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Positive and Negative Symptom Course in Chronic Community-Based Patients

A Two-Year Prospective Study

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Background. The long-term symptom profile of chronic out-patients was studied.
Method. 242 out-patients receiving neuroleptic medications (109 with schizophrenia and 133 non-schizophrenics), were studied for positive (SAPS) and negative (SANS) symptoms at baseline and at 24 months to investigate whether these symptom groups changed over out-patient maintenance treatment.
Results. Overall and within groups, negative symptoms decreased and positive symptoms increased. While the sums of the SANS scores for the schizophrenic patients were initially higher, their mean SANS score dropped more over time ($P<0.001$), to show no difference from non-schizophrenics at follow-up. Positive symptoms increased in both groups, although schizophrenics were higher at both times; sub-scales within the SANS showed different patterns of change.
Conclusion. Support is found for a multidimensional view of both positive and negative symptoms and for a reconsideration of the notion of 'progressive downward course' in schizophrenia.

The DSM–III and III–R diagnostic systems have focused on specific 'Schneiderian' or 'first rank' symptoms of schizophrenia, especially specific types of hallucinations, delusions, bizarre behaviour, and formal thought disorder. Strauss *et al* (1974) reintroduced attention to deficit or 'negative' symptoms. Several investigators (Strauss *et al*, 1974; Crow, 1980; Andreasen & Olsen, 1982) have elaborated this subclass of symptoms, described as a 'lack' of critical behaviour types, including affective flattening, alogia, apathy, anhedonia and attention disturbance. Negative symptoms have been associated with a chronic or downward course, and were initially thought to be less responsive to neuroleptic medication, although present evidence (Goldberg, 1985) demonstrates that some negative symptoms may respond to neuroleptics.

Temporal course

Investigations of the temporal course of symptoms in schizophrenia have varied widely in their samples and their methods of selecting cases, whether subjects were in-patients or out-patients, phase of illness, time of treatment, recruitment and follow-up, neuroleptic dosage, and other treatment variables. Studies addressing the long-term course of illness (e.g. Knight *et al*, 1979; Pfohl & Winokur, 1982) leave a number of intervening factors in treatment and course unexamined and uncontrolled. Subjects followed during or shortly after a hospitalisation episode (e.g. WHO, 1979) vary in clinical status at recruitment, and in subsequent treatment. Studies designed around therapeutic trials (e.g. Lewine, 1990) generally control treatment and environmental variables, although the period of study is short. Other studies examine the course of symptoms during a single acute or a long-term hospitalisation (e.g. Andreasen & Olsen, 1982; Johnstone *et al*, 1986). Studies of a single episode typically employ multiple assessments over a relatively short period. Other longitudinal studies include time spent out of the hospital (e.g. Pogue-Geile & Harrow, 1984; Regin *et al*, 1989).

Negative symptoms

Negative symptoms have been associated with poor outcome in schizophrenic patients; positive symptoms are usually unrelated to outcome or to a favourable prognostic sign (e.g. Pogue-Geile & Harrow, 1984; Knight *et al*, 1979). The phenomenology, predictive power, and prognostic significance of negative symptoms appear to depend on the *phase* of illness studied (Pogue-Geile, 1989) and change at first break, during an acute exacerbation, or after the hospitalisation period. Fenton & McGlashan (1991) found that negative symptoms found at first admission were of less prognostic significance than those assessed later. Kay & Lindenmayer (1987) found negative symptoms to be a *positive* prognostic sign during the acute phase, possibly tapping an affective depressive syndrome.

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Although long-term changes in the Scale for the Assessment of Negative Symptoms (SANS) and Scale for the Assessment of Positive Symptoms (SAPS) scores have not been extensively investigated, there is evidence for the short-term (Lewine, 1990) and longer-term stability of negative symptoms over time (e.g. Knight *et al*, 1979; Pfohl & Winokur, 1982; Johnstone *et al*, 1986; Schuldberg *et al*, 1990), evidence that is often taken to support the immutability or 'Kraepelinian' nature of negative symptoms. However, some studies show non-significant test–retest correlations for negative symptoms (e.g. Kay & Lindenmayer, 1987; Pogue-Geile, 1989). The mean levels of negative symptoms have been shown in different studies to remain unchanged, increase (Ragin *et al*, 1989), or decrease (e.g. WHO, 1979), possibly varying in different types of patients (Fenton & McGlashan, 1991).

