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Negative Symptoms and Functioning During the First Year after a Recent Onset of Schizophrenia and Eight Years Later

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Abstract

Background—Understanding the longitudinal course of negative symptoms, especially in relationship to functioning, in the early phase of schizophrenia is crucial to developing intervention approaches. The course of negative symptoms and daily functioning was examined over a one-year period following a recent onset of schizophrenia and at an 8-year follow-up point.

Methods—The study included 149 recent-onset schizophrenia patients who had a mean age of 23.7 (SD=4.4) years and mean education of 12.9 (SD=2.2) years. Negative symptom (BPRS and SANS) and functional outcome (SCORS) assessments were conducted frequently by trained raters.

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Conflict of Interest

Joseph Ventura, Ph.D., has received funding from Janssen Scientific Affairs, LLC, Brain Plasticity, Inc., and Genentech, Inc. He has served as a consultant to Brain Plasticity, Inc., and Boehringer-Ingelheim, GmbH.
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Kathleen F. Villa was an employee of Genentech, Inc. at the time that this work was completed and is now an employee of Jazz Pharmaceuticals, plc.
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Contributors

Drs. Keith Nuechterlein and Michael Gitlin conceived of the study design and obtained funding to conduct the study. Drs. Ventura and Nuechterlein trained and supervised research staff on the data collection process and the daily operations of the clinical staff. Dr. Ventura selected the variables of interest, participated in data analysis, and prepared the manuscript. All authors read and commented on initial drafts and approved the final manuscript. Dr. Hellemann conducted the data analysis and drafted portions of the results. Ms. Ered complied the raw data, coded data, created data bases used for data analysis, preformed literature searches, and created tables.

Results—After antipsychotic medication stabilization, negative symptoms during the first outpatient year were moderately stable (BPRS ICC=0.64 and SANS ICC=0.66). Despite this overall moderate stability, 24% of patients experienced at least one period of negative symptoms exacerbation. Furthermore, entry level of negative symptoms was significantly associated with poor social functioning (r =−.34, p < .01) and work/school functioning (r =−.25, p < .05) at 12 months, and with negative symptoms at the 8-year follow-up (r =.29, p <.05).

Discussion—Early negative symptoms are fairly stable during the first outpatient year, are predictors of daily functioning at 12 months, and predict negative symptoms 8 years later. Despite the high levels of stability, negative symptoms did fluctuate in a subsample of patients. These findings suggest that negative symptoms may be an important early course target for intervention aimed at promoting recovery.

Introduction

Recently, there has been a rather large resurgence of interest in virtually all aspects of negative symptoms, most likely fueled by the robust and consistent finding that negative symptoms are linked to a variety of central features of schizophrenia. Specifically, the current direction of findings in early course patients parallels findings in chronic patients that negative symptoms are prevalent (57% had at least one), persistent, and have an adverse impact on functioning (Bobes et al., 2010). The evidence is mounting that, even in first episode patients, negative symptoms are often a core feature. Like cognitive deficits, negative symptoms have prognostic importance, are associated with poor functioning, and have been shown to have their onset prior to the emergence of positive symptoms (Harvey et al., 2006). Despite their central role in the illness, negative symptoms have proven to be resistant to psychopharmalogical treatment with currently available medications. In fact, treating negative symptoms in schizophrenia patients with the aim of achieving sustained periods of remission can very challenging (Levine and Leucht, 2013). There is an interest in knowing more about the nature and impact of negative symptoms because such findings may inform the search for new drugs and the development of psychosocial interventions. Knowing early prevalence rates, including the percentage of patients with clinically significant negative symptoms at baseline and persisting at various follow-up points, would help provide general benchmarks for identifying negative symptom severity.

Follow-up studies of early course patients, although few in number, have that negative symptoms are present at baseline, tend to be stable and persistent, but can fluctuate in severity. The negative symptom assessments for most of those studies have been cross-sectional in nature, covering about a one-week to one-month period. The percentages of patients with clinically significant negative symptoms at baseline ranged from substantial to very substantial: 25.8, 33%, and 71%, (Chang et al., 2011; Evensen et al., 2012; Galderisi et al., 2013), respectively. Prevalence rates of negative symptoms at one-year and three-year follow-up varied: 6.7%, 23.7%, 27% (Chang et al., 2011; Galderisi et al., 2013; Hovington et al., 2012). These studies also suggest that early negative symptoms can persist, as they are present at subsequent follow-up points for up to 10 years (Evensen et al., 2012) and might become more prevalent over time (Chang et al., 2011). Differing definitions of negative symptoms and the cross-sectional assessment methodology used in most studies may have

impacted these rates. Interestingly, a persisting negative symptom of rate of 20% has been reported in the same patients at baseline and then again at one-year (Galderisi et al., 2013). However, baseline levels of negative symptoms can change (Subotnik et al., 1998). When patients were followed for up to 10 years and flat affect was measured at various follow-up time points, symptoms were found to change from remitted to present, or, conversely, from present to remitted (Evensen et al., 2012). The authors concluded that flat affect can fluctuate in as high as 40% of patients. However, fewer follow-through studies have been conducted in which relatively frequent assessments of negative symptoms were conducted.

