The Assessment of “Prodromal Schizophrenia”: Unresolved Issues and Future Directions

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Abstract

Because of the novelty of research with clinical high risk (“prodromal”) patients, many unresolved issues exist concerning how the prodromal state is defined and measured. Data are presented from the Recognition and Prevention (RAP) program at the Zucker Hillside Hospital to address several outstanding questions. Baseline attenuated positive symptoms were rated in 42 putatively prodromal patients in the RAP program using the Scale of Prodromal Symptoms (SOPS). Followup data of 6 months or more were available on 34 of these subjects; 9 of these (26.5%) developed psychotic disorders. Patients who developed psychosis had significantly higher SOPS positive symptom scores at baseline than those who did not. Various thresholds, using both total SOPS positive symptom scores and highest single item score, significantly predicted transition to psychosis, which calls into question appropriate cutoffs for the distinction between health, prodromal status, and psychosis. The SOPS positive symptom “conceptual disorganization” was found to be significantly related to disorganized behavior but not to other positive symptoms or to psychotic outcome, suggesting the importance of examining dimensions of psychopathology. The dimensional quantification of prodromal symptom severity may be an important direction for future studies of the assessment of at-risk states.

Keywords: Schizophrenia, prodrome, clinical high risk, positive symptoms, psychosis, disorganization, predictive validity.


The prospective study of clinical risk for psychosis (sometimes referred to as “prodromal schizophrenia”1) has emerged in the research literature in only the last 10 years. In 1991, authors in this journal noted that “for obvious logistical reasons” the examination of prodromal symptom criteria in DSM-III-R could not be evaluated prospectively, except for a few studies attempting to predict relapse after diagnosis of schizophrenia had already been established (Keith and Matthews 1991, p. 53). Since 1991, interest in conducting prospective studies of the initial prodrome has increased exponentially, with several dozen clinics and research programs launched or planned worldwide. The first step to any such endeavor is identification of putative at-risk patients and assessment of prodromal symptomatology. Preliminary work performed to date has provided a solid foundation in this regard, but it has stimulated many questions worthy of intensive future research efforts. As the field evolves, criteria for prodromal states will be tested, refined, and altered; this report aims to contribute to that process.

The examination of predictive validity for prodromal criteria, perhaps the most compelling question to clinicians, illuminates numerous unresolved issues concerning the assessment of clinical high-risk patients. Only a few studies to date have been able to follow patients long enough to present statistical measures of the diagnostic efficiency of prodromal criteria. These studies have suggested that patients presenting with attenuated (subpsychotic) positive symptoms (e.g., magical ideation, suspiciousness, and perceptual aberrations) may be at significant risk (30%-55% over 12 months) for developing later psychotic disorders (Yung et al. 1996, 1998; Phillips et al. 2000; McGorry et al. 2002; Miller et al. 2002). With the possibility of limiting the conclusions that can be reached, a construct of the schizophrenia prodrome in which subjects with a diverse set of presenting symptoms are combined into a single clinical risk group has...
been employed in these studies. Another prospective study similarly pointed to the high predictive value of symptoms such as perceptual and cognitive disturbance, but the threshold of such disturbance was unclear, as symptoms were not assessed dimensionally (Klosterkotter et al. 2001). The quantification of a spectrum of prodromal symptomatology, and the consequent identification of relevant cutoff points for defining health and illness, are fundamental to prodromal assessment.

One study has attempted to refine predictive validity by examining the role of baseline symptom severity (Yung et al. 2003). Several baseline variables, including long duration of symptoms, low global assessment of functioning (GAF) scores, and high depression scores were found to increase risk for psychosis in subjects defined as already at clinical risk based on Australian prodromal criteria (Yung et al. 1996). Most notably, the strongest statistical significance was demonstrated by level of baseline positive symptoms themselves. Specifically, baseline Brief Psychiatric Rating Scale (BPRS) scores of 3 or greater were substantially more predictive of conversion to psychosis. Because BPRS scores do not provide full breadth of coverage of the attenuated range (Miller et al. 1999), with a score of 4 representing psychosis, and because some subjects had already experienced brief psychosis, this finding does not resolve the appropriate cutoff of symptom severity to define prodromal status.

