JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 15, Number 3, 2005

Pp. 418–433

Prospective Study of Adolescents with Subsyndromal Psychosis: Characteristics and Outcome

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ABSTRACT

Objective: **The aim of this study was to examine the characteristics and outcome of adolescents with psychotic disorder not otherwise specified (PsyNOS) and brief psychotic disorder (BrPsy), two neglected subsyndromal diagnostic entities.**

Methods: **As part of an ongoing, naturalistic study investigating adolescents considered to be prodromal for schizophrenia, 29 youngsters (mean age, 16.2 ± 2.7 years) with PsyNOS or BrPsy were identified as theoretically at highest risk for schizophrenia and followed for over 6 (mean, 22.8 ± 19.4) months.**

Results: **Contrary to our expectations, only 7 of the 26 individuals (27.0%) with follow-up data developed schizophrenia or schizoaffective disorder, and only 2 subjects (7.7%) retained their diagnosis of BrPsy/PsyNOS. The most frequent other diagnoses at follow-up were mood disorders (34.6%), personality disorders (11.5%), and obsessive-compulsive disorder (7.7%). Regarding severity of outcome, 38.5% of the patients progressed to a syndromal psychotic disorder, 23.1% continued to have attenuated positive symptoms, and 38.4% improved to having attenuated negative symptoms only, or no positive or negative symptoms. BrPsy was associated with lower maximum levels of negative symptoms ($p = 0.02$) and higher likelihood of symptom remission ($p = 0.02$).**

Conclusions: **This study indicates that psychotic symptoms not fulfilling criteria for schizophrenia or a psychotic mood disorder are unreliable predictors of a syndromal psychotic disorder outcome at 2 years. Long-term studies of PsyNOS and BrPsy are needed to clarify where these disorders fall in the developmental course of schizophrenia.**

INTRODUCTION

THE PRESENCE OF POSITIVE SYMPTOMS that are suprathreshold (i.e., clearly of psychotic intensity) but subsyndromal (i.e., not meeting full diagnostic criteria for schizophrenia, schizoaffective disorder, or a psychotic mood disorder) is of unclear predictive value for future outcome. In studies of psychosis, and especially schizophrenia, research attention has typically been directed at either the chronic illness or, more recently, the prodromal phase prior to the emergence of psychosis (i.e., when positive symptom severity remains subthreshold). As a result, there is very little information in the literature available to characterize suprathreshold,

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yet subsyndromal symptoms, especially their course and outcome in adolescents. Such symptoms are typically diagnosed as psychosis, not otherwise specified (PsyNOS), and treated inconsistently in research (if included at all). Occasionally, brief psychotic disorder (BrPsy) is diagnosed when there is a sudden onset of the psychotic symptom(s), the episode lasts at least 1 day and less than 1 month, and the individual eventually has a full return to the premorbid level of functioning (American Psychiatric Association 1994). The course of BrPsy and its relationship to the schizophrenia spectrum is similarly under-researched. In this paper, the characteristics of PsyNOS and BrPsy and their predictive value for developing a schizophrenia spectrum disorder will be evaluated.

The need to clarify both constructs is apparent throughout the literature. For example, in the recently emerging field of early intervention in schizophrenia, suprathreshold subsyndromal psychotic symptoms are sometimes considered to be "late prodromal" symptoms (McGlashan et al. 2003; Woods et al. 2003) and sometimes considered to indicate "psychosis outcome" (i.e., and lumped together with fully defined schizophrenia; Yung et al. 1998; McGorry et al. 2003). At present, no evidence is available to justify either system of categorization, and diagnostic inconsistency introduces unrecognized confounds into prodromal studies. Similarly, there is little clear evidence to indicate the relationship between these symptoms and later emerging bipolar disorder. Understanding the risk for major psychotic illnesses associated with PsyNOS and BrPsy is thus critical for treatment and for possible prevention (or, at minimum, early intervention) in both major illnesses. In turn, the extent to which PsyNOS is a clinical end state that develops and remains independent of both schizophrenia and bipolar disorder is an equally unestablished possibility.

Even though PsyNOS and BrPsy can be conceptualized as the most proximal, latest prodromal stage on the trajectory to schizophrenia, these two entities have not been studied as a separate group in prodromal schizophrenia research, except in the Zucker Hillside Hospital Recognition and Prevention (RAP) Program (Glen Oaks, NY) (Correll and Kane 2004). This is surprising, as PsyNOS and BrPsy may be similar to prodromal symptoms in their relative nonspecificity (for outcome prediction), while, at the same time, raising fewer ethical concerns about preventative interventions in the prodromal phase. Ethical concerns include stigmatization, provocation of anxiety and stress in mislabeled individuals, and "unnecessary" treatment of false-positive subjects with medications that carry the potential for significant adverse effects (Cornblatt et al. 2001; McGlashan 2001; McGorry et al. 2001).

To date, most other prodromal schizophrenia research groups have lumped subjects exhibiting psychotic symptoms of self-limited duration of either 6 days (Yung et al. 1998; McGorry et al. 2003) or 3 days per week (McGlashan et al. 2003; Woods et al. 2003) together with the group of individuals that have attenuated (subpsychotic) symptoms. On the other hand, subjects with psychotic symptoms that are present for more than 1 week, again fulfilling *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria for PsyNOS or BrPsy, have also been considered to be a psychosis "outcome" group, primarily because they clinically require interventions (McGorry et al. 2002). However, this adds to the diagnostic confusion, as it is unclear what the final diagnosis will be for patients fulfilling criteria for PsyNOS or BrPsy, or the extent to which they are at-risk for the development of schizophrenia. As a result, we propose that patients meeting criteria for PsyNOS or BrPsy are an intermediate category between the prodrome and full-blown psychosis, possibly representing the stage just preceding schizophrenia in some patients (see Fig. 1).

