group is necessary, this demonstration is by no means sufficient. A more

Table 8. Summary of Differences From Prodromal Patients

	Comparison Group			
Domain (Location of Details)	NC	HSC	FHR	SPD
Positive symptom severity (table 3)	↓↓	↓	↓↓	0
Negative symptom severity (table 3)	↓↓	↓	…	↑
Functioning at baseline (table 5)	↓↓	↓	↓↓	↑
Premorbid adjustment (table 5)	↓↓	0	0	↑↑
Affective comorbidity (supplementary table S1)	↓↓	↓	…	0
Substance disorder comorbidity (supplementary table S1)	↓↓	0	0	0
Axis II comorbidity (supplementary table S1)	↓↓	0	…	NA
Family history of psychosis (table 6)	NA	↓	NA	↓
Family history of nonpsychotic illness (table 6)	↓↓	↓	↓	0
Conversion to psychosis (figure 2)	↓↓	↓↓	↓↓	0

Note: ↓↓ indicates that the comparison group was significantly less impaired than prodromal patients on all or most measures, ↓ indicates significantly less impaired on some measures or numerically less impaired on the sole measure in the domain, 0 indicates nonsignificance on all measures or significantly more impaired on some measures but significantly less impaired on others or numerically similar on the sole measure in the domain, ↑ indicates that comparison group was significantly more impaired than prodromal patients on some measures or numerically more impaired on the sole measure in the domain, ↑↑ indicates significantly more impaired than prodromal patients on all or most measures, … indicates that data were sparse. NA indicates that groups differed from prodromal patients by definition. NC, normal comparison; HSC, help-seeking comparison; FHR, familial high risk; SPD, schizotypal personality disorder.

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rigorous test of syndromal validity would be provided by a comparison group from the same referral pool: those who were clinically referred for prodrome evaluation but who did not meet prodrome criteria on interview. We identify such patients here as "HSC subjects." Few previous studies have compared prodromal patients with HSC subjects,[4,16–18,21,26] and these either limited themselves to 1 or 2 measurement domains[4,17,18,21,26] or had a small prodromal sample.[16] The multiple differences from HSC subjects on most cross-sectional variables, as well as the profound differences in conversion outcomes, provide very strong evidence of validity of the prodromal risk syndrome.

FHR subjects had historically offered the available research paradigm with the highest risk of psychosis, prior to the advent of prospective prodromal research. Prodromal patients were robustly distinguished from FHR subjects on all measures of current functioning and on risk of transition to psychosis over the near term. Although prodromal patients and FHR subjects are quite distinct on theoretical grounds, this is the first study to our knowledge to make empirical comparisons between these groups.

The symptoms of the psychosis prodrome and the symptoms of SPD are similar on a cross-sectional basis.[54] The 2 syndromes are, however, clearly delineated by definition: Prodromal patients must show progression of illness in the past year while SPD patients may have been stably ill; SPD patients must exhibit symptoms in at least 5/9 areas while prodromal patients may exhibit fewer symptoms. Clear delineation of the 2 syndromes also permits them to co-occur. In our sample, 26% of prodromal patients met SPD criteria, and 67% of schizotypally diagnosed patients met prodrome criteria.

Because the 2 syndromes share membership in the psychosis-spectrum group of conditions, however, the interpretation of comparisons between the 2 groups does not speak as straightforwardly as the previous comparisons to issues of discriminant (or convergent) validity. These comparisons are nevertheless of interest. The final rate of transition to psychosis in patients with SPD alone was similar to that in the prodromal group (figure 2). Thus, our results suggest that SPD in adolescents and young adults may be like the prodrome in that it may also constitute an identifiable risk syndrome for psychosis.

The conclusion that SPD can constitute a risk syndrome for psychosis does have some precedents. While SPD has often been conceptualized as a stable condition, this stability may primarily apply to older samples. Others have also reported that adolescents and young adults with SPD are at substantial risk of developing psychosis,[55,56] although neither of these studies removed comorbid prodromal patients from the SPD analysis group as in the current analyses.