While the investigation of positive symptoms and the threshold of psychosis are of obvious clinical and theoretical significance, an equally important consideration is the identification and clarification of other related dimensions or domains of psychopathology. The significance of a factorial approach to understanding symptomatology has long been recognized in schizophrenia (Crow 1980; Andreasen and Olsen 1982). Furthermore, a three-factor model (typically including positive, negative, and disorganized symptoms) has been widely replicated in both schizophrenia (Grube et al. 1998; Smith et al. 1998) and schizotypal personality disorder (Raine et al. 1994; Reynolds et al. 2000; Rossi and Daneluzzo 2002). These efforts have been driven by an attempt to clarify and dissociate the pathophysiological (neuroanatomic, neurocognitive, psychophysiological, etc.) contributions to the disease process (Bilder et al. 1985; Cornblatt et al. 1985; Liddle et al. 1992; Lencz et al. 2001a). Such understanding can also have direct implications for novel treatment approaches (e.g., Javitt 2001).

To date, only one study has performed factor analysis on prodromal symptom items (Hawkins et al., in press). In that study, three factors of the SOPS (Miller et al. 1999; McGlashan et al. 2001) were identified: positive, negative/disorganized, and general symptoms. A few noteworthy loadings were obtained; specifically, “conceptual disorganization” from the SOPS positive symptom subscale loaded with disorganized behavior but not positive symptoms. In another contribution to this special issue, we describe the etiologic, pathophysiological, and clinical implications of a cluster of symptoms reflecting attenuated negative and deteriorative features of the prodrome (Cornblatt et al., this issue; see also Cornblatt 2002; Cornblatt et al. 2002; Lencz et al., in press).

In this article, we attempt to clarify the somewhat blurry boundaries between normality, attenuated positive symptoms, and psychosis. We present data from a relatively homogeneous group of subjects, defined by presence of attenuated positive symptoms, in order to examine the dimensional nature of such symptoms. It is hypothesized that a greater degree of attenuated positive symptoms at baseline will be related to a greater likelihood of deterioration to psychosis. To test this hypothesis, the diagnostic efficiency of various cutoff scores on the SOPS will be compared. Patients who have already experienced psychosis, however briefly, are excluded from the current report in order to more clearly examine the role of attenuated positive symptoms.

In addition, we will present initial data concerning the relationships of attenuated positive symptoms to other symptom domains. Factor analysis will not be performed, pending larger samples, but illustrative correlational analyses will be presented for attenuated positive symptoms. It is hypothesized that conceptual disorganization will be correlated with behavioral disorganization symptoms and that suspiciousness will be correlated with both positive symptoms and social isolation, as has been found in studies of schizotypal symptomatology (Raine et al. 1994).

Methods

Subjects. All research subjects were recruited from referrals to the clinical arm of the RAP program (the RAP clinic). Upon acceptance into the clinic, all individuals and their family members were fully informed about the research protocol, given an opportunity to ask questions, and invited to participate. Written informed consent was obtained from the patient if he or she was 18 years of age or older, or from the parent (with written assent from the patient) if the patient was under 18. The research protocol was approved by the Institutional Review Board at 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 treatment decisions would always be in the best interests of the patient regardless of research participation.

Approximately 80 percent of the RAP clinic patients have elected to participate in the research protocol, which is designed to collect longitudinal information about pro-
gression of symptoms and functioning and is not a treatment trial. For purposes of clarity, the focus of the present report is a subsample of 42 RAP research patients who were recruited during the initial phase of the study (Phase I, January 1998 to July 2001) and met criteria for attenuated positive symptoms (see below). Further details on recruitment and baseline characteristics of the full Phase I sample are presented in another publication (Lencz et al., in press). Of these 42 subjects, 17 (40.5%) were female and the mean age at intake was 16.4 years (standard deviation [SD] = 2.3, range = 11.4–22.1).