Potentially conflicting with this view, several studies in adults have documented the lack of stability and prognostic power of a diagnosis of PsyNOS as well as BrPsy. One of the reasons may be that psychosis-like symptoms have been found to occur in up to 50% of nonclinical, community samples (Eaton et al. 1991; Kendler et al. 1996; McGee et al. 2000; McGorry et al. 1995; Ohayon 2000; Poulton et al. 2000; Tien 1991; Ulloa et al. 2000; van Os et al. 2000, 2001; Verdoux et al. 1998). An additional problem is that conflicting results have been reported

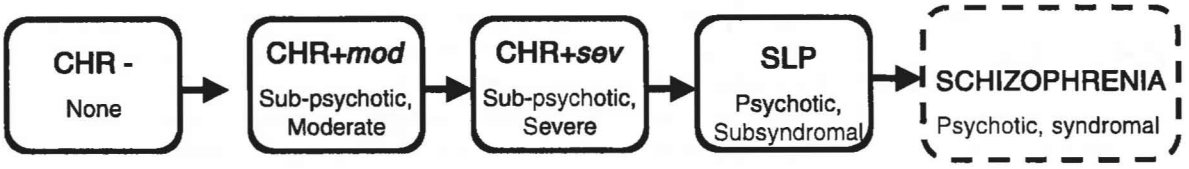

FIG. 1. RAP program diagnostic model of clinical high risk (CHR). Stages differentiated by degree of positive symptomatology as noted. RAP, recognition and prevention; SLP, schizophrenia-like psychosis, including psychotic disorder not otherwise specified and brief psychotic disorder.

from follow-up studies on the outcome of youths with self-reported psychotic symptoms. Two smaller studies with long follow-up durations of 17 years (Gerralda 1984) and 8 years (Dhossche et al. 2002) found no relationship between self-reported hallucinations and future psychotic disorders. However, it is possible that the lack of predictive value for future syndromal psychotic disorders could have been the result of a selective attrition of subjects with more severe outcomes. By contrast, a birth cohort study of 716 children (Poulton et al. 2000) found that self-reported psychotic symptoms at 11 years of age predicted a risk for schizophreniform disorder at 26 years of age (odds ratio of 16.4; 95% confidence interval: 3.9–67.8). In another sample of hallucinating pediatric inpatients with strong family histories of psychosis, 20% had suffered an acute psychosis and another 28% had developed atypical psychoses (Del Beccoro et al. 1988) after a mean of 4 years of follow-up.

Data from clinical samples also suggest that the outcome of subjects meeting criteria for PsyNOS or BrPsy is highly variable. In trials with average follow-up periods of 1–4 years, diagnostic stability ranged from 23% to 87.5% (Fennig et al. 1995; Jorgensen et al. 1996; Kumra et al. 1998; McClellan and McCurry 1999; Nicolson et al. 2001; Pillmann et al. 2002; Sajith et al. 2002; Schwartz et al. 2000; Susser et al. 1995). In these prospective studies, PsyNOS has been observed to be a precursor state for the future development of a schizophrenia spectrum disorder in 0%–50.0% of patients. However, between 11% and 39% of patients were also found to end up with a diagnosis of mood disorders or personality disorders. To date, only one group has reported on comorbidities in children with PsyNOS (Kumra et al. 1998; Nicolson et al. 2001). In general, there was a high rate of comorbidity, consisting mainly of attention-deficit/hyperactivity disorder and disruptive behavior disorders (65.4% each). Information about comorbidity is relevant, as comorbid conditions affect treatment and may also mediate the risk to future psychosis. Nevertheless, few, if any, previous studies have indicated rate and type of comorbid disorders at baseline or the extent to which these diagnoses are stable or tend to covary with changes in positive symptom severity.

Despite the conflicting data about diagnostic stability and outcome of PsyNOS or BrPsy, several studies seem to suggest a biological resemblance to schizophrenia. While the heterogeneous outcome of PsyNOS was reconfirmed in the Irish Roscommon Family Study (Kendler and Walsh 1995), it was also observed that PsyNOS patients closely resembled schizophrenia with respect to symptoms, familial psychopathology, and outcome. Similarly, Kumra et al. (1998) compared treatment-refractory, "multidimensionally impaired" pediatric PsyNOS patients with those having very early-onset schizophrenia (i.e., before 12 years of age), and found that both groups showed elevated rates of schizophrenia spectrum disorders among first-degree relatives. These investigators further identified similarities between PsyNOS and schizophrenia in terms of clinical features, cognitive deficits, and biological correlates, such as brain morphology and smooth pursuit eye movements (Kumra et al. 1998, 2000, 2001). Genetic and cognitive similarities have also been recently reported by other groups investigating young, early-onset psychosis patients (Addington et al. 2004; McClellan et al. 2004).

To summarize, although the unclear nature of subsyndromal psychosis presents a diagnostic and treatment challenge to clinicians and researchers alike, PsyNOS and BrPsy have

been neglected in research, particularly by the prodromal schizophrenia field. Thus far, researchers have not reported why patients diagnosed as PsyNOS and BrPsy failed to meet criteria for schizophrenia. Further, limited information is available on the presence of psychiatric comorbidities. Finally, none of the studies focusing on patients considered to be at-risk for schizophrenia has separately studied subjects with suprathreshold psychotic symptoms.

The aim of this paper is to provide initial data characterizing PsyNOS and BrPsy within the context of a naturalistic schizophrenia prodrome study. Specific focus will be directed to the following issues: (1) the clinical characteristics associated with these diagnoses; (2) presence and course of comorbid conditions, and (3) the outcome and stability of PsyNOS and BrPsy in adolescents and young adults. Lack of stability in this case involves both progression to fully specified psychotic disorders, as well as improvement or remission in positive symptomatology. In the absence of relevant prodromal outcome literature regarding patients with PsyNOS or BrPsy and based on the theoretical notion that these psychotic conditions are most proximal to schizophrenia, we hypothesized that individuals with these conditions are likely to progress to schizophrenia or, at best, retain their diagnosis of PsyNOS or BrPsy.

METHODS

Recruitment procedures

Individuals in this study represent a consecutively enrolled subsample drawn from a large prospective, naturalistic study, currently underway at the Zucker Hillside Recognition and Prevention (RAP) Program. The RAP program, under the direction of Dr. Barbara Cornblatt, focuses on the course and outcome of help-seeking adolescents considered to be prodromal for schizophrenia. The treatment arm of the program is the RAP clinic. Pharmacologic treatment follows a naturalistic, symptom-based framework that is derived from the patient's clinical need and best-practice guidelines, without influence by the research staff or procedures. Psychosocial treatment is available to all participants, including family, group, or individual therapy, or some combination of the three. The RAP program and clinic have been described in detail in previous reports (Cornblatt 2002; Cornblatt et al. 1998, 2002, 2003; Lencz et al. 2003, 2004).