Important predictive links have been found in the early course of schizophrenia, mostly indicating that higher negative symptom severity is associated with poor daily functioning and worse long-term outcomes (Chang et al., 2013; Evensen et al., 2012; Hovington et al., 2012; White et al., 2009). Because cognition is a robust predictor of functioning, some studies have examined the differential impact of cognition and negative symptoms on outcome. Interestingly, negative symptoms can make a separate, non-overlapping contribution to the prediction of functioning, beyond the joint contribution with cognition (Henry et al., 2007; Milev, 2005; Peña et al., 2012). In addition, a meta-analysis that focused primarily on studies of chronic patients indicated that negative symptoms mediated the relationship between neurocognition and functional outcome (Ventura et al., 2009a). This relationship has recently been observed in first episode patients cross-sectionally and in a 5-year follow-up study, confirming the influence of negative symptoms on functioning (González-Ortega et al., 2012; Lin et al., 2013). Further, the presence of negative symptoms at baseline has been proposed as a risk factor that contributes to the failure to achieve functional recovery (Albert et al., 2011; Leslie et al., 2004; Siegel et al., 2006). Studies of First Episode Psychosis (FEP) concurred with previous studies indicating that negative symptoms are a rate limiting factor that often accounts for absence of functional recovery in schizophrenia patients (Leslie et al., 2004; Savla et al., 2013; Ventura et al., 2011). There is very strong support for the importance of negative symptoms in the early course of schizophrenia in that negative symptoms, whether they were present at baseline, were stable or persisting, or acted as a mediator, have a broad influence on functional outcome. However, most of the studies used a follow-up design, rather than a design in which patients were continuously treated, assessed, and then followed-up.

We aimed to examine in recent-onset schizophrenia patients: 1) prevalence rates of negative symptoms at baseline, 2) stability of negative symptoms in a first follow-through year and at 8-year follow-up point, 3) the percentage of patients who show a remitting and relapsing negative symptom course similar to positive symptoms, and 4) relationships between negative symptoms and daily functioning.

Methods

Subjects

The sample involved 149 schizophrenia patients who had an initial onset of psychosis within two years prior to study entry, 82% of whom were experiencing a first episode. Subsamples were used to address some questions, as the number of subjects varied with available data of a given type. All subjects were participants in Samples 1 and 2 of the Developmental

Processes in Schizophrenic Disorders Project and were followed clinically in the UCLA Aftercare Research Program, which specializes in the treatment of recent-onset schizophrenia patients. The demographic and diagnostic characteristics of the combined sample, as well as medication dose in chlorpromazine equivalents (Andreasen et al., 2010) are provided in Table 1.

The patient characteristics and research protocols for Samples 1 and 2 are described in detail elsewhere so will only be briefly reviewed (Nuechterlein et al., 1992; Nuechterlein et al., 2011). For both samples, diagnostic, demographic, psychiatric, and social history data were collected at study entry, usually immediately following a psychiatric hospitalization. All raters were trained to criterion levels of interrater reliability and administered either an expanded version of the Present State Exam (Wing et al. 1974) or the Structured Diagnostic Interview for DSM-IV (SCID) to determine the diagnosis (First et al., 1996). After discharge from the index hospitalization, the patients were treated during their first outpatient year by a team of psychiatrists, psychologists, and social workers. Outpatient medication stabilization (but not necessarily clinical remission) was established on average three months after hospital discharge. All patients completed an informed consent process and signed UCLA IRB-approved informed consent documents.

Procedures

Treatment Protocols

Sample 1: Sample 1 (n=102) included patients who received individual and group therapy conducted by a case manager focusing on social skills and psychoeducation while working within the context of a treatment team. Patients were initially seen weekly by their case manager and psychiatrist, and then at two-week intervals. Family members were provided with psychoeducation. Medication treatment for all patients involved the administration of a standard starting dosage of injectable maintenance antipsychotic medication, 12.5 mg fluphenazine decanoate every two weeks, with adjustments within the 6.25 mg to 12.5 mg range if intolerable side effects developed. Dosages above 12.5 mg were given if clinically necessary to control psychotic symptoms. Of the 102 patients in Sample 1, 53 were reassessed at a follow-up point 8 years later (Table 2), an attrition rate of 48%. Patients successfully assessed after 8 years were generally demographically similar to those who could not be located and assessed at 8 years, except that those assessed were somewhat more likely to be single at baseline.

Sample 2: The research protocol, including entry criteria, assessment measures and procedures, and psychosocial treatments, etc., for Sample 2 (n=48) was very similar to that of Sample 1. However, oral risperidone was used as the standardized initial antipsychotic medication. Dosage was set by the treating psychiatrist during the initial stabilization phase to optimize clinical response. Changes in antipsychotic medication could be made for lack of a therapeutic response or if intolerable side effects occurred. There was no attempt for follow-up at 8 years with the patients from Sample 2.

In both samples (Table 1), we did not use specific work or school training or vocational rehabilitation interventions, such as Individual Placement and Support (Becker and Drake,

2003). Rather, patients were encouraged to use the Los Angeles County Vocational Rehabilitation Service after a period of convalescence.

