Published in final edited form as:

J Psychiatr Res. 2016 October ; 81: 95–101. doi:10.1016/j.jpsychires.2016.06.021.

Duration of attenuated positive and negative symptoms in individuals at clinical high risk: Associations with risk of conversion to psychosis and functional outcome

Ricardo E. Carrión^{a,b,c,*}, Docia Demmin^a, Andrea M. Auther^{a,c}, Danielle McLaughlin^a, Ruth Olsen^a, Todd Lencz^{a,b,c,d}, Christoph U. Correll^{a,b,c,d}, and Barbara A. Cornblatt^{a,b,c,d}

^a Division of Psychiatry Research, The Zucker Hillside Hospital, Northwell Health, Glen Oaks, NY, USA

^b Center for Psychiatric Neuroscience, The Feinstein Institute for Medical Research, Northwell Health, Manhasset, NY, 11030, USA

^c Department of Psychiatry, Hofstra Northwell School of Medicine, Hempstead, NY, 11549, USA

^d Department of Molecular Medicine, Hofstra Northwell School of Medicine, Hempstead, NY, 11549, USA

Abstract

Research in individuals at clinical high-risk (CHR) for psychosis has focused on subjects with no more than 12 months of present or worsened attenuated positive symptoms. However, the impact of long duration attenuated positive and/or negative prodromal symptoms on outcomes is unclear. Seventy-six CHR subjects with attenuated positive symptoms and at least moderate severity level negative symptoms rated on the Scale of Prodromal Symptoms (SOPS) were prospectively followed for a mean of 3.0 ± 1.6 years. Social and Role functioning was assessed with the Global Functioning: Social and Role scales. Correlations between attenuated positive and negative symptom duration and severity and conversion to psychosis and functional outcomes were analyzed. The average onset of SOPS rated negative symptoms ($M = 53.24$ months, $SD = 48.90$, median = 37.27) was approximately twelve months prior to the emergence of attenuated positive symptom ($M = 40.15$ months, $SD = 40.33$, median = 24.77, $P < 0.05$). More severe positive symptoms ($P = 0.004$), but not longer duration of positive ($P = 0.412$) or negative ($P = 0.754$) symptoms, predicted conversion to psychosis. Neither positive symptom duration ($P = 0.181$) nor

* Corresponding author. Zucker Hillside Hospital, Psychiatry Research, 75-59 263rd Street, Glen Oaks, NY, 11004, USA. RCarrion@northwell.edu (R.E. Carrión).

Contributors

BC developed and oversaw the research protocol. RO and AA contributed to participant recruitment. AA, DM, and TL conducted clinical assessments. CC oversaw treatment decisions. DD collected data. RC and DD performed the literature review. RC and DD performed statistical analysis. All authors contributed to and approved the final manuscript.

Conflicts of interest

Drs. Carrión, Auther, Lencz, and Ms. McLaughlin, Olsen, and Demmin report no financial relationships with commercial interests. Dr. Cornblatt has been an advisor for Hoffmann-La Roche.

Dr. Correll has been a consultant and/or advisor to or has received honoraria from AbbVie, Acadia, Actavis, Alkermes, Eli Lilly, Genentech, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, Lundbeck, MedAvante, Medscape, Otsuka, Pfizer, ProPhase, Reviva, Roche, Sunovion, Supernus, and Takeda. He has received grant support from Bristol-Myers Squibb, Otsuka, and Takeda.

severity ($P = 0.469$) predicted role or social functioning at study endpoint. Conversely, longer negative symptom duration predicted poor social functioning ($P = 0.004$). Overall, our findings suggest that the severity of attenuated positive symptoms at baseline may be more important than symptom duration for determining individuals at increased risk of developing psychosis. In contrast, long-standing negative symptoms may be associated with persistent social difficulties and therefore have an important position in the treatment of disability.

Keywords

Early intervention; Psychosis; Negative symptoms; Clinical high risk; Attenuated positive symptoms; Functional outcome

Interventions designed to prevent psychosis by starting treatment during the prodromal (or pre-illness) stage were based on the assumption that the longer early symptoms were present, the more severe the underlying illness and risk for leading to psychosis (McGlashan, 1998, 1999; McGlashan and Johannessen, 1996). The prevention assumption was derived from the notion that in already fully psychotic patients, the duration of untreated symptoms was related to prognosis in general, and that the earlier treatment was started after onset, the better the outcome (McGorry et al., 2007). While there has been evidence to support the latter (Boonstra et al., 2012; Bottlender et al., 2003; Buchanan, 2007; Keshavan et al., 2003; Perkins et al., 2005), there are few findings to support the pre-illness association between a longer symptom duration and increased symptom severity leading to full-blown psychosis. The current assumption is that accurately identifying individuals at clinical high-risk [(CHR) also called ultra high risk (UHR), or at-risk mental state (ARMS)] of developing psychosis may provide an opportunity to reduce the duration of the untreated illness by targeting the first appearance of subtle (i.e., attenuated) forms of positive and negative symptoms (Cornblatt et al., 2003; Yung and McGorry, 1996; Yung et al., 1996). However, there is little information on the impact of long duration attenuated positive and negative symptoms on the severity of prodromal symptoms or conversion to full-blown psychosis and functional outcomes. Given the possibility that long-term outcomes may be improved by reducing the duration of prodromal symptoms (Keshavan et al., 2003), this information may provide new insights for establishing effective early intervention programs (Yung and McGorry, 1996).