Subjects

Subjects included in this study were youths 12–22 years of age with a DSM-IV diagnosis of PsyNOS or BrPsy. Although diagnosis of PsyNOS is often used tentatively in clinical settings to reflect the absence of sufficient diagnostic information, this study utilized specific criteria for inclusion in this category. Diagnoses were based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Version (K-SADS-E; Orvaschel and Puig-Antich 1994) and the Scale of Prodromal Symptoms (SOPS), a novel instrument designed to specifically assess attenuated schizophrenia-like symptomatology for identifying prodromal states (McGlashan et al. 2001; Miller et al. 2002). Ratings are based on information that is elicited by the companion interview, the Structured Interview for Prodromal Symptoms (SIPS) (McGlashan et al. 2001; Miller et al. 2002). The SOPS contains detailed anchors in order to quantify degree of psychotic-like symptomatology in five domains: Unusual thought content, suspiciousness, grandiosity, perceptual abnormalities, and conceptual disorganization. For subjects indicating psychotic-level positive symptomatology on the SOPS (e.g., unusual beliefs with full delusional conviction), the K-SADS-E was used to carefully delineate DSM-IV criteria for schizophrenia. In addition to the presence of psychosis, inclusion criteria for the present study were any one or a combination of the following: (1) failure to meet A criteria for schizophrenia, owing to the presence of only one nonbizarre psychotic symptom; (2) failure to meet B criteria for schizophrenia, owing to sustained adequate role functioning; or (3) failure to meet C criteria for schizophrenia, owing to sporadic, noncontinuous episodes. Note that it was possible for some subjects to meet more than one of these

inclusion criteria for this study. Subjects meeting the third criterion, reflecting short duration, all met criteria for brief psychotic disorder and are so labeled, regardless of whether there was a single episode or multiple brief episodes. It should further be noted that none of these subjects met criteria for schizophreniform disorder, or for any other specified DSM-IV psychotic disorder (such as schizoaffective disorder, bipolar disorder with psychotic features, major depressive disorder (MDD) with psychotic features, or substance-induced psychotic disorder), which were all exclusionary criteria.

These criteria were developed within the RAP program as part of a larger developmental model of risk for schizophrenia (Cornblatt 2002; Cornblatt et al. 1998, 2002, 2003; Lencz et al. 2003, 2004). Although details are outside the scope of this report, we have defined clinical high risk (CHR) for schizophrenia on the basis of the presence of attenuated levels of negative and positive schizophrenia-like symptoms, as measured primarily by the SOPS. As shown in Fig. 1, there are three nonpsychotic risk groups: CHR− subjects have attenuated negative symptoms only (e.g., social isolation) and no positive symptoms even in attenuated form; CHR+ subjects are marked by attenuated (subthreshold psychotic) positive symptoms, such as suspiciousness, unusual thought content, and perceptual aberrations, which can be further quantified as moderate (i.e., CHR + mod: SOPS total positive sum score less than 10) or severe (i.e., CHR + sev: SOPS total positive sum score of at least 10) in degree. All patients in this study are members of the fourth clinical risk group, marked by subsyndromal psychotic symptoms, referred to as SLP (schizophrenia-like psychosis). One of the primary interests of the RAP research program is to chart the developmental course of the disorder, beginning at the negative symptom stage, which is presumably least severe, and continuing through the gradual emergence and increasing severity of positive symptoms. The subjects in the fourth RAP program subgroup, with positive symptoms that have just passed into psychosis and that are closest to schizophrenia in terms of positive symptom severity, make up the sample in this study.

Patients were recruited between January 1998 and January 2004. Diagnostic interviews were first administered to the parent or legal guardian to provide information useful for probes when interviewing the patients, and to alleviate patients' potential concerns about confidentiality. Following the informant's interview, the same rater interviewed the patient and sought to clarify any discrepancies with the parental information. All interviews were administered by trained masters or doctoral-level psychologists. In addition to inclusion criteria noted above, reasons for excluding patients from the study included: (1) history of neurological, neuroendocrine, or other medical condition known to affect the brain; (2) IQ below 70; and (3) severe or imminent risk of harm to self or others, as obtained from the clinical interview. The research protocol was approved by the Institutional Review Board at the Long Island Jewish Medical Center, and potential subjects were informed that treatment in the RAP Clinic was in no way contingent upon participation in the RAP research program, and that the treatment decisions would always be made by the treating clinicians in the best interests of the patient regardless of research participation. Written, informed consent was obtained from the patient if 18 years of age or older, or from the parent (with written assent from the patient) if under 18 years.

Baseline assessments

Demographic and background information were obtained from the informant and included past treatment history and socioeconomic status (SES), which was categorized according to Hollingshead (1957), ranging from 1 (highest) to 5 (lowest). Patients underwent diagnostic assessments for DSM-IV Axis I and Axis II disorders, using the K-SADS-E and the SIDP-IV (Pfohl et al. 1995), respectively. Presence and severity of positive and negative psychotic symptoms, including subthreshold, attenuated levels, were rated using the SOPS, based on information elicited during its companion interview, the SIPS ($n = 20$), or on the basis of all other available information for those subjects who had entered the study before the development of the SIPS ($n = 9$). Furthermore, patients also underwent IQ

testing, using the Wechsler Adult Intelligence Scale—Revised (WAIS-R; Wechsler 1981) for youngsters 16 years of age and older and the Wechsler Intelligence Scale for Children—3rd Edition (WISC-III; Wechsler 1991) for subjects 12–15 years of age. Full-scale IQ was estimated with a two-subtest short form, using Vocabulary and Block Design Subtests. These two subtests, individually, have excellent reliability and correlate highly with the Full-scale IQ over a wide age range. The IQ estimate derived from these scores has satisfactory reliability (r = 0.91) and validity (r = 0.86) (Sattler 2001).