Assessment Protocol—Symptom assessments were conducted by trained raters during the index hospitalization and immediately after discharge, as well as from the initial point of outpatient medication stabilization. Raters were trained to conduct symptom assessments to a criterion ICC=.80 or greater and were entered into a quality assurance program to prevent rater drift (Ventura et al., 1993a). Symptoms were assessed every two weeks during the first outpatient year and once at the 8-year follow-up using the Brief Psychiatric Rating Scale (Ventura et al., 1993b). The full Schedule for Assessment of Negative Symptoms (Andreasen, 1984) was added in the latter part of this study and was administered every 3 months to provide an assessment of a more complete range of negative symptoms. Functional assessments with the Strauss-Carpenter Outcome Scale (Strauss and Carpenter, 1972) were completed at the outpatient stabilization baseline point, at 3 months, 6 months, 9 months, 12 months, and at an 8-year follow-up point.

Assessment Measures

Psychiatric and Social History Schedule: Demographic information and premorbid history data were collected at intake using a structured form. Data included age, gender, patient level of education, first appearance of psychotic and prodromal symptoms, and prior psychiatric treatments including antipsychotic medications and hospitalizations.

Symptom Assessment

Brief Psychiatric Rating Scale (BPRS): Each BPRS rater achieved a median intraclass correlation coefficient (ICC) of .80 or higher across all items compared with the criterion ratings, and participated in a quality assurance program (Ventura et al., 1993a). Each patient was rated by a trained rater on an expanded version of the BPRS (Lukoff et al., 1986) at the point of outpatient medication stabilization and every two weeks during the first post-hospitalization year.

Scale for the Assessment of Negative Symptoms (SANS): Trained raters administered the SANS which is widely used to assess two negative symptom domains: 1) Expressive symptoms, which consists of Affective Flatting (blunted affect) and Alogia, and 2) Experiential symptoms, which consists of Avolition/Apathy and Asociality/Anhedonia. The global ratings for each of these negative symptom domains were combined to create the SANS composite. The Attention subscale was not included in these analyses due to the strong correlational relationship to cognitive functioning (Andreasen et al., 2005).

Functional Assessment

Strauss-Carpenter Outcome Rating Scale (SCORS) (Strauss and Carpenter, 1972): This scale contains four discrete dimensions of outcome. Two were relevant to functional outcome: the frequency of social contacts and the amount of school or useful work participation. The SCORS was administered at the point of outpatient medication stabilization, every three months during the first out-patient year, and at the 8-year follow-up point. The assessment covered the period three-months prior to assessment.

Data Analysis

For prediction of negative symptom stability and functional outcome at the 8–year point, we calculated negative symptom levels for each of three time periods during the first outpatient year: **Study Entry** (period immediately after an episode), **Medication Stabilization** (the period of initial medication stabilization on average three months post-hospitalization), and the **One-Year Average** of negative symptoms across the first outpatient year after Medication Stabilization (months 0 to 12).

We calculated the stability of BPRS and SANS rated negative symptoms obtained during the first outpatient year by using an ICC statistic from the statistical software program R. The ICC has advantages over a zero-order correlation coefficient in that it is adjusts for the effects of variability in scale measurement. The ICCs in this study were calculated following the methods of Bliese (1998), allowing for an unequal number of observations for the different subjects. From the BPRS, we examined a negative symptom factor that was comprised of three symptoms: Blunted Affect, Emotional Withdrawal, and Motor Retardation. The results of most factor analyses of the BPRS show that these three items form a negative symptom factor (Ventura et al., 2000). From the SANS, we used: 1) Expressive symptoms, 2) Experiential symptoms, and 3) the SANS total score (without the Attention domain).

Using the same BPRS ratings, another approach was used to examine the possible occurrence of periods of negative symptom exacerbation in the first outpatient year. We adapted a classification system developed for positive symptom episodes in order to identify periods of significant exacerbation, remission, and persisting negative symptoms (Nuechterlein et al., 2006). This categorization involves explicit criteria for identifying significant fluctuations in symptoms over time, distinguishes among different types of relapsing outcomes, identifies individuals with gradual improvement of symptoms, and continuous remissions. It provides high interrater agreement.

To examine the domains of functional outcome: social functioning, and employment/school functioning we used ratings that were made for the period of 9–12 months and at the 8 year follow-up point. Hierarchical logistic regression was used to determine if the three negative symptom periods predicted the level of functional outcome at 9–12 months and at the 8-year follow-up point.

Results

Stability of Negative Symptoms During the First Outpatient Year

Negative symptoms assessed with the BPRS every two weeks from the point of outpatient stability to the one-year point during the first outpatient year were moderately stable (ICC=. 64; Table 3), as were the three negative symptoms that were included in the negative symptom factor. This analysis included n=119 patients who had between 11 and 53 BPRS assessments (M=24.9; SD=6.6) that covered between 284 and 432 outpatient days (M= 365; SD=20.4). The total number of BPRS observations was 2,975.

The pattern of stability for the SANS assessments was similar to the negative symptoms measured using the BPRS. We found that the three SANS negative symptom scores were stable: SANS Negative Symptom Total score (ICC=.66), the Expressive score (ICC=.64), and the SANS Experiential score (ICC=.60).