**Baseline Assessment.** Attenuated positive symptoms were rated using the SOPS, a novel instrument designed by Dr. Thomas McGlashan, Dr. Tandy Miller, and colleagues to specifically assess attenuated schizophrenialike symptomatology for identifying prodromal states (Miller et al. 1999; McGlashan et al. 2001). The SOPS contains five items designed to measure positive symptoms: unusual thought content, suspiciousness, grandiosity, perceptual abnormalities, and conceptual disorganization. Additionally, there are six items measuring attenuated negative symptoms, four items measuring disorganized symptoms, and four items measuring general symptoms. Each item is rated on a scale of zero (not present) to six (extreme or psychotic intensity), with specific probes and detailed anchors provided to determine level of severity. We have previously identified excellent interrater reliability (intraclass correlation coefficients [ICCs] > 0.80) for 12 of these symptoms, with acceptable reliability (ICCs ranging from 0.67 to 0.79) for the remaining symptoms (Lencz et al., in press). One item, bizarre thought from the disorganized symptom subscale, was deemed to be redundant with other positive symptoms and not included in analyses.

The companion interview for the SOPS is the Structured Interview for Prodromal Symptoms (SIPS). Because it was just recently developed, the SIPS was introduced into the RAP study in the middle of Phase I. Twenty-six subjects in the present study received the full SIPS interview. A parent informant was always interviewed before the patient, to provide information useful for probes when interviewing the patients and to alleviate patients' potential concerns about confidentiality. Following the parent interview, the same rater interviewed the patient and sought to clarify any discrepancies between patient information and parent information. The original subjects not administered the SIPS (n = 16) were retrospectively rated on the SOPS positive symptoms using data obtained from other interviews administered to all subjects: (1) the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Version (Orvaschel and Puig-Antich 1994); and (2) the Structured Interview for DSM-IV Personality (Pfohl et al. 1995). These interviews included detailed probes for all of the positive symptoms rated on the SOPS. However, individual negative, disorganized, and general symptom items from the SOPS were not rated for these subjects. Subjects not administered the full SIPS did not significantly differ from the remaining 26 subjects on any demographic variables or scores on any of the five SOPS positive symptoms (all p's ≥ 0.35).

All semistructured interviews were administered by a trained masters- or doctoral-level psychologist. All SOPS ratings were made on the basis of all available information by consensus of the first author and the interviewer.

**Inclusion/Exclusion Criteria.** A score of 3, 4, or 5 (moderate, moderately severe, or severe but not psychotic) on any SOPS positive symptom constituted inclusion criteria for the present study, but a score of 6 (severe and psychotic) on any item was an exclusion factor; these inclusion/exclusion criteria correspond closely with the inclusion criteria met by nearly all of the prodromal subjects recently described by Miller et al. (2002). We have previously referred to subjects meeting this criterion as clinical high risk, with positive symptoms (CHR+, Cornblatt et al. 2002; Lencz et al., in press). Note that in the present study, recent onset (within the last year) of attenuated positive symptoms is not required. Interrater reliability analysis of 11 cases as described above yielded 100 percent concordance of ratings of subgroup membership (CHR+ vs. non-CHR+, Lencz et al., in press). Exclusion criteria for the current study included age younger than 11 years old, history of any psychotic disorder, and severe or imminent risk of harm to self or others.

**Classification of Outcome—Followup Ratings.** SOPS item anchors were also used for classification of outcome. A rating of 6 on any positive symptom item represented deterioration to psychosis, the key outcome of interest. It should be noted that different research groups have established varying duration criteria for establishing psychotic states: Yung et al. (1998) require a 1-week duration, whereas McGlashan et al. (2001) require a minimum of 4 days/week over 1 month (unless symptoms are dangerous or disorganizing). For each subject obtaining a 6, duration of psychosis and related features were examined with respect to these criteria as well as DSM-IV (APA 1994) criteria for major psychotic disorders.

Subjects who did not develop psychosis either had continued presence of one or more symptoms rated 3 to 5 (stable outcome) or had no positive symptoms scored higher than 2 (improved). For all comparisons in the present study, subjects who did not become psychotic are grouped together as "nonpsychotic outcome."
Followup consensus ratings were made on the basis of all available clinical information from three sources: clinician reports, telephone interviews, and in-person followup interviews. Followup ratings were made approximately 6 months after entry into the RAP program, and regularly every 6 to 9 months, as well as at termination of treatment. Followup ratings of 6 months or more were available on 34 (81%) of the intake sample. Fifteen of these subjects were female; 19 were male. The remaining eight subjects did not continue in treatment for 6 months (and so did not have clinician data) and were unavailable for followup phone and in-person interviews (one was killed in a motor vehicle accident, three declined participation, and four could not be located). As of October 1, 2002, the mean total duration of followup was 24.7 months (SD = 15.9). Subjects not included in the followup sample did not significantly differ from the remaining subjects on any demographic variables or baseline scores on any of the SOPS positive symptoms (all p's > 0.20).