SPD in adolescents and young adults may capture individuals with a more gradual progression of illness than the prodrome criteria. Evidences in the current study consistent with such speculation are the greater impairment of premorbid adjustment in the SPD-alone group than the prodromal group, the lack of dramatic progression in the year before baseline in the SPD-alone subjects (by virtue of their not meeting prodrome criteria), and the suggestion in figure 2 that conversions occurred somewhat later in the patients with SPD alone than in prodromals. A factor that may contribute to the possibly later conversion in the SPD group is their younger age at ascertainment because more time would be required to enter the age of maximum risk.

Strengths and Limitations

The primary strength of the study is the large sample size of well-characterized patients meeting prodrome criteria: Three hundred seventy-seven is 2–3 times as large as the next largest reported samples.[8,21,25,26] An additional strength is the use of the SIPS for evaluating subjects. Psychometric properties for this instrument have been favorable,[4,5,20,33,34] and reliability in its use was established cross-site.

An important potential limitation is that comparisons involving symptom severity, family history, and functional decline could be viewed as tautological because these domains contribute to making a prodromal diagnosis. However, several considerations suggest that these comparisons reflect discriminant validity largely independently from definitional issues. First, only 1.7% of the prodromal sample qualified for a prodromal diagnosis based solely on family history and functional decline.[30] Removal of this small number of subjects would have little impact on the family history findings in table 6 or the functional findings in table 5. Second, only positive symptoms contribute to the prodrome definition, and the pattern of the data for the nonpositive symptoms is similar to that for the positive symptoms (table 4). Lastly, the contribution of severity of positive symptoms to a prodromal diagnosis is not a deterministic one, as the prodromal syndromes defined by positive symptoms require symptom frequency and recent symptom change criteria in addition to symptom severity. Thus, prodromal patients are not required by definition to have more severe positive symptoms than HSC subjects.

Other limitations stem from the study data having been originally collected through independent protocols. Such limitations include the variability of statistical power across pairwise comparisons, the absence of symptom data other than those from the SOPS, methods of recruitment and evaluation that varied somewhat, the need to estimate SOPS data for most FHR subjects, the uncertain agreement between the Axis II interviews employed, and our inability to subdivide family history of nonpsychotic illness into finer-grained categories.

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Because the large majority (table 2) of the prodromal patients met only 1 of the 3 sets of prodrome criteria, those for attenuated positive symptoms, another limitation is that the current evidence of syndromal validity applies almost exclusively to this common prodromal syndrome. The current data do not provide an adequate test of the validity of the other 2 less common prodromal syndromes (brief intermittent frank psychosis and genetic risk with functional decline).

A further limitation is that the current data do not address the probability of diagnostic changes after baseline other than conversion. For example, initial HSC subjects or schizotypal patients may meet prodrome criteria during follow-up, and FHR subjects or prodromal patients may develop schizotypal personality during follow-up.

Lastly, the aim of the current prodromal definition focused on positive symptoms was to identify patients relatively late in an ongoing prodrome. Retrospective work suggests that identifiable negative, anxiety, and depressive symptoms may precede the onset of attenuated positive symptoms during the prodrome,[57] but the specificity of such early symptoms in prospectively identifying patients who will transit to psychosis remains an area that requires further investigation. Some self-perceived mental functioning deficits, known as "basic symptoms,"[58] may also provide a means to identify patients as prodromal before the onset of attenuated positive symptoms.

Specific Psychotic Outcomes of the Prodromal Risk Syndrome

Following usual practice among prodromal research clinics, this article reports on conversion to psychosis, including cases of affective psychosis, rather than conversion more narrowly to schizophrenia. Conversions to affective psychosis from the prodrome represented a substantial, albeit a minority, proportion (10%, table 7). This proportion is in general agreement with previous reports.[8–10,19]

The initial reason that prodromal clinics reported conversion to the broader psychosis construct related to the perceived relative instability of specific diagnoses in early first-episode psychosis.[3] Recent studies have confirmed that the initial *DSM-IV* diagnosis is somewhat unstable in the first episode.[59–65] The large majority of first-episode affective psychosis diagnoses in these studies were stable, however, with 82% of the 488 patients again receiving affective psychosis diagnoses at 12- to 36-month follow-up. Based on these previous findings, many of our affective psychosis converters might remain cases of affective psychosis if further follow-up were available.