Positive symptoms

Positive symptoms appear more variable than negative symptoms (Johnstone *et al*, 1986), although some studies find significant rank stability and stable levels both during an acute episode and across admissions, as well as different trajectories related to outcome (Fenton & Mcglashan, 1991). However, disordered thought has been found to vary between young adulthood and middle age (Knight *et al*, 1979) or to decline (WHO, 1979).

Course of negative and positive symptoms

The present study measures the course of positive and negative symptoms in a stable population of neuroleptic-maintained out-patients over 24 months.

There is need to delineate the course of these two classes of symptoms during the period of out-patient treatment. Since most studies have been carried out on acute patients from hospitalisation to discharge or on long-stay in-patients, it is important to understand the course of these symptoms during a period of potential 'steady state', i.e. during the period after hospitalisation. Changes over time are not confounded with changes in status or with effects of a long-term institutionalisation. Furthermore, the design of our study allowed us to explore two of the leading hypotheses about these phenomena: do the positive and negative symptoms vary inversely over time, as was at first suggested by Andreasen & Olsen in 1982, or do they vary as independent manifestations of a single process, as suggested by Crow (1980)?

It is also important to compare the course of these symptoms in schizophrenic and non-schizophrenic patients. The present study examined a large cohort of patients, both schizophrenics and non-schizophrenics, over the course of post-hospital maintenance treatment with neuroleptics.

Method

The patients in the sample studied were part of a larger study of 398 out-patients at risk for tardive dyskinesia, but who did not evidence tardive dyskinesia at the outset of the study, and who were expected to receive neuroleptic medications for 6 months or more. This formed part of a study of the incidence of tardive dyskinesia (cf. Glazer *et al*, 1988).

At intake, all prospective participants were given a diagnostic interview, including lifetime portions of the SADS (Spitzer & Endicott, 1977), the Abnormal Involuntary Movement Scale (Psychopharmacology Review Branch, 1975), and other test instruments. Patients who subsequently met the criteria for tardive dyskinesia at two consecutive assessments were dropped from the present portion of the study and entered into a protocol for following diagnosed cases of tardive dyskinesia.

Patients were followed at 6-month intervals. Various test instruments were administered at the different follow-up appointments: only those relevant to symptoms are reported here. As part of the baseline and 24-month follow-up interviews, the patients were rated on the SANS and the SAPS (Andreasen & Olsen, 1982; Arndt *et al*, 1991).

The SANS rates five sub-areas of symptoms and the SAPS rates four sub-areas. After rating each symptom within a sub-area, the rater gives a 'global sub-area' score. This study used the global sub-area scores and the overall sums of the global sub-area ratings. Similar results were obtained in analyses using the sums of the individual items within sub-areas and overall. Intra-class correlation coefficients among five raters for the summary sub-area measures were high ($r_{ICC} = 0.826–0.915$). The ratings were given at an average of 25.8 (s.d. = 4.4) months apart.

Medications

Neuroleptic medications were noted at baseline, and a record of dosage changes was compiled. The daily dosages at baseline and at 24 months were converted to equivalent dosages of chlorpromazine.

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Table 1
Demographic characteristics of the samples

	Schizophrenics	Non-schizophrenics	Total
Sex: M	64	63	127
F	49	66	115
Total	113	129	242
Sub-types		Diagnoses	
Acute	5	Schizoaffective 57	
Subacute	6	Manic or bipolar manic 14	
Subchronic	17	Major depression 22	
Chronic	85	Other[1] 36	

1. Including unspecified functional psychosis (5), Other psychiatric disorder (29), drug or alcohol disorders (1), and no RDC diagnosis (1).

Sample

A sub-group of patients was selected who:

(a) had completed the 24-month interview in the protocol and were tested on SANS and SAPS at baseline and 24 months;

(b) were 55 years of age or under (to avoid confounding symptoms with changes associated with ageing); and

(c) had not developed persistent symptoms of tardive dyskinesia by 24 months.

Of the 398 patients who began the study, 72 were older than 55; for 20, no baseline SANS or SAPS results were available; and persistent tardive dyskinesia was diagnosed in 16, who were dropped from the present analysis. Six patients died; eight moved from the area; four refused to participate; 28 were discharged from treatment and could not be contacted. For two subjects no follow-up SANS or SAPS results were available. This left 242 patients whose gender and diagnoses are given in Table 1.