Follow-up assessments

This report includes 29 youngsters with complete baseline and diagnostic data. Three of the 29 patients were excluded from the prospective analyses, as they were either lost to follow-up (n = 2) or are still actively followed at the time of the analyses, but for less than 6 months (n = 1). For each of the remaining 26 subjects with at least 6 months of follow-up, prodromal outcome diagnoses (CHR− or CHR+; see Fig. 1) were assigned based on SOPS item anchors. All other diagnoses were based on DSM-IV criteria. We have previously reported high reliability both for individual item ratings from SOPS, as well as 100% concordance of the consensus ratings for each prodromal and psychotic symptom outcome stage (Lencz et al. 2004). Follow-up consensus ratings in the 26 patients were made unblind to baseline diagnoses and on the basis of all available clinical information from three sources: Clinician reports, telephone interviews, and in-person follow-up interviews of patients and/or their caregivers. As part of the routine RAP procedures, all prodromal and DSM-IV baseline and follow-up diagnoses were subsequently validated by independent, blind consensus diagnosticians. Follow-up ratings were made approximately 6 months after entry to the RAP Program, and regularly every 6–9 months, as well as at termination of treatment or conversion to a syndromatic psychotic disorder, such as schizophrenia, schizoaffective disorder, or bipolar disorder with psychotic features.

Statistical analysis

Distribution of baseline data was analyzed using descriptive statistics. Between-group comparisons of continuous variables (e.g., age, duration of follow-up, symptom severity) were performed using analyses of variance (ANOVAs). Between-group comparisons of dichotomized or categorical variables were performed using either chi-square statistics, or Fischer's Exact Test, whenever individual numbers per cell were too small to use chi-square statistics. Whenever subjects had missing data, statistical tests on that variable were only performed on subjects with complete information and only when less than 50% of subjects in any given group had missing data. For analyses of outcome data, only patients with at least six months of follow-up were used, unless conversion to a syndromal psychotic disorder took place as a primary endpoint before this time (n = 3).

RESULTS

Baseline characteristics

To date, 151 adolescents and their parents have provided research consent, completed all baseline research procedures, and have been prospectively followed as part of the Zucker Hillside Hospital Recognition and Prevention (RAP) Research Program. Of these participants, 29 (19.2%) were diagnosed with either PsyNOS (n = 24) or BrPsy (n = 5). The mean age of this sample (PsyNOS plus BrPsy) was 16.2 ± 2.7 (range, 12–22) years, 65.5% were male, 48.3% were Caucasian, and the mean IQ was 96.5 ± 19.2 (see Table 1).

As indicated in Table 1, when the PsyNOS and BrPsy subgroups were compared, few differences were found. As a result, findings will be discussed primarily for the combined sample. Across the combined sample, the majority of patients (n = 25; 86.2%) had only one psychotic symptom and, thus, failed to meet criterion A for schizophrenia. Thirteen patients (44.8%) had nonbizarre delusions only, 10 (34.5%) had only hallucinations, and two youngsters (6.9%) had only thought disorder at a psychotic level. All but 6 patients

TABLE 1. BASELINE CHARACTERISTICS FOR 29 YOUTHS WITH PSYCHOTIC DISORDER NOT OTHERWISE SPECIFIED AND BRIEF PSYCHOTIC DISORDER

Baseline characteristic	*Total (n = 29)*	*Psychotic disorder not otherwise specified (n = 24)*	*Brief psychotic disorder (n = 5)*	F/χ^2	*p value*
Mean Age (years ± SD)	16.2 ± 2.7	15.8 ± 2.5	18.1 ± 3.2	3.11	0.09
Male Gender (*n*, %)	19 (65.5)	15 (62.5)	4 (80.0)	0.60	0.44
Ethnicity (*n*, %):				**8.48**	**0.04**
Caucasian	14 (48.3)	13 (54.2)	1 (20.0)	1.93	0.16
African-American	7 (24.1)	7 (29.2)	0 (0.0)	1.92	0.17
Hispanic	6 (20.7)	3 (12.5)	3 (60.0)	**5.69**	**0.02**
Asian	2 (6.9)	1 (4.2)	1 (20.0)	1.61	0.20
Education (years ± SD)	9.9 ± 2.1	9.6 ± 2.1	11.4 ± 2.0	3.21	0.09
IQ (mean ± SD)[a]	96.5 ± 19.2	98.5 ± 19.4	87.3 ± 18.2	1.12	0.30
Socioeconomic Status[a]	2.3 ± 1.0	2.2 ± 0.9	2.8 ± 1.5	1.49	0.23
A criteria for SCZ Not Met (*n*, %)	25 (86.2)	22 (91.7)	3 (60.0)	3.49	0.06
Delusions only	13 (44.8)	10 (41.7)	3 (60.0)	0.56	0.45
Hallucinations only	10 (34.5)	10 (41.7)	0 (0.0)		
Thought d/o only	2 (6.9)	2 (8.3)	0 (0.0)		
B criterion for SCZ Not Met (*n*, %)	6 (20.7)	4 (16.7)	2 (40.0)	1.21	0.27
C criterion for SCZ Not Met (*n*, %)	5 (17.2)	0 (0.0)	5 (100.0)	**29.0**	**<0.0001**
Total SOPS Positive Score (mean ± SD)	14.5 ± 4.6	14.8 ± 4.7	13.4 ± 4.3	0.71	0.50
Highest SOPS Negative Score (mean ± SD)[b]	4.0 ± 1.6	4.3 ± 1.4	2.4 ± 2.3	**6.09**	**0.02**

SCZ = schizophrenia; SOPS = Scale of Prodromal Symptoms; SD = standard deviation.
[a]data available for 22 subjects
[b]total negative SOPS scores are not available for this population

(79.3%) met criterion B requiring deterioration in psychosocial, academic, or vocational functioning. The majority of subjects (82.8%; all but 5), fulfilled criterion C, of 1 month or more duration of psychotic symptoms. All PsyNOS subjects met criterion C, whereas none of those with BrPsy did so (χ^2: 29.0; $p < 0.0001$). Consistent with the presence of suprathreshold psychotic symptoms (i.e., at least one item with a positive symptom SOPS score of a 6), the mean total SOPS positive symptom score of 14.5 ± 4.6 was relatively high (maximum score, 25). No comparable requirement was made for negative symptoms. Nevertheless, patients in this population had a mean maximum negative symptom score of 4.0, which falls within the moderately severe range. As shown in Table 1, BrPsy patients evidenced a significantly lower maximum SOPS negative symptom score (maximum score, 6) compared to PsyNOS subjects (χ^2: 6.09; $p < 0.02$).