Thus, the preliminary conclusion is that affective psychoses may share with schizophrenia-spectrum psychosis a prodrome characterized by attenuated positive symptoms. Similarly, recent work describing prodromal symptoms for mania found attenuated positive symptoms more predictive of psychotic mania than nonpsychotic mania.[66] This preliminary conclusion of a similar prodrome in schizophrenic and affective psychosis is consistent with genetic epidemiology and molecular genetic data suggesting a similarity between schizophrenic and affective psychoses.[67–72] Additional emerging data from the NAPLS collaboration suggest that the converse may be true as well: The prodromal risk syndrome for psychosis may not confer high specific risk for nonpsychotic affective disorder. Nonpsychotic mania at follow-up was more common in the HSC subjects than in the prodromal group.[73]

Comorbidity in the Prodromal Risk Syndrome

The common comorbidity of established *DSM-IV* diagnoses in prodromal patients, reported previously,[17] is not dissimilar to the range of comorbidity reported for schizophrenia itself, when no diagnostic hierarchy is imposed as in the current study.[74–82] The presence of the comorbid diagnoses should not rule out consideration of a prodrome diagnosis if the comorbid diagnoses do not account for the symptoms, distress, and functional impairment that the patient experiences.

Next Steps for the Prodromal Risk Syndrome

The current construct validity findings comprise part of the work necessary to establish a fully valid diagnosis; however, several other questions remain which will require additional studies.

One of the most important questions is whether the prodromal diagnosis can be refined so as to increase the proportion of cases that convert to psychotic illness. Our group has focused on this question elsewhere.[52] We found that the addition of 3 clinical severity criteria to the current prodromal diagnostic criteria can increase the proportion of converting patients to 80%. Unfortunately, imposing 3 additional severity criteria also leads to a substantial loss of sensitivity, such that 70% of converting cases are now falsely predicted not to convert. Thus, further studies are needed to refine the prodromal diagnosis, both to replicate that more stringent criteria continue to predict conversion in a high proportion of individuals and to determine whether other revisions to the criteria could substantially restore sensitivity.

Because only 89% of the converters in our clinically referred sample had met prodrome criteria at baseline, another question is whether to revise prodrome criteria to try to capture the 11% of converting cases that were not diagnosed as prodromal at baseline. Most of these subjects met schizotypal criteria, but a few did not. Some cases may have met prodrome or SPD criteria at an intervening time point, as discussed earlier.

An additional challenge for this field is to characterize the outcomes of a prodromal diagnosis more rigorously. Fully formed psychosis is likely not to be the only psychosis-spectrum outcome. Developing psychosis

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captured as an initial diagnosis of prodrome may stabilize at a subsyndromal or "schizotypal" level. Such outcomes are worthy of increased attention. Similarly, we need to know more about how often and how completely apparently "prodromal" symptoms remit spontaneously and how often nonpsychotic diagnoses such as depression newly emerge or persist.

Another important question centers on the effect of the patient pool from which evaluations for the prodrome are drawn. Recent reports of a declining rate of conversions to psychosis (16% at 2 y[26] compared with 30% in the present sample, 12% at 12 mo[25] compared with 22% in the present sample) have emphasized the possible role of referral of subjects whose "prodromal" symptoms are not associated with distress, help seeking, or reduced functioning but are only incidental to help-seeking behavior associated with other psychiatric syndromes.[25,26] This interpretation is consistent with a well-documented literature on the frequency of nonpathologic and asymptomatic self-reported psychotic symptoms in the general population.[83–88] Future studies on subsequent course should address the impact of imposing additional phenomenological requirements such as distress, help seeking, and/or loss of functioning associated with the psychotic-like symptoms. Inclusion of indices of disturbance of the basic sense of self could potentially increase conversion rates as well.[89] In the meantime, the apparent recent attraction of higher proportions of low-risk patients to prodromal diagnostic evaluation stresses the importance of investigating low-risk treatment options, such as cognitive therapy[9] and medications other than antipsychotics.