The few prospective studies with individuals at CHR that have examined the duration of prodromal symptoms prior to study entry have yielded mixed results (Chung et al., 2010; Fusar-Poli et al., 2009; Yung et al., 2003, 2007). For example, an earlier study by Yung and colleagues (Yung et al., 2003) found that a longer duration of attenuated positive symptoms increased the likelihood of conversion to psychosis. CHR individuals who developed psychosis had a longer time between the onset of positive symptoms and first contact with a prodromal service compared to those who did not (2.5 vs. 0.9 years), suggesting that shortening the window between early symptom onset and first contact may delay or reduce likelihood of developing psychosis. In fact, a reduction in the time between the onset of attenuated positive symptoms and first contact may be partially responsible for a decline in conversion rates in recent CHR cohorts (Yung et al., 2007). However, a recent study by

Chung et al. (2010) found no relationship between the duration and severity of attenuated positive symptoms in CHR individuals, making it difficult to draw any conclusions regarding the relationship between attenuated positive symptoms and outcome.

Along with positive symptom duration, there is some evidence from patients with schizophrenia that longer duration negative symptoms may adversely impact functional outcomes (Choi et al., 2009; Cuesta et al., 2012; Murphy et al., 2008). In contrast to positive symptoms, negative symptoms (i.e., social anhedonia, avolition) are now understood as most likely to begin early in development and pre-date psychosis by many years, with positive symptoms appearing in relatively later stages of the illness (Haas and Sweeney, 1992; Häfner, 2000; 1999; 2013; 2003; Iyer et al., 2008; Tan and Ang, 2001). This trajectory would imply that a longer duration of attenuated negative symptoms would relate to increased functional impairments in CHR individuals. Surprisingly, however, no study to date has investigated a relationship between the duration of negative symptoms and outcome in this vulnerable population. Given that early declines in social functioning and academic performance have a prominent role in determining functional outcome (Carrión et al., 2011, 2013; Cornblatt et al., 2012), establishing the onset and time course of negative symptoms before the emergence of full-blown psychosis in individuals at CHR for psychosis may have important implications for the treatment and prevention of long-term functional disability. While positive and negative symptoms are related to the disease process, the relative onset of attenuated positive symptoms and negative symptoms may indicate differing stages of symptom progression (Lencz et al., 2004). Along the same lines, attenuated positive and negative symptom duration may be differentially related to the risk of psychosis onset and poor functional outcomes, indicating that different stages of the prodrome and different levels of attenuated positive symptoms and/or clinically relevant negative symptoms may require different interventions (Cornblatt et al., 2003).

The goal of the present study was therefore to explore the severity and duration of attenuated positive symptoms and negative symptoms present at study entry and determine the association between higher symptom severity and longer symptom duration and the risk of conversion to psychosis and functional outcomes in a prospective sample of individuals at CHR for psychosis. In the current study, individuals were included only if they exhibited attenuated positive symptoms at clinically significant severity levels as defined by the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 2003, 2002, 1999). In contrast to most CHR studies, duration of symptoms was treated as a continuous variable and was not limited to an onset or worsening over the year prior to baseline, as specified by the criteria in standard use (Correll et al., 2010). Based on prior findings, we hypothesized the following: (1) Negative symptoms would precede the onset of attenuated positive symptoms; (2) Longer duration attenuated positive symptoms would be related to a higher likelihood of conversion to full-blown psychosis; and (3) A longer duration of negative symptoms would be related to an increased likelihood of poorer functioning at study outcome rather than conversion to psychosis.

1. Methods and materials

1.1. Participants

The Recognition and Prevention (RAP) program is an ongoing longitudinal study of treatment-seeking adolescents and young adults considered to be at CHR for psychosis initiated in 1998 and funded by the National Institute of Mental Health in 2000. This article reports data for participants recruited during Phase 1 (2000–2006) of the study. Patient referrals were made to the RAP Program by affiliated outpatient and inpatient psychiatry departments, local mental health providers, school psychologists or counselors, or were self-referred. All procedures were approved by the Institutional Review Board at Northwell Health (formerly the North Shore-Long Island Jewish Health System). Written informed consent (with assent from participants under 18) was obtained from all participants.

The original intake sample consisted of 101 participants that met criteria for Clinical High-Risk, Positive (CHR+) derived from the Scale of Prodromal Symptoms (SOPS) with its companion interview the SIPS (Miller et al., 2003, 2002, 1999). Inclusion criteria were based on the presence of one or more moderate, moderately severe, or severe (scores of 3, 4, or 5) SOPS rated (scale of 0–6) attenuated positive symptoms. A score of 6 (severe and psychotic) on any item was exclusionary for the CHR group. Although not used as entry criteria, in addition to the positive symptoms, CHR+ subjects also received ratings on the SOPS Negative Symptom scale: 1. Social Anhedonia, 2. Avolition, 3. Expression of emotion, 4. Experience of emotions and self, 5. Ideational richness, and 6. Occupational Functioning. Additional inclusion criteria required participants to be between the ages of 12 and 22 years. Exclusion criteria for all participants included: (1) Schizophrenia-spectrum diagnosis; (2) Non-English speaking; (3) A medical or neurological disorder; (3) Estimated IQ < 70. Detailed sample characteristics, including full demographics and clinical characteristics are presented elsewhere (Cornblatt et al., 2015).

Symptom onset was calculated relative to the baseline assessment date. In most cases specific dates were obtained from the SIPS interview in which time of first onset the prodromal symptom is estimated from a retrospective account and logged on the SOPS summary sheet located at the end of the SIPS. Informant and patient interview versions were used to provide the most accurate date of onset. In the cases where dates were not recorded on the SOPS summary sheet, clinician based best-estimates were made by extensive review of all available intake information. Inconsistent reports from the subject and family members were reconciled by consensus based on all available information. Only attenuated positive symptoms rated at a moderate, moderately severe, or severe (scores of 3, 4, or 5) level and negative symptoms rated at a moderate, moderately severe, severe, or extreme (scores of 3–6) level were used for determining symptom onsets (i.e., symptoms that met CHR criteria or were at least at a “prodromal” level of intensity).