Classifying Periods of Negative Symptom Exacerbation

Beyond the overall moderate stability of negative symptoms in the early course of schizophrenia, 24% of patients (36/149) had at least one period of negative symptom exacerbation that met criteria for one of the following: 1) remission followed by relapse, 2) remission followed by significant exacerbation, or 3) persisting symptoms followed by significant exacerbation. Of those 36 patients with a negative symptom exacerbation, 5% (7/149) of patients had two periods of negative symptom exacerbations within the first outpatient year. Thus, although negative symptoms appear to be moderately stable over time, a small minority of patients have periods of negative symptom exacerbations.

Relationship of Negative Symptoms to Functional Outcome Rated During the First Outpatient Year

We note that the level of BPRS negative symptoms at study entry moderately predicted social functioning ($r = -.34$, $p < .01$) and work/school functioning ($r = -.25$, $p < .05$) at the 9–12 month follow-up point (Table 4). Analyses with the SANS total score at **Study Entry** and **Medication Stabilization** suggest that negative symptoms predict work/school functioning ($r = -.53$, $p < .01$, $r = -.62$, $p < .01$, respectively), and to a lesser extent, social functioning ($r = -.23$, $p < .05$)(Table 4). However, these findings are based on a subsample of patients for whom the SANS was collected later in the study.

Relationship of Negative Symptom Severity During the First Outpatient Year to Negative Symptoms and Functioning at the 8-Year Follow-Up

The BPRS **Study Entry** and **One-Year Average** negative symptom levels M(SD) = 2.10(0.99) and M(SD) = 2.13(0.90), respectively) were significantly higher than the BPRS negative symptom levels at the 8-year follow-up point M(SD) = 1.77(1.00), (n=53), $p = .05$ and $p = .02$, respectively). However, BPRS negative symptoms at the **Medication Stabilization** M(SD) = 2.10 (1.60) were not significantly different from negative symptom levels at the 8-year follow-up M(SD) = 1.80(1.03), (n=51), p=.10). For the SANS, negative symptom levels **Study Entry** [M(SD) = 2.58 (1.11) vs. 1.78 (1.13), F(1,18) = 2.49, $p = .02$], **Medication Stabilization** [M(SD) = 2.65 (0.81) vs. 1.90 (1.13), F(1,17) = 3.25, $p = .01$], and **One-year Average** [M(SD) = 2.20 (0.86), n = 23 vs. 1.71 (1.10), F(1,22) = 2.53, $p = .02$] were all significantly higher compared to the 8-year follow-up point.

The BPRS **Study Entry** level of negative symptoms was significantly predictive of the level of negative symptoms rated at the 8–year follow-up ($r = .29$, $p = .02$; Table 5). In addition, BPRS negative symptoms rated at **Medication Stabilization** and the **One-year Average** were both correlated at about the same magnitude with negative symptoms rated 8 years later, indicating that this relationship is moderately stable despite the long intervening interval (Table 5). Although BPRS negative symptoms in the first year showed relationships

to social and work/school functioning at 8 years that were in the expected direction, the correlations were not strong enough to reach statistical significance.

Additional evidence for stability was found in that SANS negative symptom levels at **Medication Stabilization** (r = .54) and the **One-year Average** (r = .54) yielded somewhat higher correlations (than the BPRS) with negative symptoms 8 years later (Table 5). However, the SANS involved a smaller sample size. Also, negative symptoms at **Study Entry** were significantly related to social functioning 8 years later (r = −.47).

Cross-sectional Relationships Between Negative Symptoms and Functioning at the 8 year follow-up Point

Cross-sectional relationships at the 8-year follow-up indicated moderate associations between BPRS negative symptoms and work/school functioning (Table 6). There were no other statistically significant cross-sectional relationships between symptoms and functioning. However, cross-sectional relationships between SANS negative symptoms were stronger in magnitude than for the BPRS with both social functioning, and work/school functioning (Table 6).

BPRS Negative Symptom Severity and Medication Dosage

We conducted an analysis of negative symptoms, including motor retardation, and mediation dose. Correlations were near zero between medication dose in chlorpromazine equivalents (Andreasen et al., 2010) for the BPRS negative symptom factor (r = .00, p = .95) and for the BPRS item Motor Retardation (r = .08, p = .37), a BPRS symptom that has been linked to medication side effects. Similar results were found for medication dose and SANS Expressive (r = −.13, p = .39), SANS Experiential (r = −.26, p = .09), SANS total (r = −.22, p = .15) symptoms indicating that there were no statistically significant relationships with negative symptom severity.

Discussion

This is one of the few follow-through studies that evaluated the longitudinal stability of negative symptoms assessed regularly using two symptom measures (BPRS, SANS) administered to recent-onset schizophrenia patients during their first outpatient year. Analyses of BPRS and SANS ratings demonstrated that there was generally moderate stability of negative symptoms over the first outpatient year. When negative symptoms are present, they tend to remain present in patients, even when assessed frequently. In both the cross-sectional and longitudinal analyses, severity of negative symptoms rated at baseline was moderately predictive of poor social and employment/school functioning during the first outpatient year. A significant level of negative symptom stability extended to the 8-year follow-up period, where despite the number of intervening years, negative symptom severity levels in the first year were correlated with negative symptom severity 8 years later. The implication of this observation is that negative symptoms do not appear to remit spontaneously. Although the impairments associated with negative symptoms identified in this study have previously been found in first-episode patients, this study is among the first

to systematically examine longitudinal patterns of stability with follow-through assessments and to document marked fluctuations of negative symptoms.