Future studies should also address what proportion of the *general population* actually receive prodromal diagnoses on specialized structured interviews like the SIPS and what are the psychosis conversion rates in this group. The current normative data suggest that the proportion will be quite low, but NC subjects are prescreened for health and thus cannot estimate prevalence in the general population. Previous epidemiologic studies[83–88,90] unfortunately cannot address these questions directly. In the meantime, use of prodromal diagnostic assessments should be reserved for patients clinically referred specifically because of concerns about psychosis.

Conclusions

In this article, we have demonstrated that prodromal patients are not only distinguished from 3 comparison groups on risk for psychosis but also are more symptomatic and more impaired functionally relative to these groups. This dual status of patients meeting prodromal criteria, ie, both currently symptomatic and at risk for getting worse in the future,[91] is captured by our use of the term "risk syndrome." Our finding of an average GAF score in the 40s is supported by preliminary studies from other samples demonstrating that these young people have impairments more severe than treated patients who had already become psychotic.[3,6] Even without concerns about conversion, such impairment raises questions about need for treatment. Determining valid criteria for this syndrome should contribute to the development of appropriate treatments.

At some point during the research process, the diagnosis of the prodromal risk syndrome for psychosis may be ready for acceptance and codification for clinical use by psychiatric professional societies, such as in the *DSM* of the American Psychiatric Association. The present data allow the research diagnosis of the psychosis prodrome to move in that direction. Formal acceptance and codification need not imply that prodromal diagnostic criteria are "set into stone." Rather, the prodromal diagnosis should be subject to a continuous process of testing and refinement as are the established *DSM* diagnoses.

Should the prodromal risk syndrome for psychosis eventually be officially sanctioned, it will differ from many of the diagnoses currently used in *DSM-IV* in that it will be a "transitional" diagnosis, intended to be used for a limited period of time during the patient's life course and to be supplanted by other *DSM* diagnoses later, should their criteria be met. As a transitional diagnosis, the prodromal risk syndrome for psychosis would be akin to "mild cognitive impairment" as a prodromal risk syndrome for Alzheimer disease[92] or "clinically isolated syndromes" as prodromal risk syndromes for multiple sclerosis.[93] Apart from these medical examples, there is already some precedent in *DSM-IV* for transitional diagnoses that are expected over time either to remit or to progress or to be reclassified but not to endure. Examples in the psychotic disorders section include provisional cases of schizophreniform disorder and some cases of psychosis NOS. The concept of transitional diagnoses has much in common with proposals for "staging" psychiatric illness[94] and proposals for considering a developmental perspective in classifying disorders for *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (*DSM-V*).[95,96]

A *DSM-V* diagnosis of prodromal risk syndrome is supported by the evidence of validity presented here and by the patients' current need for treatment in addition to the high probability of illness progression. On the other hand, risks associated with a prodromal diagnosis must be taken into account as well.[19,97,98] Patients will be exposed to risks of any medications used, as well as the possibility of stigma or even discrimination from friends, families, community organizations, or insurance companies. Similar risks come with any diagnosis, but they become even more salient when a proportion of the patients are expected to remit spontaneously without treatment. Moreover, if a process of widening clinical indications for treatment without waiting for the results of well-designed clinical trials were accelerated by a *DSM-V* prodromal risk syndrome diagnosis, this process could

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increase patient exposure to risk. Lastly, sanctioning a prodromal diagnosis could contribute to the diagnosis being made inappropriately among populations where the criteria have not been carefully studied, and hence, the outcomes cannot be predicted, such as asymptomatic or general clinical populations.