**Statistical Analysis.** Between-group comparisons of continuous variables (age, duration of followup, symptom severity) were performed using Kolmogorov-Smirnov's z (for two groups) or Kruskal-Wallis tests (for more than two groups), as assumptions for parametric tests (including normality of distributions, and equality of variances and sample sizes) were violated (Siegel 1956). The association between dichotomized thresholds of baseline symptom severity and outcome was evaluated with two-sided Fisher's exact tests. For all such comparisons, diagnostic efficiency statistics including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are presented. Spearman rank-order correlations were utilized to examine the relationships between attenuated positive symptoms and other prodromal symptoms at baseline. Because of the number of correlations performed, a threshold of significance for each comparison was set at p < 0.005.

**Results**

**Distribution of Positive Symptoms at Baseline.** The mean sum of the five SOPS positive symptom scores at baseline was 9.6 (SD = 4.5). As presented in another publication (Cornblatt et al., this issue), there was a bimodal distribution of total positive symptom scores, with approximately half (55%, n = 23) of the subjects having total scores below 10. Subjects with scores of 9 or below did not significantly differ from the remaining subjects on age or sex distribution (p's > 0.75). An examination of each individual's highest item score revealed that nine subjects (21.4%) had no positive symptom SOPS scores above a 3. Sixteen subjects (38.1%) had at least one score of 4 but no scores of 5, and 17 subjects (40.5%) had at least one score of 5. These three groups also did not differ with respect to age or sex distribution (p's > 0.23).

**Outcome.** A total of nine subjects (26.5% of those with outcome data) demonstrated an exacerbation of symptoms into the psychotic range over the followup period. For all of these subjects, psychotic symptoms met the duration criteria of both Yung et al. (1996) and Miller et al. (1999). DSM-IV diagnoses were as follows: schizophrenia (n = 4), schizoaffective disorder (n = 2), delusional disorder (n = 1), and psychotic disorder not otherwise specified (n = 2).

Of the 25 subjects who did not become psychotic, 12 (35.3% of the outcome sample) had attenuated positive symptoms at followup, although it should be noted that 4 of these subjects experienced remission of positive symptoms for a time before returning to baseline. The remaining 13 (38.2%) experienced remission of attenuated positive symptoms (i.e., no symptoms rated 3 or higher at followup). There was no significant difference between subjects with psychotic versus nonpsychotic outcome in age at intake (mean [SD] = 16.8 [1.5] vs. 15.9 [2.6]; z = 0.84, p = 0.38) or months of followup (mean [SD] = 22.1 [13.5] vs. 25.7 [16.7]; z = 0.77, p = 0.49). Although seven of the nine subjects who deteriorated to psychosis were male, the difference in sex distribution was not significant (Fisher's exact test, p = 0.24).

**Relationship Between Baseline Positive Symptoms and Outcome.** As shown in figure 1, the 9 subjects who experienced psychotic exacerbation during the followup had significantly greater positive symptoms (total score) at baseline compared with the 25 subjects who remained stable or improved (mean [SD] = 13.67 [4.97] vs. 7.84 [3.60]; z = 1.72, p = 0.001). To further examine the relationship between positive symptom severity at baseline and subsequent deterioration to psychosis, a 2 × 2 table was constructed to determine the efficiency of using a split around the mean of the baseline total SOPS score as a cutoff (i.e., score of 10) (table 1). Fisher's exact test for this 2 × 2 table was statistically significant (p = 0.025). As seen in table 2, sensitivity and specificity were moderately high, with a PPV of 0.47. However, inspection of figure 1 reveals that all of the subjects scoring above 15 at baseline later showed deterioration to psychosis, resulting in strongly significant prediction using this cutoff (table 1). As shown in table 2, a baseline threshold of 15 yielded a PPV of 1.0, although there were three false negatives.