Although negative symptoms are generally stable, to determine whether negative symptoms sometimes do show fluctuations similar to episodes of positive symptoms, we used a system that was previously developed for classifying positive symptom episodes. We found that a substantial subgroup of patients (24%) had periods of negative symptom change that were similar to positive symptom episodes. Interestingly, the percentage of early course patients (21%) that showed positive symptom exacerbations (Nuechterlein et al., 2006) is very similar to the percentage that show negative symptom exacerbations (24%). This similarity, as well as the fluctuating nature of negative symptoms suggests that attempts to determine triggers of these exacerbations might prove fruitful. There are several possibilities to explore, such as stressful life events (Ventura et al., 1989), periods of medication non-compliance (Subotnik et al., 2011), or exacerbations of positive symptoms (Ventura et al., 2004). Considering that this is a rather newly observed phenomenon, additional research is needed to determine likelihood and relevance of these possible contributors to negative symptom exacerbations.

In the first outpatient year, we found that negative symptom level was significantly correlated with social functioning, which is consistent with prior studies showing that even early in the course, negative symptoms adversely impact functioning (Evensen et al., 2012). In addition, we found that negative symptom severity was associated with poor employment and school functioning. Perhaps the lack of motivation (avolition) and social withdrawal that is associated with negative symptoms contributes to poor work functioning and school performance. This is consistent with a large literature in chronic schizophrenia indicating the strong association between negative symptoms and functioning (Ventura et al., 2009b). For the 8-year follow-up, cross-sectional relationships between negative symptoms and work / school functioning were similar to those rated during the first outpatient year. Current levels of negative symptoms at the 8-year follow-up point are likely to be a determinant of their current level of employment and school functioning. However, we did not find statistically significant evidence that negative symptoms rated at the 8-year follow-up were associated with current levels of social functioning.

These findings indicate that negative symptom severity rated during the first year is related to negative symptom severity rated 8 years later, showing moderate stability even over long time periods. The stability of negative symptoms was found despite the fact that during the intervening years the patients may have gone through periods of psychotic symptom remission, exacerbation, relapse, or even rehospitalization (Subotnik et al., 2011; Ventura et al., 2004; Ventura et al., 2011). Stressful life events (Ventura et al., 1989) and periods of medication non-adherence during these intervening years could also have further contributed to symptom exacerbation (Subotnik et al., 2011). Considering all of the factors that could have intervened, the finding of moderate stability of negative symptoms is remarkable. We did not find evidence that negative symptoms rated during the first year significantly predicted social functioning or employment and school status at the 8-year point. Given longer durations of follow-up, the predictive value of negative symptoms on subsequent functional outcome might decrease due to a variety of factors such as treatment with

antipsychotic agents, availability of comprehensive psychosocial rehabilitation programs, and the accumulation of environmental factors during the course of illness. On the other hand, this lack of 8-year predictive significance for functional outcome may be due to limited sample size.

One limitation of this study is that the predictive relationships between negative symptoms and functioning are not proof of causation as they are correlational in nature. Also, correlations found in this study among the variables we examined might be due to third variables that influence both correlated variables, such as premorbid adjustment, duration of untreated psychosis, etc. In addition, the sample size for the 8-year follow-up was only moderate.

These converging cross-sectional and longitudinal results indicate the significance of developing interventions that decrease negative symptoms to maximize long-term recovery for FEP. Such interventions are needed to actively prevent negative symptoms in the first outpatient year from persisting into the chronic period of illness (Crespo-Facorro et al., 2013; González-Ortega et al., 2012). Following a recovery model, these results provide support for intervening and treating negative symptoms early in the hope that this may prevent those symptoms from disrupting both short-term and long-term work and school functioning.

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References

Albert N, Bertelsen M, Thorup A, Petersen L, Jeppesen P, Le Quack P, Krarup G, Jørgensen P, Nordentoft M. Predictors of recovery from psychosis: Analyses of clinical and social factors associated with recovery among patients with first-episode psychosis after 5 years. Schizophrenia Research. 2011; 125(2–3):257–266. [PubMed: 21056926]

Andreasen, NC. The Scale for the Assessment of Negative Symptoms (SANS). The University of Iowa; Iowa City, IA: 1984.

Andreasen NC, Carpenter WT Jr, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. American Journal of Psychiatry. 2005; 162(3):441. [PubMed: 15741458]

Andreasen NC, Pressler M, Nopoulos P, Miller D, Ho BC. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. Biological psychiatry. 2010; 67(3):255–262. [PubMed: 19897178]

Becker, D.; Drake, R. A Working Life for People with Severe Mental Illness. Oxford Press; New York: 2003.

Bliese PD, Halverson RR. Group size and measures of group-level properties: An examination of eta-squared and ICC values. Journal of Management. 1998; 24(2):157–172.