Many of the risks of a prodromal diagnosis detailed above are aggravated by the paucity of research on outcomes and interventions in these patients. Inclusion of the prodromal risk syndrome in *DSM-V* is likely to stimulate research on these questions that in turn would reduce the risks of a prodromal diagnosis and enhance the benefits. Lastly, the problem of well-meaning clinical practice racing ahead of the research evidence is occurring even in the absence of a *DSM* prodromal risk syndrome diagnosis. It is not certain that a *DSM-V* diagnosis would accelerate the process, and it may actually ameliorate it by making criteria available that indicate who is not likely to be prodromal.

Supplementary Material

Supplementary tables S1 and S2 are available at http://schizophreniabulletin.oxfordjournals.org.

Funding

National Institute of Mental Health (U01 MH066160 to S.W.W., U01 MH066134 to J.A., R01 MH60720 and K24 MH76191 to K.S.C., R01 MH065079 to T.D.C., R01 MH061523 to B.A.C., U01 MH066069 and P50 MH064065 to D.O.P., R01 MH065562 and P50 MH080272 to L.J.S., R21MH075027 to M.T.T., RO1MH062066 to E.F.W., K05MH01654 to T.H.M.); Donaghue Foundation (to S.W.W.); Eli Lilly and Co (study HGGF to T.H.M., J.A., D.O.P.).

Acknowledgments

Dr Woods reports that he currently or in the past 12 months has received investigator-initiated research funding support from multiple not-for-profit entities including the NIMH, Donaghue, Stanley, and National Alliance for Research on Schizophrenia and Depression (NARSAD) foundations. In addition, he has received investigator-initiated research funding support from multiple for-profit entities including UCB Pharma, Pfizer, and Bristol-Myers Squibb and has consulted to Otsuka Pharmaceutical Co Ltdand Schering-Plough. Dr Woods reports that he has not served on speaker's bureaus. Dr Addington reports that she currently or in the past 12 months has received investigator-initiated research funding support from multiple not-for-profit entities including the NIMH and Ontario Mental Health Foundation. Dr Addington reports that she has served as a consultant for Pfizer and AstraZeneca. Dr Cadenhead reports that she currently or in the past 12 months has received investigator-initiated research funding support from the NIMH. Dr. Cannon reports that he currently or in the past 12 months has received investigator-initiated research funding support from multiple not-for-profit entities including the NIMH, the NASAD, and the Staglin Music Festival for Mental Health. Dr Cornblatt reports that she currently or in the past 12 months has received investigator-initiated research funding support from not-for-profit entities including the NIMH and the Stanley Medical Research Institute. She has also served as a consultant for Lilly, Bristol-Myers Squibb, and Janssen Pharmaceuticals and has received unrestricted educational grants from Janssen Pharmaceuticals. Dr Heinssen is an employee of the non-profit National Institutes of Health. He reports having no financial relationships with for-profit entities. In the past 12 months, Dr Perkins reports having received research funding from AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb, Otsuka Pharmaceutical Co Ltd, Eli Lilly and Co, Janssen Pharmaceutica Products, and Pfizer Inc and consulting and educational fees from AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb, Eli Lilly and Co, Janssen Pharmaceuticals, GlaxoSmithKline, Forest Labs, Pfizer Inc, and Shire. Dr Seidman reports that he currently or in the past 12 months has received investigator-initiated research funding support from multiple not-for-profit entities including the NIMH, the National Institute of Aging, the Commonwealth of Massachusetts Department of Mental Health, the National Association for Research in Schizophrenia and Depression, and Sidney R. Baer Foundation. Dr Tsuang reports that he has no financial relationships with for-profit or non-profit entities. Dr Walker reports that she currently or in the past 12 months has received investigator-initiated research funding support from not-for-profit entities including the NIMH and the NARSAD. She has not received funding from for-profit entities. Dr McGlashan reports that he currently or in the past 12 months has received investigator-initiated research funding support from not-for-profit entities including the NIMH; the University of Oslo in Norway; the University Hospital, Stavanger, Norway.

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