In addition to being diagnosed with PsyNOS or BrPsy, all but two patients (93.1%) had a wide array of lifetime, nonpsychotic, comorbid diagnoses (mean number of comorbid diagnoses, 2.5 ± 2.1; range, 0–9; see Table 2). Roughly half of the sample met criteria for a lifetime diagnosis of nonpsychotic depressive disorders. As shown in Table 2, other common comorbidities included personality disorders, anxiety disorders, disruptive behavior disorders, and attention-deficit hyperactivity disorder. On the other hand, substance use disorders, adjustment disorders, Asperger's disorder, and mood disorder NOS were relatively infrequent.

Treatment characteristics of youths with follow-up of at least 6 months

On average, the combined sample has been prospectively followed for close to 2 years (mean, 22.8 ± 19.8 months). Treatment charac-

TABLE 2. BASELINE DSM-IV COMORBID DISORDERS

No. of comorbid disorders (mean ± SD)	*2.5 ± 2.1*
Diagnostic category	*n (%)*
Depressive Disorder	15 (51.7)
major depressive disorder	9 (31.0)
depressive disorder NOS	6 (20.7)
Personality Disorder[a]	13 (44.8)
Cluster A	11 (37.9)
Cluster B	3 (10.3)
Cluster C	5 (17.2)
Anxiety Disorder[a]	10 (34.5)
obsessive compulsive disorder	6 (20.7)
generalized anxiety disorder	4 (13.8)
anxiety disorder NOS	4 (13.8)
social/specific phobia	3 (10.3)
posttraumatic stress disorder	1 (3.5)
Oppositional Defiant/Conduct Disorder	10 (34.5)
Attention-Deficit/Hyperactivity Disorder	8 (30.8)
Adjustment Disorder	2 (6.9)
Substance Use Disorder	2 (6.9)
Mood Disorder NOS	1 (3.5)
Asperger's Disorder	1 (3.5)

DSM-IV = The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; SD = standard deviation; NOS = not otherwise specified.

[a]Sum of percentages for subdiagnoses are greater than for the overall category owing to several subjects meeting criteria for more than one subdiagnoses within a category.

teristics of all adolescents with follow-up data of at least 6 months are summarized in Table 3. After admission into the RAP program, the majority of subjects (89.7%) received psychotropic medications at least at some point during their follow-up; the remaining patients (10.3%) refused treatment. Most of the treated youths received second-generation antipsychotic drugs (80.8%), predominantly in combination with other medications (57.7%). However, patients were also treated frequently with antidepressants (57.7%). By contrast, relatively few patients received treatment with agents other than antipsychotics or antidepressants, although there was some use of anxiolytics ($n = 4$; 13.8%), psychostimulants ($n = 4$; 13.8%), and mood stabilizers ($n = 2$; 6.9%). The mean duration of psychotropic treatment was 14.1 ± 14.5 months. More than half (56.5%) of the combined sample with available information became noncompliant with treatment. At follow-up, only 38.5% of subjects were taking any type of psychotropic medication.

Diagnostic and symptomatic outcome in youths with follow-up of at least 6 months

Table 4 shows the diagnostic outcome for 26 youths with follow-up of 6 months or more. Follow-up ratings include both DSM-IV criteria and the level of positive and negative psychotic symptoms, based on SOPS scores (i.e., the stages identified in Fig. 1). There was very little diagnostic stability observed with follow-up. None of the patients receiving a baseline diagnosis of PsyNOS had that same diagnosis at follow-up. Only 2 of the 26 subjects (7.7%) did not develop any other Axis I or Axis II diagnosis and "retained" their initial diagnosis, both having been diagnosed with BrPsy at baseline and at follow-up.

Broadly speaking, the sample was divided into subjects who deteriorated to a specified psychotic disorder over the follow-up period (38.5%), those who showed some moderate improvement in positive symptoms (23.1%), and those who showed considerable improvement (38.4%). In those who deteriorated, schizophrenia was the most common outcome (23.1%), though 1 subject (3.9%) developed schizoaffective disorder and another 3 subjects (11.5%) developed bipolar disorder with psychotic features. Six youths (23.1%) were minimally or moderately improved, as they were found to have attenuated, but no suprathreshold positive symptoms. Ten youngsters (38.5%) improved much or very much, being free of psychotic symptoms at follow-up; of these, half (5 subjects) had residual attenuated negative symptom, while the other half had no discernable subsyndromal psychotic-like symptoms of the positive or negative variety. A greater percentage of BrPsy subjects (75.0%) were symptom-free at follow-up, as compared to PsyNOS patients (9.1%) (Fisher's Exact Test; $p < 0.02$).

These outcomes did not seem to be affected by rates of treatment nonadherence. In the 22 subjects with available information on adherence (defined as an interruption of pharmacological or nonpharmacological treatments for

TABLE 3. TREATMENT CHARACTERISTICS OF 26 YOUTHS WITH PSYCHOTIC DISORDER NOT OTHERWISE SPECIFIED AND BRIEF PSYCHOTIC DISORDER FOLLOWED FOR AT LEAST 6 MONTHS

Treatment characteristic	*Total (n = 26)*	*Psychotic disorder not otherwise specified (n = 22)*	*Brief psychotic disorder (n = 4)*	*F/χ²*	*p value*
Duration Follow-Up (Months ± SD)	22.8 ± 19.8	22.5 ± 20.6	24.5 ± 13.0	0.04	0.85
Duration of Psychotropic Treatment (Months ± SD)[a]	14.1 ± 14.5	13.3 ± 14.7	18.9 ± 12.3	0.39	0.54
Psychotropic Treatment (*n*, %):				3.54	0.62
Antipsychotics alone	6 (23.1)	4 (18.2)	2 (50.0)		
Antidepressants alone	2 (7.7)	2 (9.1)	0 (0.0)		
Antipsychotics + antidepressants	6 (23.1)	6 (27.3)	1 (25.0)		
Antipsychotics + antidepressants + others[b]	7 (26.9)	6 (27.3)	1 (25.0)		
Antipsychotics + mood stabilizers	2 (7.7)	2 (9.1)	0 (0.0)		
None	3 (11.5)	3 (13.6)	0 (0.0)		
Medication Nonadherent (*n*, %)[c]	13 (56.5)	11 (57.9)	2 (50.0)	0.08	0.77
Treatment Status at Endpoint (*n*, %):				2.63	0.62
Antipsychotics alone	3 (11.5)	2 (9.1)	1 (25.0)		
Antidepressants alone	3 (11.5)	3 (13.6)	0 (0.0)		
Antipsychotics + antidepressants	3 (11.5)	2 (9.1)	1 (25.0)		
Off all psychotropic medications	16 (61.5)	14 (63.6)	2 (50.0)		
Unknown	1 (3.9)	1 (4.6)	0 (0.0)		