The patients had an average age of 37.0 years (s.d. = 8.9) at baseline; 74% were white, 23% Afro-American, 2% Hispanic, with two from other ethnic groups and one unspecified. At entry, mean duration of illness was 15.0 years (s.d. = 8.1), mean duration of hospitalisation was 1.5 years (s.d. = 1.9), and the estimated daily dose of neuroleptic medications was equivalent to 483 mg of chlorpromazine at baseline and 432 mg at follow-up. Between the baseline assessment and the 24-month follow-up, the mean duration of in-patient treatment was 15.1 days; only a few patients (20 schizophrenics (18%) and 38 non-schizophrenics (30%)) were hospitalised. More non-schizophrenics tended to have at least one rehospitalisation (χ^2 [1,242] = 4.57, P = 0.03). Only 25 patients (10.3%) spent 30 days or more in hospital during the follow-up period.

Method of analysis

Patients studied at the 24-month follow-up were compared with those not in the follow-up for demographic, diagnostic, and baseline symptom variables. The retained samples are compared, by diagnosis and time period (baseline v. 24 months), for overall differences on the SANS and SAPS summary variables using multivariate analysis of variance (MANOVA). When significant differences are found, univariate ANOVAs are performed on the summary scores and on the individual sub-scales. Supplementary analyses further examine the nature of the differences.

The sizes of the differences are discussed in terms of the 'effect size', the ratio of the mean difference over the pooled standard deviation. Effect sizes range from 'small' (0.10–0.35), through 'medium' (0.36–0.65) to 'large' ($\geq$0.65).

Results

Retention in the study

No differences in retention are found which correlate with diagnosis or gender. The patients dropped from the study were not significantly different on baseline SANS or SAPS summary scores, although there was a tendency for subjects not included to have lower mean SANS global scores (6.06 v. 6.72, F[1,302] = 3.07, P = 0.081).

Correlations with medication levels

To assess whether the changes in SANS and SAPS scores could be the effect of medication, the two score components were correlated with the mean daily dosage of neuroleptics converted to chlorpromazine equivalents. For the baseline time period, r[240] = 0.15, P = 0.02 for global SANS, r[240] = 0.21, P < 0.001 for global SAPS; for individual symptoms, all r < 0.26. At follow-up there was a significant correlation between medication dose level and SANS summary scores (r[240] = 0.38, P < 0.001) overall, r[111] = 0.26, (P = 0.006) within the schizophrenics, and r[127] = 0.39 (P < 0.001) within the non-schizophrenics). For overall follow-up SAPS, the correlation overall was r[240] = 0.38, within schizophrenics r[111] = 0.33, and within non-schizophrenics r[127] = 0.39 (P < 0.001). Thus average levels of drug dosage were correlated weakly (in terms of effect size) but significantly with the global summary scores and the individual symptom scores.

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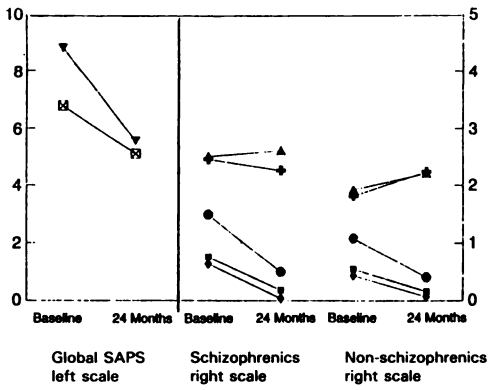


Fig. 1 Mean raw scores, SANS global and sub-scales, at baseline and 24 months. ▼ Global schizophrenic; ☒ Global non-schizophrenic; ■ Hallucinations; ◆ Delusions; ▲ Bizarreness; ✚ Formal thought disorder.

Diagnostic differences and changes over time

Repeated measures MANOVAs were performed on the summary of the global sub-area ratings. The results for the SANS and SAPS scores are shown in the left part of Fig. 1. Univariate F ratios indicate that the scores are lower for non-schizophrenic patients on both scales. The mean difference between schizophrenics and non-schizophrenics (combined for both times) is 1.265 points on the SANS. This corresponds to an effect size of 0.37 of the pooled within-group standard deviation. The combined mean difference of 1.425 points on the SAPS is an effect size of 0.69. These effect sizes are in the range labelled as small to medium by Cohen (1988). Similar results with respect to size, direction and significance are found when statistical controls are introduced for the effects of baseline medications using analysis of covariance. Overall, both the SANS and SAPS scores are higher for schizophrenics, combining the two time periods. The MANOVA for diagnosis with the SANS and SAPS as dependent variables is significant (approximate $F[2,239] = 14.44$, $P<0.001$). For effects across time, including interactions, degrees of freedom are adjusted by the Geisser-Greenhouse correction. Thus the degrees of freedom for different tests vary.