Of the initial 101 CHR+ subjects, 92 (91%) had follow-up clinical ratings (described in more detail in Carrión et al. (2013)). From the 92 subjects with follow-up data, 90 subjects (97.8%) had a least one negative symptom rated 3. Fourteen additional subjects were excluded from the current data analyses for having no information on positive (n = 6) or negative symptom duration (n = 8). There was no difference between included and excluded

subjects on any major demographic or clinical feature, including baseline age, gender, and total positive and negative symptoms. Therefore, the final sample in the present study consisted of 76 (83%) CHR+ subjects (68% male, mean age = 16, age range 12–22 years old), with a Kaplan Meier (Kaplan and Meier, 1958) estimated conversion rate to psychosis of 19% (SE = 0.06) at the end of year 4 and 30.5% (SE = 0.12) at the end of year 5.

1.2. Measures

Social and role functioning was assessed using the GF:Social and GF:Role scales (Cornblatt et al., 2007). Conversion to psychosis was defined as the presence of a psychotic level positive symptom (SOPS score of 6 with a minimum duration of 1 week). The Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Version (K-SADS-E) (Orvaschel and Puig-Antich, 1994) was used to confirm a psychotic disorder diagnosis. As in previous reports (Carrión et al., 2011, 2013; Cornblatt et al., 2012) GF scores at the last follow-up visit were used as measures of good (current functioning scores 7, mild impairments to superior functioning) and poor outcome (scores 6, moderate impairments to extreme dysfunction).

1.3. Statistical analyses

All analyses were conducted using SPSS 16.0 (SPSS Inc., Chicago, Illinois). Comparisons of clinical characteristics were performed with Student's T-tests for continuous variables (Two-tailed, $P < 0.05$). Pearson's correlational analyses were conducted to examine the relations between positive and negative duration and severity levels at baseline. Cox proportional-hazards regression was conducted to examine the association between the duration of symptoms and conversion to psychosis after adjusting for potential confounding variables including age, SOPS positive and negative symptom total scores, and GAF score at baseline ($P < 0.05$). Logistic regression analysis with forward (stepwise, likelihood ratio method, $P < 0.05$) inclusion was conducted to predict the independent contributions of symptom duration to functional status at study outcome. Two logistic regression models were performed with the duration of negative and positive symptoms as the independent variables and functional status (social and role) at study outcome as the dependent variable, adjusting for age, SOPS positive and negative symptom total scores, and GAF score at baseline. Significant relationships were followed-up with a duration of negative symptoms that was restricted to Negative-SIPS items that did not include content related to the GF: Social and Role scales. Specifically, regressions with GF:Social scores were re-run after removing N1-Social anhedonia and regressions with GF:Role scores were re-run after removing N6-Occupational functioning. In addition, we adjusted the final logistic regression models for the possible confounding effects of individuals that developed psychosis over the follow-up period.

2. Results

CHR+ subjects had a mean age of 16.0 ± 2.2 years and were mostly male (68.4%) and white (78.9%) (see Table 1). In terms of symptoms, suspiciousness was the most prevalent positive symptom (68.4%) rated at a moderate intensity or above (3 on the SOPS) at baseline, while grandiosity (6.6%) was the lowest reported symptom. Within the negative symptom

dimension, Decline in Occupational/Academic Functioning (77.6%), Social Anhedonia (59.2%), and Avolition (46.1%) were most prevalent at baseline (see Table 1).

As shown in Fig. 1, the positive attenuated symptom with the longest duration prior to baseline was Disorganized Communication ($n = 14$, $M = 61.77$ months, median = 25.49). In terms of negative symptoms, Decreased Expression of Emotion ($n = 9$, $M = 57.49$, median = 39.03 months) and Social Anhedonia ($n = 45$, $M = 52.75$, median = 20.60 months) had substantial pre-baseline duration. Decreased Ideational Richness actually had the longest pre-baseline duration ($M = 102.13$, median = 113.58 months), however, it was the least occurring negative symptom ($n = 7$, 10.5%).

The mean onset of attenuated negative symptoms ($M = 53.24$ months, $SD = 48.90$, range 0.62–174.92, median = 37.27) was approximately twelve months prior to the emergence of attenuated positive symptom ($M = 40.15$ months, $SD = 40.33$, range 2.23–191.67, median = 24.77) ($t = 2.12$, $df = 75$, $P = 0.037$). The mean difference in time between the onset of negative and positive symptoms was 398.34 ($SD = 1636.69$) days. The mean age at onset of SIPS-Negative symptoms ($M = 11.55$ Years, $SD = 4.26$) was approximately one year earlier than the mean age of onset of attenuated positive symptoms ($M = 12.64$ Years, $SD = 3.77$).

The duration of attenuated positive and negative symptoms ($r = 0.29$, $P = 0.01$) were weakly correlated, suggesting some shared variance, but a low covariation between the constructs. The duration of attenuated positive symptoms was not correlated with attenuated positive ($r = 0.11$, $P = 0.37$) or negative symptom ($r = 0.01$, $P = 0.97$) severity. Negative symptom duration was also not significantly correlated with the severity of negative ($r = 0.10$, $P = 0.40$) or attenuated positive symptoms ($r = 0.10$, $P = 0.40$).

In a univariable Cox regression model, neither the duration of attenuated positive symptoms (hazard ratio (HR) = 1.00, 95% CI = 0.999–1.000, $P = 0.41$) nor negative symptoms (HR = 1.00, 95% CI = 1.000–1.000, $P = 0.75$) significantly predicted conversion (Table 2). The lack of association between duration of symptoms and conversion to psychosis was confirmed after adjusting for baseline variables, including age, SOPS total attenuated positive and negative symptoms (Table 2). Total SOPS attenuated positive symptom severity was the only significant predictor of conversion to psychosis (HR = 1.229, 95% CI = 1.068–1.413, $P = 0.004$, see Table 2). Overall, there was no difference in the proportion of converters and non-converters with symptom onsets less or greater than 1-year prior to ascertainment ($P = 1.00$). For both the converters and non-converters, 75% had attenuated positive symptoms with onsets greater than 1-year relative to the baseline assessment and 25% of both groups included participants with attenuated symptom onsets of less than 1-year.