[a]Data available for 21 subjects
[b]Others: Anxiolytics/sedative hypnotics and psychostimulants
[c]Data available for 23 subjects

TABLE 4. OUTCOME IN 26 YOUTHS WITH SUBSYNDROMAL PSYCHOSIS FOLLOWED FOR AT LEAST 6 MONTHS BASED ON SOPS PSYCHOTIC SYMPTOM SEVERITY AND CONVERSION TO A DSM-IV SYNDROMAL PSYCHOTIC DISORDER

Outcome	*Categorical change*	*Total (n = 26)*	*PsyNOS (n = 22)*	*BPsy (n = 4)*	*p value*[b]
Syndromal Psychotic Disorder	*Much to very much worse*	**10 (38.5)**	**9 (40.9)**	**1 (25.0)**	1.00
Schizophrenia		6 (23.1)	5 (22.7)	1 (25.0)	
Schizoaffective disorder		1 (3.9)	1 (4.5)	0 (0.0)	
Bipolar disorder with psychotic features		3 (11.5)	3 (13.6)	0 (0.0)	
Severe[a] Attenuated Positive Symptoms	*Minimally improved*	**1 (3.9)**	**1 (4.5)**	**0 (0.0)**	—
Personality disorder[d]		1 (3.9)	1 (4.5)	0 (0.0)	
Moderate[c] Attenuated Positive Symptoms	*Moderately improved*	**5 (19.2)**	**5 (22.7)**	**0 (0.0)**	—
Bipolar disorder not otherwise specified		1 (3.9)	1 (4.5)	0 (0.0)	
Major depressive disorder w/o psychosis[d]		2 (7.7)	2 (9.1)	0 (0.0)	
Obsessive-compulsive disorder[d]		1 (3.9)	1 (4.6)	0 (0.0)	
Asperger's disorder[d]		1 (3.9)	1 (4.6)	0 (0.0)	
Attenuated Negative Symptoms Only	*Much improved*	**5 (19.2)**	**5 (22.7)**	**0 (0.0)**	—
Personality disorder[d]		2 (7.7)	2 (9.1)	0 (0.0)	
Anxiety disorder not otherwise specified[d]		1 (3.9)	1 (4.5)	0 (0.0)	
Obsessive-compulsive disorder[d]		1 (3.9)	1 (4.5)	0 (0.0)	
Attention-deficit/hyperactivity disorder[d]		1 (3.9)	1 (4.5)	0 (0.0)	
No Subsyndromal Psychotic Symptoms	*Very much improved*	**5 (19.2)**	**2 (9.1)**	**3 (75.0)**	0.014
Brief psychotic disorder (remitted)[d]		2 (7.7)	0 (0.0)	2 (50.0)	
Major depressive disorder w/o psychosis[d]		3 (11.5)	2 (9.1)	1 (25.0)	

SOPS = Scale of Prodromal Symptoms; DSM-IV = The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; PsyNOS = psychotic disorder not otherwise specified; BPsy = brief psychotic disorder.
[a]SOPS positive psychotic symptom score ≥10
[b]Fischer's Exact Test
[c]SOPS positive psychotic symptom score <10
[d]Diagnoses already present at baseline

at least 1 month), nonadherence rates for patients who progressed to a syndromal psychotic disorder, or who showed moderate or considerable improvement in positive symptoms, were 57.1%, 80.0% and 60.0%, respectively ($p = 0.665$).

Comorbid diagnoses were present at both baseline and at the follow-up ratings and appeared to be independent of, and considerably more stable than, positive symptoms. Sixteen subjects (61.5%) had improved positive symptoms but, at follow-up, displayed a comorbid disorder, often the same as diagnosed at intake. As at baseline, DSM-IV follow-up diagnoses included primarily major depressive disorder, a personality disorder, and obsessive-compulsive disorder. Of all follow-up diagnoses, 57.7% had been present at baseline. It should be noted that the 2 subjects who retained the diagnosis of BrPsy evidenced no symptomatology at outcome and were considered BrPsy on the basis of previous episodes only.

DISCUSSION

This is the first study of individuals with PsyNOS and BrPsy conducted within the framework of the schizophrenia prodrome. It is also the first to report on both diagnostic and positive symptom severity outcome. As mentioned earlier, individuals with these diagnoses have been classified inconsistently by prodromal research groups, considered by some to be a primary psychotic endpoint and by others to be a prodromal subgroup. We have followed this group of patients longitudinally as a separate and theoretically enriched high-risk group (intermediate between the psychotic prodrome consisting of attenuated positive symptoms and syndromal psychosis).

The main finding of this study was that, contrary to our hypothesis, only 38.5% of patients progressed to a syndromal psychotic disorder (27.0% with schizophrenia or schizoaffective disorder and 11.5% with psychotic bipolar disorder). In addition, there was very little diagnostic stability for PsyNOS and BrPsy when followed for 6 months or more. Rather than progressing to schizophrenia or stabilizing at a subsyndromal psychotic level, positive symptom severity improved, in most patients, over time; 23.1% of patients had only attenuated, subthreshold positive symptoms, and 38.4% of patients had only attenuated negative symptoms or no psychotic symptoms at follow-up. This outcome was observed, even though at least 61.5% of patients were not receiving any psychotropic medications at follow-up, mostly because of nonadherence to treatment. While positive psychotic symptoms were unstable over time, the presence and persistence of comorbid psychiatric disorders was high, with the most frequent primary follow-up diagnoses consisting of mood disorders, followed by personality disorders and obsessive-compulsive disorder. Additional findings of this study include: (1) The overwhelming majority of youths with PsyNOS or BrPsy failed to meet the diagnosis of schizophrenia at baseline because only one psychotic symptom was present; (2) BrPsy was associated with significantly lower maximum levels of attenuated negative symptoms at baseline; and (3) Patients with BrPsy had a significantly higher likelihood of symptom remission than patients with PsyNOS. Of particular interest were the findings addressing the three issues raised at the outset of this paper: (1) outcome/stability; (2) comorbidity; and (3) the nature of the subsyndromal psychosis.