To investigate whether single item severity at baseline (as opposed to total baseline SOPS score) might predict outcome, subjects who had a score of 5 (the highest sub-
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Figure 1. Baseline scores of 34 patients on the sum of the positive symptom items of the Scale of Prodromal Symptoms, by long-term outcomes (mean duration = 24.7 months)

Table 1. Long-term outcomes (mean duration = 24.7 months) of 34 patients evaluated for suspected schizophrenia prodromal symptoms, by baseline scores on the positive symptom items of the Scale of Prodromal Symptoms

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total Score(^1)</th>
<th>Total Score(^2)</th>
<th>Highest Item Score(^3)</th>
<th>Highest Item Score(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10+</td>
<td>&lt;10</td>
<td>15+</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Psychotic</td>
<td>7</td>
<td>2</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Nonpsychotic</td>
<td>8</td>
<td>17</td>
<td>0</td>
<td>25</td>
</tr>
</tbody>
</table>

1 Significant relationship of baseline status to outcome (2 x 2 Fisher's exact test, p = 0.025).
2 Significant relationship of baseline status to outcome (2 x 2 Fisher's exact test, p < 0.001).
3 Significant relationship of baseline status to outcome (2 x 2 Fisher's exact test, p = 0.013).
4 Trend relationship of baseline status to outcome (2 x 2 Fisher's exact test, p = 0.077).

psychotic score) on any positive symptom item at baseline were compared with subjects who had ratings of 3 or 4 only. As shown in table 1, there was a significant relationship between this baseline threshold and subsequent outcome; seven out of the nine subjects who deteriorated had a score of 5 on at least one item. This criterion resulted in a PPV greater than 50 percent, with comparable sensitivity, specificity, and NPV to that obtained for a total score of 10 or greater (table 2). By contrast, comparison of subjects with either 4 or 5 as their highest score with subjects who had no item scores higher than 3 yielded only marginally significant prediction of outcome (p = 0.077, table 1). Although sensitivity was 1.0, meaning all subjects developing psychosis had at least one baseline item of 4 or 5, there were many false positives (table 2).
Between-group differences and the predictive validity of individual SOPS items were also examined. Compared with subjects with nonpsychotic outcomes, subjects who developed psychosis had significantly greater levels of unusual thought content, suspiciousness, and grandiosity at baseline (table 3). However, baseline ratings of perceptual abnormalities and conceptual disorganization did not significantly differ between groups. Using dichotomous cutoffs (item scores between 3 and 5 vs. scores less than 3), the presence of subsympathetic suspiciousness and grandiosity at baseline significantly predicted psychotic outcome, although in different ways (tables 4 and 5). All patients who developed psychosis were at least moderately suspicious at baseline (sensitivity = 1.0). However, suspiciousness was the most commonly reported baseline positive symptom, thereby resulting in many false positives (62.5%). On the other hand, grandiosity was very rarely observed but had a relatively high PPV (0.67) when it was present. Notably, perceptual abnormalities/hallucinatory behavior had the lowest predictive validity, indicating that many patients experienced subsympathetic hallucinatory experiences without further exacerbation.

### Table 2. Diagnostic efficiency of the SOPS positive symptom scores in predicting dichotomous outcomes (psychotic vs. nonpsychotic) for 34 patients with attenuated positive symptoms at baseline

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total SOPS positive symptoms ≥ 10</td>
<td>0.78</td>
<td>0.68</td>
<td>0.47</td>
<td>0.89</td>
</tr>
<tr>
<td>Total SOPS positive symptoms ≥ 15</td>
<td>0.67</td>
<td>1.00</td>
<td>1.00</td>
<td>0.89</td>
</tr>
<tr>
<td>Highest item score = 5</td>
<td>0.78</td>
<td>0.76</td>
<td>0.54</td>
<td>0.90</td>
</tr>
<tr>
<td>Highest item score &gt; 3</td>
<td>1.00</td>
<td>0.32</td>
<td>0.35</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Note.—SOPS = Scale of Prodromal Symptoms.