As shown in Table 2, the duration or severity of attenuated positive symptoms was not significantly related to role or social outcome. In contrast, longer duration of negative symptoms ($P = 0.004$) and greater total SOPS negative symptom severity at baseline ($P = 0.001$) were significant predictors of poor social functioning at study outcome (Table 2).

When this regression analysis was re-run after removing N1-Social Anhedonia from the calculation of duration and severity levels, the duration of negative symptoms ($P = 0.014$)

and total SOPS negative symptom severity at baseline ($P = 0.045$) continued to contribute significantly to the prediction of social outcome.

3. Discussion

To the best of our knowledge, this is the first study to report on the pre-baseline duration of attenuated positive symptoms and negative symptoms in CHR individuals and their relationships with symptom severity and outcome. The current study did not artificially and arbitrarily restrict the duration of onset or worsening of attenuated positive symptoms to the past 12 months prior to baseline, allowing us to compare the duration of attenuated positive and negative symptoms and to examine if, in fact, the likelihood of conversion to psychosis or poor functioning at study outcome was significantly related to the duration of symptoms. Within this framework, the current study found that more severe attenuated positive symptoms at baseline, but not negative symptom severity nor the duration of attenuated positive or negative symptoms, was predictive of conversion to psychosis. In contrast, a longer duration of negative symptoms was related to poorer social functioning at study outcome.

These results suggest four distinct conclusions about the relationship between the duration of prodromal symptoms and outcome in CHR subjects: (1). In support of the established CHR criteria, attenuated positive symptoms severity is the most critical factor for identifying individuals at imminent risk of developing a psychotic disorder; (2). Duration of attenuated positive symptoms does not add additional information above severity regarding risk for conversion to psychosis; (3). Prodromal negative symptoms appear to be unrelated to the presence and progression of attenuated positive symptoms to psychosis; and (4). Longer duration of negative symptoms, but not of attenuated positive symptoms, appear to be related to long-term social impairment, even prior to the onset of psychosis. Since an important feature of early intervention is to identify deficits and behavioral disturbances that are likely to be major contributing factors to later developing psychotic illness and functional disability, these findings have implications for treatment and prevention.

The current findings that baseline attenuated positive symptom severity levels are the strongest predictors of subsequent psychosis is consistent with long-established previous research (Cornblatt et al., 2015; Ruhrmann et al., 2010; Yung et al., 2003). Given that attenuated positive symptoms represent early, more subtle forms of fully psychotic symptoms, it is likely that the more severe the attenuated symptoms the poorer the prognosis and the more intense the risk of developing a psychotic disorder. In fact, recent findings from the RAP program (Cornblatt et al., 2015) lend support to the notion of using increased severity levels above those used in the standard CHR criteria to identify those individuals at an elevated risk for the development of psychosis. CHR individuals were at particularly higher risk if they displayed disorganized communication at a 3 level or higher on the SOPS and very high levels of suspiciousness (SOPS rated at level 5). However, as also indicated by the RAP study and a number of other prediction studies (Cannon et al., 2008; Cornblatt et al., 2015; Ruhrmann et al., 2010), positive symptoms alone, regardless of severity, are not sufficient for accurately predicting future psychosis. To date, best accuracy levels are reported for studies that also include negative symptoms, principally social decline, and, in

the case of the RAP study, baseline cognitive deficits (specifically verbal memory) (Cornblatt et al., 2015).

In contrast to our expectations and previous reports in at-risk subjects (Nelson et al., 2013; Yung et al., 2003), we did not find a relationship between psychosis risk and attenuated positive symptom duration. On the surface, these findings stand in direct contrast to reports with FEP patients that have found adverse consequences of untreated illness (Robinson et al., 1999). However, these conflicting findings may be related to several factors. First, as detailed above, compared to most CHR/UHR studies, the RAP program does not place a limitation on eligibility based on the duration of attenuated positive symptoms. This approach to duration was very similar to the initial CHR/UHR criteria used by Yung and colleagues (based on the Comprehensive Assessment of At-Risk Mental States, or CAARMS), which allowed positive symptoms that had been present up to five years (Yung et al., 2003). Moreover, since the attenuated positive symptom duration in the present study was comparable to the duration found by Yung and colleagues (Yung et al., 2003), accepting longer duration symptoms does not fully explain our conflicting findings. Second, age differences between CHR samples may also impact the length of symptoms, as the present sample is slightly younger than the CHR sample reported in Yung et al. (2003) (mean age of 19), for example. Finally, the present study did not include CHR subjects with transient psychotic level (SOPS rating of 6) positive symptoms (referred to as Brief Limited Intermittent Psychotic Symptoms or BLIPS, also referred to as Brief Intermittent Psychotic Symptom syndrome or BIPS). Inclusion of BIPS subjects in CHR populations has been understudied (Fusar-Poli et al., 2013). It is possible that since these are among the most severely ill patients, there might be a stronger association between severity, duration, and conversion (Nelson et al., 2013) in the samples that include BIPS as compared to studies such as the current RAP sample that have excluded this subgroup.