Changes over time

Examination of the means indicates that over time, there is a drop in summary SANS scores averaged for both groups from 6.91 to 5.32, a medium effect size of 0.46 ($F[1,234] = 43.48$, $P<0.001$), and an increase in the summary SAPS scores from 1.47 to 2.84, a medium effect size of 0.49 ($F[1,234] = 44.95$, $P<0.001$). Over time, the changes are reflected in the overall MANOVA for the two summary scores (approximate $F[2,239] = 49.63$, $P<0.001$).

Examination of the univariate F ratios indicates that the interaction of diagnosis by time for the SANS is large and significant ($F[1,234] = 12.04$, $P<0.001$), while for the SAPS the interaction is not ($F[1,234] = 0.01$, n.s.). The interaction reflects the fact that schizophrenics' SANS scores drop 2.25 scale points (a moderate effect size of 0.66), while those of non-schizophrenics drop less, only 0.70 (a 'small' effect size of 0.21). The SAPS scores increase to approximately the same degree (1.36 and 1.39 points, respectively). The overall multivariate interaction between diagnosis and time is significant (approximate $F[2,239] = 6.04$, $P=0.003$). Similar results are found with the composite scores (composed of all of the rated items) for both scales, which are highly correlated with the global summary scores reported here.

Influence of medication levels

Analyses of medication levels indicated that the results are not substantially affected by drug dosage. To assess the effects of medication levels on symptoms, the average baseline dose level in chlorpromazine equivalents was used to divide the patients into four quartiles, and the drug quartiles were entered into a MANOVA, assessing diagnosis, drug level and time. As expected, there were a number of significant effects for medication level on both global and individual item global scales; there was a significant positive linear relationship between drug level and level of both SANS and SAPS ($P<0.001$). There were also a limited number of 'drug level by time' interactions.

However, there were no significant 'diagnosis by drug level' or 'diagnosis by time by drug level' interactions. Thus, while patients receiving higher levels of medication tended to have higher levels of both positive and negative symptoms, drug level differences did not affect the basic results for diagnosis, time, or the interaction. Levels of significance were at the same level or higher when drug level was taken into account.

Individual sub-scale areas

The middle portion of Fig. 1 shows the levels of the sub-scale scores for the SANS. The repeated-measures MANOVA show differences for diagnostic groups: higher flatness, avolition and anhedonia in schizophrenics ($F[1,240] = 5.01$, 9.42 and 5.49,

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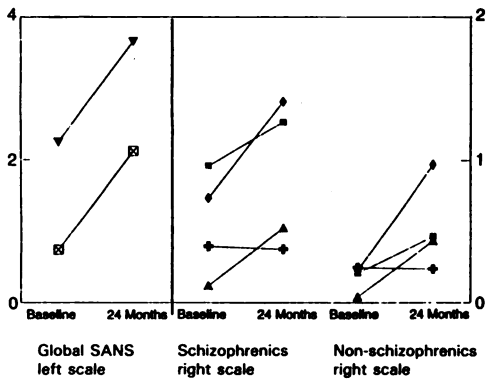


Fig. 2 Mean raw scores, SAPS global and sub-scales, at baseline and 24 months. -▼- Global schizophrenic; -⊠- Global non-schizophrenic; -●-Flatness; -■- Alogia; -▲- Avolition; -✚- Anhedonia; -◆- Attention.

$P=0.026$, 0.002 and 0.02, respectively). Alogia and attention are not substantially different.

Examination of time effects in the individual subscales in Fig. 1 reveals a mixed pattern of change: flatness, alogia, and attention show a substantial decrease ($F[1,232]=84.33$, 5.360 and 63.62, $P<0.001$); avolition shows an increase over time ($F[232]=6.25$, $P=0.013$), while anhedonia shows a minimal change. The overall multivariate effect for change over time is highly significant ($P<0.001$).

The tests of the diagnosis-by-time interactions show a mixed pattern. With flatness, there is a trend to show a sharper decrease in the schizophrenic group than in the non-schizophrenic group ($F[1,232]=3.01$, $P=0.084$). Anhedonia shows opposite trends for the two groups, dropping in the schizophrenic group and increasing in the non-schizophrenic group ($F[1,232]=10.92$, $P<0.001$). The other interaction terms are small. The multivariate test of the interaction term shows an overall significant effect ($F[5,179]=2.53$, $P=0.031$).