### Table 3. Means (and SDs) of baseline scores on the positive symptom items of the SOPS, by long-term outcomes (mean duration = 24.7 months)

<table>
<thead>
<tr>
<th></th>
<th>Psychotic outcome (n = 9)</th>
<th>Nonpsychotic outcome (n = 25)</th>
<th>Kolmogorov-Smirnov value</th>
<th>Exact p (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unusual thought content</td>
<td>3.33 (1.73)</td>
<td>1.96 (1.74)</td>
<td>1.20</td>
<td>0.045</td>
</tr>
<tr>
<td>Suspiciousness</td>
<td>4.56 (0.73)</td>
<td>2.40 (1.76)</td>
<td>1.57</td>
<td>0.003</td>
</tr>
<tr>
<td>Grandiosity</td>
<td>2.00 (2.12)</td>
<td>0.44 (1.16)</td>
<td>1.22</td>
<td>0.013</td>
</tr>
<tr>
<td>Perceptual abnormalities</td>
<td>1.56 (1.33)</td>
<td>1.88 (1.81)</td>
<td>0.62</td>
<td>0.451</td>
</tr>
<tr>
<td>Conceptual disorganization</td>
<td>2.22 (1.86)</td>
<td>1.16 (1.49)</td>
<td>0.92</td>
<td>0.134</td>
</tr>
</tbody>
</table>

Note.—SOPS = Scale of Prodromal Symptoms.
Table 4. Long-term outcomes (mean duration = 24.7 months) of 34 patients evaluated for suspected schizophrenia prodromal symptoms, by baseline scores on the individual positive symptom items of the Scale of Prodromal Symptoms

<table>
<thead>
<tr>
<th>Baseline Criterion</th>
<th>Unusual Thought Content</th>
<th>Suspiciousness</th>
<th>Grandiosity</th>
<th>Perceptual Abnormalities</th>
<th>Conceptual Disorganization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>3-5</td>
<td>&lt;3</td>
<td>3-5</td>
<td>&lt;3</td>
<td>3-5</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>9</td>
<td>4</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Nonpsychotic</td>
<td>11</td>
<td>15</td>
<td>2</td>
<td>12</td>
<td>5</td>
</tr>
</tbody>
</table>

1 No significant relationship of baseline status to outcome (2x2 Fisher’s exact test, p = 0.125).
2 Significant relationship of baseline status to outcome (2x2 Fisher’s exact test, p = 0.034).
3 Significant relationship of baseline status to outcome (2x2 Fisher’s exact test, p = 0.031).
4 No significant relationship of baseline status to outcome (2x2 Fisher’s exact test, p = 0.697).
5 Trend relationship of baseline status to outcome (2x2 Fisher’s exact test, p = 0.085).

Table 5. Diagnostic efficiency of the presence (rating of 3-5) of individual positive symptom items of the Scale of Prodromal Symptoms. In predicting dichotomous outcomes (psychotic vs. nonpsychotic) for 34 patients with attenuated positive symptoms at baseline

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unusual thought content</td>
<td>0.78</td>
<td>0.56</td>
<td>0.39</td>
<td>0.88</td>
</tr>
<tr>
<td>Suspiciousness</td>
<td>1.0</td>
<td>0.40</td>
<td>0.38</td>
<td>1.00</td>
</tr>
<tr>
<td>Grandiosity</td>
<td>0.44</td>
<td>0.92</td>
<td>0.67</td>
<td>0.82</td>
</tr>
<tr>
<td>Perceptual abnormalities</td>
<td>0.33</td>
<td>0.52</td>
<td>0.20</td>
<td>0.68</td>
</tr>
<tr>
<td>Conceptual disorganization</td>
<td>0.56</td>
<td>0.80</td>
<td>0.50</td>
<td>0.83</td>
</tr>
</tbody>
</table>

pathophysiology is further examined in a separate report (Comblatt et al., this issue). Increasing the total baseline score threshold from 10 to 15 yielded a PPV of 1.0, at the expense of a loss in sensitivity (three out of nine cases who deteriorated were not identified by this criterion). Use of varying initial cutoff thresholds in studies of predictive power always involves such tradeoffs, as will be discussed further below.