Consistent with previous findings (Lencz et al., 2004; Piskulic et al., 2012; Velthorst et al., 2009), the vast majority of the current sample reported experiencing several SOPS Negative symptom items at a moderate or greater intensity level. In fact, 77% of the sample reported a recent decline in occupational functioning (i.e., academic functioning for adolescents), making this SOPS negative item the most prevalent symptom (negative or positive) in the current sample. The present study builds upon previous findings by examining the onset and duration of attenuated negative symptoms in CHR subjects. Contrary to earlier reports on the progression of the illness (Ciompi, 1980; Pfohl and Winokur, 1982; Winokur et al., 1985), negative symptoms were not the product of positive symptoms. Rather, negative symptoms began around 1 year prior to the onset of attenuated positive symptoms and were chronic, with an average length of 4 years. Social anhedonia, for example, seems to be a long-standing problem with a duration of over 4 years prior to baseline. These findings are consistent with earlier reports from FEP patients suggesting impaired social skills are long-standing features of the prodrome and adversely impact long-term functioning (Haas and Sweeney, 1992; Häfner, 2000; Häfner et al., 1999, 2013, 2003; Iyer et al., 2008; Tan and Ang, 2001). Häfner et al. (Häfner, 2000), for example, found that about 75% of FEP patients experienced non-specific and negative symptoms, such as social withdrawal, decline in school functioning, and reduced motivation that preceded the onset of psychosis by 2–4 years (Häfner et al., 1999, 2013, 2003). Thus, data from CHR studies converge with reports

in FEP to suggest that negative symptoms may indicate vulnerability to future functional problems. Even after restricting the calculation of negative symptom duration by removing N1-Social Anhedonia, long-term negative symptoms were still adversely related to social functioning. This pattern is consistent with previous findings in adult patients with an established course of illness that have shown that negative symptoms are more related to social functioning than other aspects of everyday functional outcome (i.e., vocational outcomes), even when accounting for neurocognitive impairments (Leifker et al., 2009; Strassnig et al., 2015). Moreover, past findings from our group have shown that neurocognitive abilities are strongly related to role functioning at outcome, in particular verbal memory deficits (Carrión et al., 2013), further suggesting that certain deficits may be differentially related to specific domains of functioning at outcome. Combined with a lack of relationship with positive symptom severity and duration, negative symptoms may represent core disease components of the illness that do not result from the onset or progression of positive symptoms. Taken together, these results support an early intervention approach specifically targeting social problems and other negative symptoms such as avolition.

There are several limitations of this study that should be considered. First, there were cases that did not have an exact date of onset and were not included in the current analysis. However, every effort was made to ensure the accuracy of symptom onset dates for the subjects that were included, based on clinician-rated best estimates from all available information. Second, while originally modeled after the Positive and Negative Syndrome Scale (PANSS), the SIPS negative symptom scale may not be as comprehensive as other negative symptom rating scales, such as the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982), which measure a broader range of negative symptoms (e.g., apathy and amotivation). However, these scales may not be fully appropriate for assessing the onset of negative symptoms in an adolescent/young adult population (Pelletier and Mittal, 2013). Finally, the differing and sometimes low prevalence rates for individual symptom items make it difficult to draw any conclusions regarding the relationship between any one symptom item and specific outcomes. Future research should confirm the ability of negative symptom duration and the duration of specific negative symptoms to prospectively identify risk of future social functioning impairments in individuals at clinical high risk for developing psychosis.

Taken together, our findings may be relevant to the proposed onset criteria (i.e., symptom(s) must have begun in the past year) of attenuated positive symptoms that was applied to the Attenuated Psychosis Syndrome (APS) diagnosis currently included in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) in Section III under “conditions for further study” as well as in Section II as an example of “Other Specified Schizophrenia Spectrum and Other Psychotic Disorders.” The APS criteria were based on the premise that attenuated positive symptoms with a more recent onset (i.e., within the past year) would confer a greater risk of progression to full-blown psychosis, as opposed to longstanding symptoms that may reflect other conditions that have a lower risk of developing psychosis (i.e., schizotypal personality disorder) (McGlashan et al., 2010). In the present study participants were not excluded if the “prodromal” level attenuated positive symptom (i.e., SOPS rated 3–5) was of a long duration (i.e., onset greater than a year prior to ascertainment). Indeed, many of the CHR+ subjects had attenuated positive symptoms

that were more broadly defined and not limited to an onset during the past 1-year. Despite these differences in the research criteria, our sample had a low baseline rate of schizotypal personality disorder (9%) and a conversion rate of almost 20% after 4 years of study. This would suggest that the SIPS restrictions may be more relevant for clinical practice and research concerned with immediate intervention, especially clinical trials with short follow-up periods. However, symptoms of duration longer than a year may be of value in flagging a second type of risk population, particularly suitable for research focusing on early developmental processes and mechanisms in addition to prevention. Prodromal populations might well be expanded to include durations of up to five years pre-onset as was originally proposed by Yung, McGorry, and colleagues (Schultze-Lutter et al., 2013).

In conclusion, our findings further clarify the course of early positive and negative symptoms and their relationships to clinical and functional outcome. Severity of attenuated positive symptoms plays a more important role than duration for predicting those at increased risk of conversion to psychosis. In contrast, longer duration negative symptoms may be more related to increased risk of poor social functioning and long-term functional disability.

Acknowledgments

We thank the study participants and entire staff of the RAP Program for their time and effort from the very onset of these studies.

Funding

Supported by grants from the National Institute of Mental Health (NIMH): MH61523 (Dr. Cornblatt), the Zucker Hillside Hospital Advanced Center for Intervention and Services Research for the Study of Schizophrenia MH 074543 (John M Kane, M.D.). No funding source exerted any editorial direction or censorship on any part of this manuscript.