Outcome/diagnostic stability

Contrary to our expectations, most adolescents with PsyNOS or BrPsy did not develop schizophrenia over a mean of 2 years. Moreover, most patients had no suprathreshold psychotic symptoms at endpoint. Considered overall, these findings support our model indicating that PsyNOS and BrPsy individuals are a distinct group in their own right that must be separately identified and prospectively followed. The diverse outcomes and lack of diagnostic stability in our sample suggest that neither type of patients should be categorized as a psychosis outcome, on the one hand, or a subpsychotic prodrome, on the other.

While the conversion rate to schizophrenia or schizoaffective disorder of 27.0% found in our study is in the middle of previously reported

frequencies in clinical samples (i.e., 0%–50%) (Fennig et al. 1995; Jorgensen et al. 1996; Kumra et al. 1998; McClellan and McCurry 1999; Nicolson et al. 2001; Pillmann et al. 2002; Sajith et al. 2002; Schwartz et al. 2000; Susser et al. 1995), this is the first study to report on the outcome of patients with PsyNOS or BrPsy selected for being putatively prodromal for schizophrenia. The wide range of conversion rates found in previous studies underscores the relevance of differences in sample selection and recruitment procedures. However, the fact that only 38.5% of patients progressed to a syndromal psychotic disorder suggests a relative nonspecificity of positive psychotic symptoms, which are not severe enough in symptom domain, duration, or impact on psychosocial or educational-vocational functioning to fulfill criteria for schizophrenia. The nonprogression to a syndromal psychotic disorder in our "enriched" sample (i.e., thought to be at especially high risk for schizophrenia) could be the result, at least in part, to the still relatively short follow-up period or the effectiveness of naturalistic treatment. However, because the majority of patients in our sample did not receive any treatment at follow up, a significant treatment effect seems less likely. An alternative explanation is that psychotic symptoms are the product of multiple underlying and biologically diverse mechanisms, and that the risk for the persistence or worsening of these psychotic symptoms is altered by environmental factors that need to be elucidated further.

In this regard, a symptomatic overlap with Asperger's disorder (Wolff 1991) or borderline personality traits (Miller et al. 1993; Schulte-Markwort and Schimmelmann 2004), could add to the nonspecificity of subsyndromal psychotic symptoms. In addition, the nonspecificity of psychotic symptoms may be accentuated in adolescents where biological, psychological, and social processes are still very dynamic (Menezes and Milovan 2000; Reimherr and McClellan 2004).

Although the lack of diagnostic stability of PsyNOS and BrPsy in the majority of our sample is consistent with the previous literature in mixed clinical samples (Fennig et al. 1995; Jorgensen et al. 1996; Kumra et al. 1998; McClellan et al. 1999; McClellan and McCurry 1999; Nicolson et al. 2001; Pillmann et al. 2002; Sajith et al. 2002; Schwartz et al. 2000; Susser et al. 1995), the overall diagnostic stability rate of only 7.7% is lower than rates reported to date that ranged from 23% to 87.5%. This difference could be explained by a selection bias, because the aim of our study was to recruit patients at high risk for conversion to schizophrenia, which implies a focus on the dynamic nature of the symptomatology. Moreover, help-seeking patients took part in a treatment program that included psychotropic medications, psychoeducation, and psychotherapy, which, despite high rates of medication nonadherence, could also have contributed to symptom improvement.

Diagnostic stability and outcome are particularly interesting for the subgroup of patients with BrPsy. Though based on a very small and preliminary sample, in our study 75% of patients that failed to meet the duration criterion for schizophrenia were in remission at follow-up (50% of these having no active psychiatric diagnosis, and, therefore, retaining BrPsy as their only lifetime diagnosis). A favorable outcome in patients with BrPsy has been described before (Fennig et al. 1995; Jorgensen et al. 1996; Pillmann et al. 2002; Susser et al. 1995, 1998). A positive outcome in patients diagnosed with BPsy may be potentially confounded by the acute onset, predominance of female gender in most samples, and the brief and treatment-responsive nature of the condition. However, 3 of the 4 subjects with BrPsy in our sample were male, with 2 of them being in the good-outcome group.

In addition, we found that lower maximum scores of SOPS attenuated negative symptoms may be associated with complete psychotic symptom remission and a favorable functional outcome. This association complements the established relationship between negative symptoms and poor functional outcome in schizophrenia (Fenton and McGlashan 1991; Moller et al. 2000). It is important to note that the diverse outcome range, including nonpsychotic diagnoses in the majority of patients, appeared, in the short term, to be independent of treatment status at follow-up. Even though the rate of nonadherence to treatment in our sample is relatively high (56.5%), it is consistent with the literature of psychiatric disor-

ders, in general (Cramer and Rosenheck 1998), reflecting clinical reality.

Comorbidities

In contrast with the lack of persistence of PsyNOS and BrPsy, we found high rates of patients with stable mood disorders (major depressive disorder: 19.2%; bipolar-spectrum disorder: 15.4%) and personality disorders (11.5%) at follow-up. This matches rates found in the literature of 11.1%–38.5% for mood disorders and 11.1% for personality disorders as outcome diagnoses for patients initially categorized as PsyNOS and BrPsy. The primary follow-up diagnosis of obsessive-compulsive disorder in 7.7% of patients points to the difficulties that patients with schizo-obsessive symptoms can present regarding symptom overlap and/or comorbidity (Poyurovsky et al. 2003) with psychotic symptomatology. In contrast to McClellan and McCurry (1999) in our sample, we did not find a predominance of patients with abuse histories or posttraumatic stress disorder in our sample (n = 1/29; 3.5%).

It is important to note that, in this study, these comorbidities represent lifetime-ever diagnoses made with the K-SADS-E, and are not necessarily completely overlapping in time with the PsyNOS diagnosis. In particular, no patients with comorbid depressive disorders met criteria for MDD with psychotic features, either at baseline (which was an exclusion criterion) or at follow-up. Depressive and other comorbid disorders may follow a time course at some variance with the waxing and waning of psychotic symptomatology.