It is notable that each of the six subjects with a baseline total score of 15 or greater had at least one item score of 5. Furthermore, the highest diagnostic efficiency was achieved by examination of the highest single-item score at baseline (although a total score cutoff of 10 was only marginally lower in diagnostic efficiency). Subjects with at least one baseline symptom that was already very close to psychotic intensity had a 54 percent chance of further deterioration. The SOPS criteria for rating positive symptoms rely on several factors, including duration and frequency, but the predominant requirement for psychosis is full conviction in delusional beliefs or hallucinatory experiences. (It should be noted that the appropriate balance between consideration of symptom intensity and symptom frequency is also an unresolved issue and cannot be determined from the present data.)

Thus, the assessment of doubt/conviction must be highly accurate at baseline; otherwise, the distinction between “prodromal” and “psychotic” runs the risk of losing its meaning. This can be particularly difficult in adolescents, and subjects who are not very articulate. In our experience, two important probes of conviction are (1) influence on behavior, including taking active measures to ward off delusional fears; and (2) the ability of an adolescent to seek reality testing from a parent. When patients stop seeking reassurance from a parent or cannot accept such reassurance, it is often a sign of delusional conviction. This last “wedge” of insight separating a rating of 5 from a rating of 6 is thus an important target of treatment. Maintenance and improvement of insight into illness, perhaps using cognitive therapy (Morrison et al. 2002), may therefore be an important clinical goal for such patients.
The various baseline thresholds examined had different degrees of diagnostic efficiency. Use of a total baseline score threshold of 15 resulted in no false positives, but use of a single-item threshold of 5 resulted in only one false negative. Perhaps most notably, subjects who had no positive symptom scores above a 3 (moderate level) did not deteriorate to psychosis, suggesting the need for further examination of this prodromal criterion. The determination of which type of criterion is preferable, ethically and clinically, is a function of the relative risks and benefits of the types of treatment to be provided. These considerations necessarily include the risks of side effects in patients who are needlessly treated (false positives), as well as the risks of failing to identify, and therefore to appropriately treat, someone truly at risk for severe mental illness (false negatives) (Cornblatt et al. 2001; McGlashan 2001; McGorry et al. 2001). Treatment in the RAP program to date has been naturalistic, meaning that all medication decisions are made by the treating clinician based on presenting symptoms (Cornblatt et al. 2001, 2002). Results of the present study can therefore be viewed as reflecting a "natural history" of prodromal symptoms and can help inform inclusion criteria and ascertainment strategies for future clinical trials and clinical practice by providing data relevant to the risk-benefit analysis described above. Medication issues are discussed further in another report (Cornblatt et al., this issue).

In this study, 26.5 percent of the total sample of adolescents and young adults with attenuated positive symptoms developed psychosis after approximately 6 months or more of followup. These results support previous research indicating that such symptoms are predictive of later psychosis in treatment-seeking samples; these risk rates are also substantially higher than those reported in studies of non-treatment-seeking schizotypal patients (Chapman et al. 1994; Kwapił et al. 1997) and first degree relatives of patients with schizophrenia (Gottesman and Erlenmeyer-Kimling 2001). Still, this rate of transition to psychosis is somewhat lower than the 36 to 54 percent incidence in prospective studies using comparable inclusion criteria (Yung et al. 1996, 1998; Phillips et al. 2000; McGorry et al. 2002; Miller et al. 2002). There are several...
possible explanations for these discrepancies, the most important of which is the fact that all such studies to date have employed relatively small sample sizes, which of course necessitates further investigations.

The sample ascertainment for the present study also differs from those of prior studies in several ways that might account for lower total incidence. First, RAP subjects were somewhat younger (both in mean age and in age range) than subjects in previous reports, possibly necessitating longer duration of followup in order to capture a more complete risk window. Second, there was no requirement in the present study that positive symptoms at baseline be of recent onset or exacerbation. It is possible that such a requirement serves to catch subjects closer to the point of deterioration, particularly in subjects who are already young adults in the peak period of schizophrenia risk (i.e., in their twenties). At the same time, the requirement of acute onset or exacerbation in prior studies may have excluded subjects with a longer, more insidious prodrome. Prior retrospective studies have shown great variability in duration of the prodromal period, with the prodrome often extending over many years (Yung and McGorry 1996; Hafner and an der Heiden 1999).