References

- Andreasen NC. Negative symptoms in schizophrenia. Definition and reliability. *Archives General Psychiatry*. 1982; 39:784–788.
- Boonstra N, Klaassen R, Sytema S, Marshall M, De Haan L, Wunderink L, Wiersma D. Duration of untreated psychosis and negative symptomsea systematic review and meta-analysis of individual patient data. *Schizophrenia Res*. 2012; 142:12–19.
- Bottlender R, Sato T, Jager M, Kunze I, Groll C, Borski I, Moller HJ. Does considering duration of negative symptoms increase their specificity for schizophrenia? *Schizophrenia Res*. 2003; 60:321–322.
- Buchanan RW. Persistent negative symptoms in schizophrenia: an overview. *Schizophr. Bull*. 2007; 33:1013–1022. [PubMed: 17099070]
- Cannon TD, Cadenhead K, Cornblatt B, Woods SW, Addington J, Walker E, Seidman LJ, Perkins D, Tsuang M, McGlashan T, Heinssen R. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Arch. Gen. Psychiatry*. 2008; 65:28–37. [PubMed: 18180426]
- Carrión RE, Goldberg TE, McLaughlin D, Auther AM, Correll CU, Cornblatt BA. Impact of neurocognition on social and role functioning in individuals at clinical high risk for psychosis. *Am. J. Psychiatry*. 2011; 168:806–813. [PubMed: 21536691]
- Carrión RE, McLaughlin D, Goldberg TE, Auther AM, Olsen RH, Olvet DM, Correll CU, Cornblatt BA. Prediction of functional outcome in individuals at clinical high risk for psychosis. *JAMA Psychiatry*. 2013; 70:1133–1142. [PubMed: 24006090]

- Choi JS, Chon MW, Kang DH, Jung MH, Kwon JS. Gender difference in the prodromal symptoms of first-episode schizophrenia. *J. Korean Med. Sci.* 2009; 24:1083–1088. [PubMed: 19949664]
- Chung YC, Jung HY, Kim SW, Lee SH, Shin SE, Shin YM, Park JI, An SK, Kim YH. What factors are related to delayed treatment in individuals at high risk for psychosis? *Early Interv. Psychiatry.* 2010; 4:124–131. [PubMed: 20536968]
- Ciompi L. Catamnestic long-term study on the course of life and aging of schizophrenics. *Schizophr. Bull.* 1980; 6:606–618. [PubMed: 7444392]
- Cornblatt BA, Auther AM, Niendam T, Smith CW, Zinberg J, Bearden CE, Cannon TD. Preliminary findings for two new measures of social and role functioning in the prodromal phase of schizophrenia. *Schizophr. Bull.* 2007; 33:688–702. [PubMed: 17440198]
- Cornblatt BA, Carrión RE, Addington J, Seidman L, Walker EF, Cannon TD, Cadenhead KS, McGlashan TH, Perkins DO, Tsuang MT, Woods SW, Heinssen R, Lencz T. Risk factors for psychosis: impaired social and role functioning. *Schizophr. Bull.* 2012; 38:1247–1257. [PubMed: 22080497]
- Cornblatt BA, Carrión RE, Auther AM, McLaughlin D, Olsen RH, John M, Correll CU. Psychosis prevention: a modified strategy for selecting individuals at clinical high-risk for psychosis. *Am. J. Psychiatry.* 2015; 172:986–994. [PubMed: 26046336]
- Cornblatt BA, Lencz T, Smith CW, Correll CU, Auther AM, Nakayama E. The schizophrenia prodrome revisited: a neurodevelopmental perspective. *Schizophr. Bull.* 2003; 29:633–651. [PubMed: 14989404]
- Correll CU, Hauser M, Auther AM, Cornblatt BA. Research in people with psychosis risk syndrome: a review of the current evidence and future directions. *J. Child. Psychol. Psychiatry.* 2010; 51:390–431. [PubMed: 20214698]
- Cuesta MJ, García de Jalón E, Campos MS, Ibáñez B, Sánchez-Torres AM, Peralta V. Duration of untreated negative and positive symptoms of psychosis and cognitive impairment in first episode psychosis. *Schizophr. Res.* 2012; 141:222–227. [PubMed: 22989921]
- Fusar-Poli P, Borgwardt S, Bechdolf A, Addington J, Riecher-Rossler A, Schultze-Lutter F, Keshavan M, Wood S, Ruhrmann S, Seidman LJ, Valmaggia L, Cannon T, Velthorst E, De Haan L, Cornblatt B, Bonoldi I, Birchwood M, McGlashan T, Carpenter W, McGorry P, Klosterkötter J, McGuire P, Yung A. The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA Psychiatry.* 2013; 70:107–120. [PubMed: 23165428]
- Fusar-Poli P, Meneghelli A, Valmaggia L, Allen P, Galvan F, McGuire P, Cocchi A. Duration of untreated prodromal symptoms and 12-month functional outcome of individuals at risk of psychosis. *Br. J. Psychiatry.* 2009; 194:181–182. [PubMed: 19182184]
- Haas GL, Sweeney JA. Premorbid and onset features of first-episode schizophrenia. *Schizophr. Bull.* 1992; 18:373–386. [PubMed: 1411328]
- Häfner H. Onset and early course as determinants of the further course of schizophrenia. *Acta Psychiatr. Scand. Suppl.* 2000; 102:44–48. [PubMed: 11261639]
- Häfner H, Löffler W, Maurer K, Hambrecht M, an der Heiden W. Depression, negative symptoms, social stagnation and social decline in the early course of schizophrenia. *Acta Psychiatr. Scand.* 1999; 100:105–118. [PubMed: 10480196]
- Häfner H, Maurer K, an der Heiden W. ABC Schizophrenia study: an overview of results since 1996. *Soc. Psychiatry Psychiatr. Epidemiol.* 2013; 48:1021–1031. [PubMed: 23644725]
- Häfner H, Maurer K, Löffler W, an der Heiden W, Hambrecht M, Schultze-Lutter F. Modeling the early course of schizophrenia. *Schizophr. Bull.* 2003; 29:325–340. [PubMed: 14552507]
- Iyer SN, Boekestyn L, Cassidy CM, King S, Joobar R, Malla AK. Signs and symptoms in the pre-psychotic phase: description and implications for diagnostic trajectories. *Psychol. Med.* 2008; 38:1147–1156. [PubMed: 18366823]
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J. Am. Stat. Assoc.* 1958; 53:457–481.
- Keshavan MS, Haas G, Miewald J, Montrose DM, Reddy R, Schooler NR, Sweeney JA. Prolonged untreated illness duration from prodromal onset predicts outcome in first episode psychoses. *Schizophr. Bull.* 2003; 29:757–769. [PubMed: 14989413]