Bobes J, Arango C, Garcia-Garcia M, Rejas J. Prevalence of negative symptoms in outpatients with schizophrenia spectrum disorders treated with antipsychotics in routine clinical practice: findings from the CLAMORS study. Journal of Clinical Psychiatry. 2010; 71(3):280. [PubMed: 19895779]

Chang W, Hui CL, Tang JY, Wong GH, Lam MM, Chan SK, Chen EY. Persistent negative symptoms in first-episode schizophrenia: a prospective three-year follow-up study. Schizophrenia Research. 2011; 133(1):22–28. [PubMed: 21968080]

Chang WC, Yee Man Tang J, Lai Ming Hui C, Hoi Yan Wong G, Kit Wa Chan S, Ho Ming Lee E, Yu Hai Chen E. The relationship of early premorbid adjustment with negative symptoms and cognitive functions in first-episode schizophrenia: A prospective three-year follow-up study. Psychiatry Research. 2013; 209(3):353–360. [PubMed: 23473654]

Crespo-Facorro B, Ortiz-García de la Foz V, Mata I, Ayesa-Arriola R, Suarez-Pinilla P, Valdizan EM, Vázquez-Barquero JL, Pérez-Iglesias R. Aripiprazole, Ziprasidone and Quetiapine in the treatment of first-episode nonaffective psychosis: A 12-week randomized, flexible-dose, open-label trial. Schizophrenia Research. 2013

Evensen J, Røssberg JI, Barder H, Haahr U, Hegelstad WtV, Joa I, Johannessen JO, Larsen TK, Melle I, Opjordsmoen S. Flat affect and social functioning: A 10year follow-up study of first episode psychosis patients. Schizophrenia Research. 2012; 139(1):99–104. [PubMed: 22627124]

First, MB.; Gibbon, M.; Spitzer, RL.; Williams, JBW. Biometrics Research. New York: 1996. Structured Clinical Interview for DSM-IV Axis I Disorders. Patient Edition.

Galderisi S, Mucci A, Bitter I, Libiger J, Bucci P, Wolfgang Fleischhacker W, Kahn RS, Group ES. Persistent negative symptoms in first episode patients with schizophrenia: Results from the European First Episode Schizophrenia Trial. European Neuropsychopharmacology. 2013; 23(3): 196–204. [PubMed: 22647933]

González-Ortega I, de los Mozos V, Echeburúa E, Mezo M, Besga A, Ruiz de Azúa S, González-Pinto A, Gutierrez M, Zorrilla I, González-Pinto A. Working memory as a predictor of negative symptoms and functional outcome in first episode psychosis. Psychiatry Research. 2012

Harvey PD, Koren D, Reichenberg A, Bowie CR. Negative symptoms and cognitive deficits: what is the nature of their relationship? Schizophrenia Bulletin. 2006; 32(2):250–258. [PubMed: 16221995]

Henry LP, Harris MG, Amminger GP, Yuen HP, Harrigan SM, Lambert M, Conus P, Schwartz O, Prosser A, Farrelly S. Early Psychosis Prevention and Intervention Centre long term follow up study of first episode psychosis: methodology and baseline characteristics. Early Intervention in Psychiatry. 2007; 1(1):49–60. [PubMed: 21352108]

Hovington CL, Bodnar M, Joober R, Malla AK, Lepage M. Identifying persistent negative symptoms in first episode psychosis. BMC psychiatry. 2012; 12(1):224. [PubMed: 23217020]

Leslie AM, Friedman O, German TP. Core mechanisms in 'theory of mind'. Trends in cognitive sciences. 2004; 8(12):528–533. [PubMed: 15556021]

Levine SZ, Leucht S. Attaining and sustaining remission of predominant negative symptoms. Schizophrenia Research. 2013; 143(1):60–64. [PubMed: 23218563]

Lin C-H, Huang C-L, Chang Y-C, Chen P-W, Lin C-Y, Tsai GE, Lane H-Y. Clinical symptoms, mainly negative symptoms, mediate the influence of neurocognition and social cognition on functional outcome of schizophrenia. Schizophrenia Research. 2013

Lukoff D, Nuechterlein KH, Ventura J. Manual for the Expanded Brief Psychiatric Rating Scale (BPRS). Schizophrenia Bulletin. 1986; 12:594–602.

Milev P. Predictive Values of Neurocognition and Negative Symptoms on Functional Outcome in Schizophrenia: A Longitudinal First-Episode Study With 7-Year Follow-Up. American Journal of Psychiatry. 2005; 162(3):495–506. [PubMed: 15741466]

Nuechterlein KH, Dawson ME, Gitlin MJ, Ventura J, Goldstein MJ, Snyder KS, Yee CM, Mintz J. Developmental processes in schizophrenic disorders: Longitudinal studies of vulnerability and stress. Schizophrenia Bulletin. 1992; 18(3):387–425. [PubMed: 1411329]

Nuechterlein KH, Miklowitz DJ, Ventura J, Gitlin MJ, Stoddard M, Lukoff D. Classifying episodes in schizophrenia and bipolar disorder: criteria for relapse and remission applied to recent-onset samples. Psychiatry Res. 2006; 144(2–3):153–166. [PubMed: 17011635]