Thus, patients meeting criteria for PsyNOS or BrPsy do not seem to develop suprathreshold psychotic disorders in a vacuum. Rather, in our sample, 27 subjects (93.1%) had comorbid psychiatric diagnoses, mostly consisting of mood disorders, personality disorders, anxiety disorders, disruptive behavior disorders, and attention-deficit/hyperactivity disorder. In fact, the majority (57.7%) of the nonpsychotic primary follow-up diagnoses had been present as comorbid conditions at study entry. Our rates of comorbid disruptive behavior disorders and attention-deficit/hyperactivity disorders in approximately one third of patients with PsyNOS and BrPsy are somewhat lower, compared to the cohort of multidimensionally impaired youths followed in a longitudinal NIMH study (Nicolson et al. 2001), where rates were twice as high. However, this unique cohort of children with early-onset PsyNOS was ascertained at a mean age of 11.4 years and is treatment-resistant (Kumra et al. 1998), making it difficult to compare to other samples.

Nature of subsyndromal psychosis

An initial concern of this study was to ask why subjects in the two groups of primary interest, PsyNOS and BrPsy, did not fall under the formal schizophrenia diagnosis. In our sample, it was found that the predominant reason was having only one psychotic symptom. Delusions and hallucinations were almost equally present as singular psychotic features, while isolated thought disorder was uncommon. Having two psychotic symptoms or bizarre delusions, but failing to meet either criterion B or C, the criterion of functional deterioration or duration, was also uncommon.

DSM-IV stresses the threshold of two versus one psychotic symptoms (with the exception of Schneiderian first-rank symptoms). In our data, the validity of this threshold was supported, insofar as the majority of subjects with just one psychotic symptom did not develop a syndromal schizophrenia-spectrum disorder, and many more had a relatively good (psychosis-free) outcome in spite of having discontinued treatment. By contrast, studies of first-episode schizophrenia tend to show a much more deteriorative course with frequent relapse of psychosis (Robinson et al. 1999a, 2004), even despite an initially favorable response rate (Robinson et al. 1999b). Our clinical follow-up data, including the fact that 11.5% of subjects progressed to bipolar disorder, are thus consistent with the hypothesis of Murray et al. (2004), who suggest that psychosis *per se* is diagnostically nonspecific, and that additional neurodevelopmental liabilities are required to produce syndromal schizophrenia, with its characteristic poor outcome.

Study limitations

Several limitations of this study need to be recognized. Most importantly, the small sample size and still relatively short duration of follow-up restricts the interpretation of the data and generalization of the findings. Moreover, patients received naturalistic treatment for their conditions, and missing treatment and psychopathology score data may have confounded the results. In addition, analyses were limited to diagnostic outcomes, as measures of functional outcome have only recently been added to the overall research program. However, this is the first study to date to have examined failed criteria for the presence of schizophrenia, as well as the persistence of psychiatric comorbidities among the baseline characteristics of patients with PsyNOS and BrPsy, two diagnostic entities that are elusive and under-researched. Moreover, this is the first investigation to have focused on the outcome of patients with these two diagnoses in the context of the schizophrenia prodrome.

CONCLUSIONS

Findings from this investigation have major implications for future studies of the schizophrenia prodrome. The fact that over a mean duration of 2 years only 7 of the 26 patients with PsyNOS and BrPsy developed schizophrenia or schizoaffective disorder challenges the current practice of counting these diagnoses as a psychotic outcome group or mixing them with nonpsychotic prodromal individuals. The role of subsyndromal psychosis in prodromal schizophrenia research is further challenged by the favorable outcome in a considerable number of patients, and by the subjects who progressed to psychotic bipolar disorder. Particularly, as 75% of patients with BrPsy had fully remitted from any positive or negative psychotic symptoms, even at attenuated levels, suprathreshold psychotic symptoms of less than a 1-month duration appear to be too unstable to justify their use as a primary endpoint in prodromal schizophrenia research. Thus, our findings strongly suggest that future studies in subjects at high risk for schizophrenia should classify and follow patients with PsyNOS and BrPsy as a separate group. Not doing so runs the risk of obscuring conversion rates of, and predictors for, the development of specific syndromal Axis I psychotic disorders.

Nevertheless, despite the overall nonspecificity of suprathreshold, but subsyndromal psychotic symptoms, 38.5% of patients did develop schizophrenia, schizoaffective disorder, or psychotic bipolar disorder. This indicates that timely treatment of subsyndromal psychosis is an important clinical issue in an attempt to delay or halt the progression to a syndromal psychotic disorder. Because of the presence of psychotic symptoms, second-generation antipsychotic medications should be considered as a first-line treatment in this population. Because, at least, a sizeable number of patients with PsyNOS and BrPsy appear to remit over time, an attempt at slowly withdrawing antipsychotic medications seems indicated if sustained symptom remission and functional recovery can be achieved for at least 6 months.

Based on the relatively small sample, still modest follow-up duration, and naturalistic design, however, our results should be considered preliminary. Thus, future studies should follow patients beyond the PsyNOS and BrPsy stage to determine the rates of progression to schizophrenia and other major psychotic disorders, and to clarify whether early interventions can influence the course and outcome of these disorders. Such studies should include the symptomatic as well as functional outcome and focus on clinical and treatment variables that can help to predict outcome, as well as the safe discontinuation of treatment without precipitating symptom relapse and deterioration. In this context, the predictive value of maximum levels of negative symptoms for symptomatic outcome should be investigated further. Finally, controlled studies, ideally in larger cohorts that are followed for longer periods of time, are needed to improve our understanding of the nature and course of PsyNOS and BrPsy, and to help identify predictors for the development of particular diagnostic outcomes that would enable specific, targeted interventions.

ACKNOWLEDGMENT

This work was supported by the grant MH 61523 by the National Institute of Mental Health (NIMH) to Dr. Cornblatt, and by the grant MH 65580 by the National Institute of Mental Health (NIMH) to Dr. Lencz and the The Zucker Hillside Hospital NIMH Intervention Research Center for the study of Schizophrenia MH 60575.

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