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# Negative symptoms and functioning during the first year after a recent onset of schizophrenia and 8 years later

Joseph Ventura [a,*], Kenneth L. Subotnik [a], Michael J. Gitlin [a], Denise Gretchen-Doorly [a], Arielle Ered [a], Kathleen F. Villa [c], Gerhard S. Hellemann [a], Keith H. Nuechterlein [a,b]

[a] UCLA Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, Los Angeles, CA, USA
[b] UCLA Department of Psychology, Los Angeles, CA, USA
[c] Genentech, Inc., South San Francisco, CA, USA

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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 1-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.
*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.


## 1. 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, found 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 1-week to 1-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 1-year and 3-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

* Corresponding author at: UCLA Department of Psychiatry, 300 Medical Plaza, Room 2243, Los Angeles, CA 90095-6968. Tel.: +1 310 206 5225; fax: +1 310 206 3651.
*E-mail address:* jventura@ucla.edu (J. Ventura).

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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 1-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 the following in recent-onset schizophrenia patients: (1) the prevalence rates of negative symptoms at baseline, (2) the 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) the relationships between negative symptoms and daily functioning.

## 2. Methods

### 2.1. Subjects

The sample involved 149 schizophrenia patients who had an initial onset of psychosis within 2 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 and hence will only be briefly reviewed in this study (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

**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 | | | | |
| Single | 93 (91%) | 41 (87%) | $\chi^2(3) = 5.81, p = .181$ | 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) |