For multivariate analysis of covariance, correcting for average neuroleptic equivalent dosage, the diagnosis difference for flatness drops from $P=0.026$ to $P=0.06$, and for anhedonia the diagnosis difference drops from $P=0.02$ to $P=0.082$, while the other effects remain within similar ranges of significance.

SAPS differences

The multivariate repeated-measures analyses of variance for the SAPS subscales indicate that hallucinations and delusions are more frequent in the schizophrenic group ($F[1,240]=27.32$ and 11.05, $P<0.001$); bizarreness and formal thought disorder (FTD) do not differ with diagnosis ($F[1,232]=1.48$ and 2.76 (n.s.) respectively). The overall multivariate test for diagnosis is significant ($F[4,164]=4.02$, $P=0.004$).

Over time, there is a general increase in SAPS symptoms (multivariate $F[4,164]=12.66$, $P<0.001$). Three of the four individual scales show a sizeable time effect; only FTD does not show a significant increase. ($F[1,232]=11.02$ for hallucinations, 47.38 for delusions, and 38.41 for bizarreness, all $P<0.001$, $F[1,232]=0.04$ (n.s.) for FTD). None of the interactions of diagnosis and time for the SAPS are large. Thus for the SAPS, there is a general increase in both groups on three of the four variables, with schizophrenics higher on delusions and bizarreness.

Taken in combination, the pattern of symptoms is such that the overall severity of negative symptoms falls off for flatness while the severity of avolition remains high in schizophrenics and tends to increase in non-schizophrenics. Over time, positive symptoms show a general increase, except for FTD. Thus, while overall symptom scores on the SANS decrease, symptoms of avolition and anhedonia remain at a high level; for SAPS, there is a general increase in all symptoms except for FTD.

Discussion

We have studied a large group of patients who were carefully diagnosed and followed from the time they were out-patients, in contrast to patients in other studies who were often followed during acute periods or long-term hospitalisation. The sample is considerably larger than those in comparable studies, the study evaluates the stability of positive and negative symptoms in a group of chronic out-patients, and the findings address the course of the illness of patients receiving maintenance neuroleptic medication. The groups are likely to be similar to a large portion of community-based patients with psychotic and other severe diagnoses.

The changes in the individual negative symptom areas present a complex picture, not fully represented by changes in the overall summary scores. Schizophrenics score higher than non-schizophrenics in all five of the SANS sub-scale areas. Over time, the flatness, alogia, and attention scales show a decrease, while avolition shows an increase. Anhedonia shows a different pattern, with a significant diagnosis-by-time interaction; there is a slight increase in the schizophrenic group but a sharp increase in the non-schizophrenic group. Thus, while the negative symptom summary score shows a decrease, this

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pattern is characteristic primarily of the flatness scale. It is of particular note that the avolition score remains high in the schizophrenics and increases in the non-schizophrenics.

A pattern of deterioration of negative symptoms is restricted to anhedonia and avolition. Our own work indicates that these symptoms (especially avolition) may represent a 'core' set of negative symptoms that are also strongly related to social withdrawal and isolation, as well as unemployment and social dependency. Positive symptoms, overall, climb to higher levels, something that may reflect the 'cyclic' nature of psychosis, particularly schizophrenia, characterised by multiple relapses.

Several cautions must be borne in mind in interpreting the results. First, these are patients studied outside the hospital, in active treatment. Generalisation of results to patients in an acute episode or who fail to maintain active out-patient treatment is uncertain. A second source of caution is tardive dyskinesia. Six per cent (16 of 326) of the potential participants were dropped from this analysis because of the development of this movement disorder. The effect of excluding these patients is unclear, although they did not differ at baseline from the included patients on the variables analysed.

There is also the possibility that an unknown selection factor is operating for those patients retained in the study. The direction of the results obtained for patients who were then lost to follow-up indicates a trend for patients less symptomatic in positive and negative symptoms at baseline to be less represented in our sample. The sizes of these observed differences are small and not significant, much smaller than the baseline differences observed between the schizophrenics and patients with other diagnoses (baseline global SAPS = 1.38 for not-followed patients, 1.42 for followed, $F[1,302] = 0.53$ (n.s.); baseline SANS = 6.06 for not-followed v. 6.72 for followed $F[1,302] = 3.07$, $P = 0.081$). Although it is possible that including these excluded patients would have reduced the size or even changed the direction of the changes in symptoms, more symptomatic patients would most likely have returned for treatment to the Mental Health Center and been included in the study.