- Leifker FR, Bowie CR, Harvey PD. Determinants of everyday outcomes in schizophrenia: the influences of cognitive impairment, functional capacity, and symptoms. *Schizophr. Res.* 2009; 115:82–87. [PubMed: 19775869]
- Lencz T, Smith CW, Auther A, Correll CU, Cornblatt B. Nonspecific and attenuated negative symptoms in patients at clinical high-risk for schizophrenia. *Schizophrenia Res.* 2004; 68:37–48.
- McGlashan, T.; Walsh, B.; Woods, S. *The Psychosis-Risk Syndrome: Handbook for Diagnosis and Follow-Up.* Oxford University Press; 2010.
- McGlashan TH. Early detection and intervention of schizophrenia: rationale and research. *Br. J. Psychiatry Suppl.* 1998; 172:3–6. [PubMed: 9764119]
- McGlashan TH. Duration of untreated psychosis in first-episode schizophrenia: marker or determinant of course? *Biol. Psychiatry.* 1999; 46:899–907. [PubMed: 10509173]
- McGlashan TH, Johannessen JO. Early detection and intervention with schizophrenia: rationale. *Schizophr. Bull.* 1996; 22:201–222. [PubMed: 8782282]
- McGorry PD, Killackey E, Yung AR. Early intervention in psychotic disorders: detection and treatment of the first episode and the critical early stages. *Med. J. Aust.* 2007; 187:S8–S10. [PubMed: 17908033]
- Miller TJ, McGlashan TH, Rosen JL, Cadenhead K, Cannon T, Ventura J, McFarlane W, Perkins DO, Pearlson GD, Woods SW. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophr. Bull.* 2003; 29:703–715. [PubMed: 14989408]
- Miller TJ, McGlashan TH, Rosen JL, Somjee L, Markovich PJ, Stein K, Woods SW. Prospective diagnosis of the initial prodrome for schizophrenia based on the structured interview for prodromal syndromes: preliminary evidence of interrater reliability and predictive validity. *Am. J. Psychiatry.* 2002; 159:863–865. [PubMed: 11986145]
- Miller TJ, McGlashan TH, Woods SW, Stein K, Driesen N, Corcoran CM, Hoffman R, Davidson L. Symptom assessment in schizophrenic prodromal states. *Psychiatr. Q.* 1999; 70:273–287. [PubMed: 10587984]
- Murphy BP, Stuart AH, McGorry PD. Duration of untreated negative symptoms and duration of active negative symptoms: proof of concepts. *Early Interv. Psychiatry.* 2008; 2:27–33. [PubMed: 21352128]
- Nelson B, Yuen HP, Wood SJ, Lin A, Spiliotacopoulos D, Bruxner A, Broussard C, Simmons M, Foley DL, Brewer WJ, Francey SM, Amminger GP, Thompson A, McGorry PD, Yung AR. Long-term follow-up of a group at ultra high risk (“prodromal”) for psychosis: the PACE 400 study. *JAMA Psychiatry.* 2013; 70:793–802. [PubMed: 23739772]
- Orvaschel, H.; Puig-Antich, J. *Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version.* Center for Psychological Studies, Nova Southeastern University; Fort Lauderdale, FL: 1994.
- Pelletier AL, Mittal VA. Negative symptom measurement in individuals at-risk for psychosis. *Psychiatry Res.* 2013; 205:181–182. [PubMed: 22974520]
- Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am. J. Psychiatry.* 2005; 162:1785–1804. [PubMed: 16199825]
- Pfohl B, Winokur G. The evolution of symptoms in institutionalized hebephrenic/catatonic schizophrenics. *Br. J. Psychiatry.* 1982; 141:567–572. [PubMed: 7159803]
- Piskulic D, Addington J, Cadenhead KS, Cannon TD, Cornblatt Ba, Heinssen R, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, Woods SW, McGlashan TH. Negative symptoms in individuals at clinical high risk of psychosis. *Psychiatry Res.* 2012; 196:220–224. [PubMed: 22445704]
- Robinson DG, Woerner MG, Alvir JM, Geisler S, Koreen A, Sheitman B, Chakos M, Mayerhoff D, Bilder R, Goldman R, Lieberman JA. Predictors of treatment response from a first episode of schizophrenia or schizo-affective disorder. *Am. J. Psychiatry.* 1999; 156:544–549. [PubMed: 10200732]
- Ruhrmann S, Schultze-Lutter F, Salokangas RK, Heinimaa M, Linszen D, Dingemans P, Birchwood M, Patterson P, Juckel G, Heinz A, Morrison A, Lewis S, von Reventlow HG, Klosterkötter J. Prediction of psychosis in adolescents and young adults at high risk: results from the prospective