Nuechterlein KH, Subotnik KL, Green MF, Ventura J, Asarnow RF, Gitlin MJ, Yee CM, Gretchen-Doorly D, Mintz J. Neurocognitive predictors of work outcome in recent-onset schizophrenia. Schizophrenia Bulletin. 2011; 37(Supplement 2):S33–S40. [PubMed: 21860045]

Peña J, Segarra R, Ojeda N, García J, Eguiluz JI, Gutiérrez M. Do the same factors predict outcome in schizophrenia and non-schizophrenia syndromes after first-episode psychosis? A two-year follow-up study. Journal of psychiatric research. 2012; 46(6):774–781. [PubMed: 22487311]

Savla GN, Vella L, Armstrong CC, Penn DL, Twamley EW. Deficits in domains of social cognition in schizophrenia: a meta-analysis of the empirical evidence. Schizophrenia Bulletin. 2013; 39(5): 979–992. [PubMed: 22949733]

Siegel SJ, Irani F, Brensinger CM, Kohler CG, Bilker WB, Ragland JD, Kanes SJ, Gur RC, Gur RE. Prognostic variables at intake and long-term level of function in schizophrenia. American Journal of Psychiatry. 2006; 163(3):433–441. [PubMed: 16513864]

Strauss JS, Carpenter WT. The prediction of outcome in schizophrenia, I: Characteristics of outcome. Archives of General Psychiatry. 1972; 27:739–746. [PubMed: 4637891]

Subotnik KL, Nuechterlein KH, Ventura J, Gitlin MJ, Marder SR, Mintz JM, Hellemann GS, Thornton LA, Singh IR. Risperidone nonadherence and return of positive symptoms in the early course of schizophrenia. American Journal of Psychiatry. 2011; 168(3):286–292. [PubMed: 21205805]

Subotnik KL, Nuechterlein KH, Ventura J, Green MF, Hwang SS. Prediction of the deficit syndrome from initial deficit symptoms in the early course of schizophrenia. Psychiatry Research. 1998; 80:53–59. [PubMed: 9727963]

Ventura J, Green MF, Shaner A, Liberman RP. Training and quality assurance with the Brief Psychiatric Rating Scale: “The drift busters”. International Journal of Methods in Psychiatric Research. 1993a; 3(4):221–244.

Ventura J, Hellemann GS, Thames AD, Koellner V, Nuechterlein KH. Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis. Schizophrenia Research. 2009a; 113(2):189–199. [PubMed: 19628375]

Ventura J, Hellemann GS, Thames AD, Koellner V, Nuechterlein KH. Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: A meta-analysis. Schizophr Res. 2009b; 113(2):189–199. [PubMed: 19628375]

Ventura J, Lukoff D, Nuechterlein KH, Liberman RP, Green MF, Shaner A. Brief Psychiatric Rating Scale (BPRS) expanded version: Scales, anchor points, and administration manual. International Journal of Methods in Psychiatric Research. 1993b; 3:227–243.

Ventura J, Nuechterlein KH, Green MF, Horan WP, Subotnik KL, Mintz J. The timing of negative symptom exacerbations in relationship to positive symptom exacerbations in the early course of schizophrenia. Schizophrenia Research. 2004; 69(2–3):333–342. [PubMed: 15469205]

Ventura J, Nuechterlein KH, Lukoff D, Hardesty JP. A prospective study of stressful life events and schizophrenic relapse. Journal of Abnormal Psychology. 1989; 98:407–411. [PubMed: 2592674]

Ventura J, Nuechterlein KH, Subotnik KL, Gutkind D, Gilbert EA. Symptom dimensions in recent-onset schizophrenia and mania: A principal components analysis of the 24-item Brief Psychiatric Rating Scale. Psychiatry Research. 2000; 97:129–135. [PubMed: 11166085]

Ventura J, Subotnik KL, Guzik LH, Hellemann GS, Gitlin MJ, Wood RC, Nuechterlein KH. Remission and recovery during the first outpatient year of the early course of schizophrenia. Schizophrenia Research. 2011; 132(1):18–23. [PubMed: 21764563]

White C, Stirling J, Hopkins R, Morris J, Montague L, Tantam D, Lewis S. Predictors of 10-year outcome of first-episode psychosis. Psychological Medicine. 2009; 39(09):1447–1456. [PubMed: 19187566]