Third, the present study included only subjects with attenuated positive symptoms and excluded subjects with any history of experiences that crossed the threshold into psychosis, however briefly. In so doing, we sought to maintain greater homogeneity in our sample, to more specifically examine the predictive validity of attenuated positive symptoms. The possibility that subjects with histories of brief or atypical psychosis are at even higher risk for further psychotic deterioration is currently under investigation in the RAP program; preliminary data support this hypothesis (Lencz et al. 2001b). Criteria for "brief" psychosis versus "true" psychosis are by necessity somewhat arbitrary, and the appropriate duration threshold for defining psychosis remains unsettled.

On the other hand, the PPV obtained with the single-item score threshold is comparable with the estimates of risk in the prior prospective studies cited above. It is possible that those studies contained more severely affected subjects at baseline. Even so, it should also be noted that one study using the McGorry criteria reported a very low (9%) incidence of transition to psychosis after a mean followup of 14.6 months (Carr et al. 2000). Further, McGorry et al. (2002) reported an 18 percent conversion rate in patients who refused their controlled treatment trial; these refusers were reported to have low levels of baseline symptomatology.

Still, 54 percent PPV is lower than that found in a long-term (10-year) followup study using the Bonn Scale for the Assessment of Basic Symptoms (BSABS, Klosterkotter et al. 2001). The BSABS is a very different form of prodromal assessment, with a focus on more subtle, subjective alterations in patients' thoughts and experiences. While space does not permit a detailed consideration of the BSABS in this report, the BSABS appears to complement the SOPS and its Australian counterpart, the Comprehensive Assessment of At-Risk Mental States (Yung et al. 2000). By measuring less overt behaviors, the BSABS possibly obtains information about very early prodromal changes (Huber and Gross 1989). However, the constructs of the BSABS are not entirely familiar to English-speaking clinicians and researchers and may be more difficult to assess reliably.

Given the very low base rate of schizophrenia and psychotic disorders in the general population, results of the present study are applicable only to clinical populations similar to the sample ascertainment here and cannot be applied to the screening of those who do not seek treatment (Warner 2001). The strategy employed in the present study is an extension of the "two-step" approach suggested by McGorry and Edwards (2002; also see Bell 1992). We began by limiting the sample to include only treatment seekers with attenuated positive symptoms. Then, within this sample, we tested the hypothesis that increased severity of positive symptoms at baseline would lead to significant prediction of psychotic outcome. Further studies are under way in the RAP program to improve prediction by the addition of neurocognitive and other variables to the screening battery (see Cornblatt et al., this issue). Finally, it is important to note that McGorry et al. (1995) have reported that some attenuated positive symptoms might be quite common in the adolescent population as a whole. It is therefore likely that treatment-seeking behavior, combined with severity of positive symptoms, is a necessary component of the prediction of psychotic outcomes.

Finally, an examination of individual positive symptoms revealed that suspiciousness appears to be a cardinal symptom of the prodrome, identifying all subjects who developed psychosis in our sample. By contrast, grandiosity was rare and perceptual abnormalities were both unpredictable of outcome and less strongly related to total positive symptom scores. Furthermore, conceptual disorganization did not significantly differentiate those with psychotic outcome and may be more related to a dimension of disorganized behavior than to other attenuated positive symptoms. Such a finding, which is consistent with prior factor-analytic studies (Raine et al. 1994; Hawkins et al., in press), suggests the need for pathophysiologic studies to investigate this pathologic domain. Additionally, suspiciousness was significantly correlated with social isolation, again consistent with some factor analyses of schizotypal symptoms (Raine et al. 1994). It may be necessary to develop instruments to assess social...
functioning in greater detail, so as to unravel chicken-and-egg relationships between suspiciousness and asociality, and to distinguish between anxious avoidance of social contacts and schizoid disinterest. These distinctions clearly have not only implications for understanding etiology and pathophysiology but also potential clinical implications. Just as schizophrenia (and psychotic disorders in general) appears to be a heterogeneous construct, the state of "clinical high risk" probably represents a variety of underlying pathologies with differing treatment needs.

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