- European prediction of psychosis study. Arch. Gen. Psychiatry. 2010; 67:241–251. [PubMed: 20194824]
- Schultze-Lutter F, Schimmelmann BG, Ruhrmann S, Michel C. 'A rose is a rose is a rose', but at-risk criteria differ. Psychopathology. 2013; 46:75–87. [PubMed: 22906805]
- Strassnig MT, Raykov T, O'Gorman C, Bowie CR, Sabbag S, Durand D, Patterson TL, Pinkham A, Penn DL, Harvey PD. Determinants of different aspects of everyday outcome in schizophrenia: the roles of negative symptoms, cognition, and functional capacity. Schizophr. Res. 2015; 165:76–82. [PubMed: 25868935]
- Tan HY, Ang YG. First-episode psychosis in the military: a comparative study of prodromal symptoms. Aust. N. Z. J. Psychiatry. 2001; 35:512–519. [PubMed: 11531734]
- Velthorst E, Nieman DH, Becker HE, van de Fliert R, Dingemans PM, Klaassen R, de Haan L, van Amelsvoort T, Linszen DH. Baseline differences in clinical symptomatology between ultra high risk subjects with and without a transition to psychosis. Schizophr. Res. 2009; 109:60–65. [PubMed: 19272756]
- Winokur G, Scharfetter C, Angst J. Stability of psychotic symptomatology (delusions, hallucinations), affective syndromes, and schizophrenic symptoms (thought disorder, incongruent affect) over episodes in remitting psychoses. Eur. Arch. Psychiatry Neurol. Sci. 1985; 234:303–307. [PubMed: 3987739]
- Yung AR, McGorry PD. The prodromal phase of first-episode psychosis: past and current conceptualizations. Schizophr. Bull. 1996; 22:353–370. [PubMed: 8782291]
- Yung AR, McGorry PD, McFarlane CA, Jackson HJ, Patton GC, Rakkar A. Monitoring and care of young people at incipient risk of psychosis. Schizophr. Bull. 1996; 22:283–303. [PubMed: 8782287]
- Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M, McGorry PD. Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. Schizophrenia Res. 2003; 60:21–32.
- Yung AR, Yuen HP, Berger G, Francey S, Hung TC, Nelson B, Phillips L, McGorry P. Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk? Schizophr. Bull. 2007; 33:673–681. [PubMed: 17404389]

Fig. 1.

Pre-Baseline Duration of Attenuated Negative and Positive Symptoms in subjects at CHR+. Dotted lines represent the mean duration for positive ($M = 40.15$ months, $SD = 40.33$, range 2.23–191.67 months, median = 24.77) and negative ($M = 53.24$ months, $SD = 48.90$, range 0.62–174.92 months, median = 37.27) symptoms.

Table 1

Demographic and clinical characteristics.

Characteristic	CHR+ (<i>n</i> = 76)
Baseline	
Age, y, mean (SD)	16.00 (2.19)
Gender, No. (%)	
Male	52 (68.4)
Race, No. (%)	
White	60 (78.9)
Ethnic Origin	
Hispanic, No. (%)	11 (14.5)
GAF, mean (SD)	46.29 (7.95)
Schizotypal Personality Disorder, No. (%)	7 (9.2)
GFS, mean (SD)	
Social	6.11 (1.53)
Role	5.46 (2.00)
SIPS Attenuated Positive Symptoms, Rated 3, No. (%)	
P1 – Unusual Thought Content	29 (38.16)
P2 – Suspiciousness	52 (68.42)
P3 – Grandiosity	5 (6.58)
P4 – Perceptual Abnormalities	25 (32.89)
P5 – Disorganized Communication	14 (18.42)
SIPS Total Positive symptom score, mean (SD)	8.70 (3.98)
Duration of SIPS Positive Symptoms, months, mean (SD)	40.15 (40.33)
SIPS Negative Symptoms, Rated 3, No. (%)	
N1 – Social Anhedonia	45 (59.21)
N2 – Avolition	35 (46.05)
N3 – Expression of Emotion	9 (11.84)
N4 – Experience of Emotion	12 (15.79)
N5 – Ideational Richness	8 (10.53)
N6 – Occupational Functioning	59 (77.63)
SIPS Negative symptoms score, mean (SD)	13.44 (5.29)
Duration of SIPS Negative Symptoms, months, mean (SD)	53.24 (48.90)
Outcome	
GAF, mean (SD)	54.66 (13.54)
GFS, mean (SD)	
Social	6.41 (1.61)
Role	6.04 (2.54)
SIPS score, mean (SD)	
Positive	4.94 (5.13)
Negative	9.06 (6.96)

Note: SIPS, structured interview for prodromal syndromes; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

Table 2

Relationships between the duration of attenuated positive and negative symptoms and conversion to psychosis and functional outcome.

Predictor variable	B	SE	Wald	HR/OR	95% CI	p
Conversion to psychosis						
Duration of positive symptoms	0.000	0.000	0.672	1.000	0.999–1.000	0.412
Duration of negative symptoms	0.000	0.000	0.098	1.000	1.000–1.000	0.754
Total positive symptoms	0.206	0.071	8.323	1.229	1.068–1.413	0.004
Total negative symptoms	0.055	0.076	0.524	1.056	0.911–1.225	0.469
Age at baseline	0.300	0.154	3.792	1.350	0.998–1.825	0.051
GAF	0.067	0.045	2.234	1.070	0.979–1.169	0.135
Social outcome						
Duration of positive symptoms	−0.010	0.008	1.787	0.990	0.975–1.005	0.181
Duration of negative symptoms	0.020	0.007	8.297	1.020	1.006–1.034	0.004
Total positive symptoms	0.037	0.067	0.299	1.038	0.909–1.184	0.584
Total negative symptoms	0.231	0.071	10.619	1.260	1.096–1.448	0.001
GAF	0.011	0.040	0.080	1.011	0.935–1.094	0.777
Age at baseline	−0.182	0.130	1.966	0.834	0.647–1.075	0.161
Role outcome						
Duration of positive symptoms	0.001	0.006	0.025	1.001	0.988–1.014	0.875
Duration of negative symptoms	0.001	0.005	0.048	1.001	0.991–1.012	0.827
Total positive symptoms	0.065	0.064	1.025	1.067	0.941–1.209	0.311
Total negative symptoms	0.056	0.056	1.025	1.058	0.949–1.180	0.311
GAF	−0.042	0.039	1.123	0.959	0.888–1.036	0.289
Age at baseline	−0.263	0.123	4.561	0.769	0.604–0.979	0.033

Abbreviations HR, Hazard Ratio; OR, Odds Ratio; CI, confidence interval; SE, Standard Error.

Significant values ($P < 0.05$) shown in bold.