Table 1

Sample Characteristics at Study Entry for Recent-Onset Schizophrenia Patients

	Sample 1 at Baseline (n=102)	Sample 2 at Baseline (n=47)	Difference	Samples 1 and 2 Combined (n=149)
Mean Age (SD)	23.4 (4.4)	25.0 (5.3)	F(1,148)=3.92 p=.05	23.7 (4.45)
Mean Education (SD)	12.4 (2.1)	13.5 (2.1)	F(1,147)=8.2, p<.01	12.91 (2.2)
Gender	84 (82%)	33 (70%)	$\chi^2(1)=2.7$, p=.10	117 (78%)
Marital Status			$\chi^2(3)=5.81$, p=.181	
Single	93 (91%)	41 (87%)		134 (90%)
Married	4 (4%)	4 (8%)		8 (5%)
Divorced	1 (1)	2 (4%)		3 (2%)
Separated	4 (4%)	0		4 (3%)
Race				
Caucasian	95 (93%)	23 (50%)	$\chi^2(3)=53.8$, p<.01	118 (79%)
Asian	3 (3%)	5 (11%)		8 (5%)
Native American/Pacific Islander	0	0		0
African American	0	13 (28%)		13 (9%)
Other	4 (4%)	6 (13%)		10 (3%)
Diagnosis				
Schizophrenia	61 (59%)	35 (74%)	$\chi^2(3)=11.2$, p<.01	95 (64%)
Schizoaffective	8 (8%)	6 (13%		14 (10%)
Schizophreniform	33 (33%)	5 (11%)		38 (26%)
Other Psychotic Disorder		1 (2%)		1 (1%)
Number of months (mean, SD) since psychosis onset, including prodrome, at study entry	6.8 (7.1)	8.0 (6.8)	F(1,143)=1.0, p=.32	9.08 (8.63)
Chlorpromazine equivalent dosage, mg (mean, SD)	137.4 (110.1)	275.6 (126.9)	F(1,94)=23.4, p<.01	166.22 (126.38)

Table 2

Sample Characteristics at Study Entry for Recent-onset Schizophrenia Patients Who Were Assessed 8 Years Later (n=53)

	Baseline Characteristics for Patients who were Assessed at Follow-up (n=53)	Baseline Characteristics for patients who were not Assessed (n=49)	Difference
Mean Age (SD)	23.2 (3.6)	23.6 (5.2)	F(1,103)=.32, p=.75
Mean Education (SD)	12.8 (2.0)	12.0 (2.2)	F(1,103)= −1.76. p=.08
Gender	44 (83 %) Male	38 (81%) Male	$\chi^2(1)=.08$, p=.78
Marital Status			$\chi^2(3)=8.9$, p=.03
Single	51 (96%)	40 (85%)	
Married	0	4 (9%)	
Divorced	1 (2%)	0	
Separated	1 (2%)	3 (6%)	
Race			$\chi^2(3)=3.1$, p=.38
Caucasian	47 (89%)	39 (83%)	
Latino	2 (4%)	5 (11%)	
Asian	1 (2%)	2 (4%)	
Other	3 (6%)	1 (2%)	
Diagnosis			$\chi^2(2)=.535$, p=.53
Schizophrenia	33 (63%)	26 (55%)	
Schizoaffective	5 (9%)	3 (6%)	
Schizophreniform	15 (28%)	18 (38%)	
Number of months (mean, SD) since psychosis onset, including prodrome, at study entry	8.2 (9.8)	8.0 (9.1)	F(1, 101)=.35, p=.73

Table 3

Stability of Negative Symptoms in the Early Course of Schizophrenia Over One Year (n = 119)

Negative Symptom Assessment	ICC Statistic
BPRS Negative Symptom Factor	**.64**
Blunted Affect	.61
Emotional Withdrawal	.53
Motor Retardation	.63
SANS Negative Symptom Clusters	**.66**
Expressive negative symptoms	.64
Experiential negative symptoms	.60

Table 4

Correlation from Baseline Negative Symptoms to Functional Outcome at the 12 Month Point (n=65)

	Functional Domains	
Time Period for Negative Symptoms	**Social Functioning**	**Work/School Functioning**
BPRS Study Entry	−.34**	−.25*
BPRS Medication Stabilization	−.38**	−.13
BPRS One Year Average	−.40**	−.25*
SANS Study entry (n=24)	−.08	−.53**
SANS Medication Stabilization (n=24)	−.28	−.62**
SANS One Year Average (n=24)	−.23*	−.44**

Note: Negative Symptoms are rated from the BPRS and SANS, Social Functioning and Work/School Functioning are rated from the SCORS

* $p<.05$

** $p<.01$

Table 5

Correlations Between Negative Symptoms Assessed During Baseline and Negative Symptoms, Social Functioning, Work / School Functioning at the 8 Year Follow-up Point (n=53)

	Symptom and Functional Domains			
Time Period for Negative Symptoms	**BPRS Negative Symptoms**	**SANS Negative Symptoms**	**Social Functioning**	**Work/School Functioning**
BPRS Study Entry	.29*	-	−.26	−.04
BPRS Medication Stabilization	.31*	-	−.23	.10
BPRS One Year Average	.32*	-	−.21	.04
SANS Study Entry (N=19)	-	.21	−.47*	−.12
SANS Medication Stabilization (N=18)	-	.54*	.24	.08
SANS One Year Average (N=24)	-	.54**	−.17	.06

Note: Social Functioning and Work/School Functioning were rated from the SCORS

* $p<.05$

** $p<.01$

Table 6

Cross-sectional Correlations Between Negative Symptoms, Social Functioning, Work/School Functioning at the 8 Year Follow-up point (n=53)

	Functional Domains	
	Social Functioning	**Work/School Functioning**
BPRS Negative Symptoms	−.12	−.31*
SANS Negative Symptoms (n=35)	−.35*	−.60**
Social Functioning (n=37)	--	.12

Note: Social Functioning and Work/School Functioning were rated from the SCORS

* $p<.05$

** $p<.01$