Another limit to generalisation from this sample is the fact that these are patients who had not developed tardive dyskinesia (TD) prior to the study, and did not develop TD during the first two years of the study—thus, the findings apply to those patients who have not developed TD during long-term neuroleptic treatment. It remains to be seen what, if anything, differentiates these 'TD-resistant' patients from those who develop TD.

The interpretation of the findings of increases in positive symptoms as resulting from a selective loss of subjects with falling levels of positive symptoms is also unlikely. The diagnostic group differences in both SANS and SAPS at baseline remain highly significant when patients lost to study are included.

Why do the patients, especially the schizophrenic patients, show a decline in mean negative symptoms and an increase in positive symptoms? This finding is not likely to be due to decreasing medication, which might have been expected in a sample being studied for emergence of tardive dyskinesia. With much variability, average medication levels for schizophrenics decrease over the two years of the study, while for non-schizophrenics there is a slight increase. At baseline, the schizophrenic group received 540.9 mg chlorpromazine equivalent dosage per day; they received 497.8 mg equivalent/day at follow-up. Non-schizophrenics, by comparison, received 329.6 mg equivalent/day dosage at baseline and 374.5 mg equivalent/day at follow-up. While the differences between diagnostic groups were significant, the dosage differences over time and the interaction of time with diagnosis were not.

Some tentative explanations for the changes in positive symptoms can be offered. First, after the initial period of intensive treatment at the beginning of the study, the therapeutic factors acting to suppress positive symptoms may erode, resulting in re-emergence of the active positive symptoms, for example in the patients who had active psychotic episodes and re-hospitalisations during the follow-up period.

Since the patients were identified while they were out-patients, there could be some effect of statistical regression to the mean. If there are effects of regression, the highly symptomatic group retained in the study may have returned to a higher level of symptoms after a quiescent period. But if this is the case why should there be a decline in negative symptoms? Baseline comparisons also contradict the suggestion that the patients more afflicted with negative symptoms are more likely to be lost to follow-up.

One aspect in which these patients differed from those in many, possibly more typical, forms of treatment is that they were followed up on a regular basis, and may thus be more likely to remain in treatment. If the results in this study are an artifact of this, they may indicate that negative symptoms are amenable to on-going psychosocial treatment and become less observable when patients are followed actively. The simultaneous re-emergence of positive symptoms may be more manageable when the patients are more actively engaged in the daily social interactions necessary for living.

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Relationship between positive and negative symptoms

The correlations of the SANS and SAPS scales are small and positive, supporting the current formulation of the two constellations as independent (e.g. Crow, 1980; Arndt *et al*, 1991). The rise in positive and decrease in negative symptoms cast strong doubt on whether negative symptoms can be regarded as the hallmark of a deteriorating course: these patients tended to move to a more symptomatic and less 'burnt-out' state over the course of two years.

The results also suggest that the practice of regarding positive and negative symptoms as coherent syndromes during the post-hospital phase, supported by the fact that from two to four components of these symptoms differ in course and correlates, should be reconsidered. Our analysis of the baseline data (Schuldberg *et al*, 1990), as well as the analyses of others (e.g. Walker *et al*, 1988; Arndt *et al*, 1991) has argued for several separate symptom components on both conceptual and psychometric grounds.

The results of the present study suggest that both positive, and in particular, negative symptoms present a complex picture in the out-patient course of patients on maintenance medication. Sub-groups of symptoms vary in different directions, making generalisation about all negative or all positive symptoms hazardous. Attention to such complexity is necessary if we are to further our understanding of this diverse group of illnesses.

Further work to confirm and elaborate these findings is suggested. Additional longitudinal studies are indicated to determine if the differentiation of negative symptoms is consistent, particularly with regard to the relation between employment and avolition. Additional work with neuroleptics which have beneficial effects on negative symptoms would further elucidate the relationship between these symptoms and the overall course of illness.

This study also suggests that it might be useful to pay attention to specific sub-categories of schizophrenic and affective symptoms and include appropriate measurement strategies in future research. It seems particularly important to assess sub-categories of both positive and negative symptoms. The positive–negative symptom dichotomy has contributed greatly to our understanding of the phenomenology, course, and possible aetiologies of schizophrenia and other severe mental disorders.

The results of this study are complex but provide a differentiated set of inter-relationships among symptoms, course, and adjustment. It now appears that more detailed views of symptomatology can lead to further advances in understanding aetiology, predictive factors, and differential therapeutic treatment for severe mental disorders.

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