Covariance of Positive and Negative Symptoms during Neuroleptic Treatment in Schizophrenia: A Replication

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Introduction

Although poor response to neuroleptics has traditionally been considered a characteristic feature of negative schizophrenic symptoms (Crow 1980; Andreasen et al 1982), several recent studies have documented significant improvement in negative symptoms in schizophrenic patients treated with neuroleptics (Breier et al 1987; vanKammen et al 1987; Kay and Singh 1989; Tandon et al 1990; Meltzer, 1990; Serban et al 1992). The question of whether neuroleptic-induced improvement in negative symptoms is linked to concomitant improvement in positive symptoms (vanKammen et al 1987; Tandon et al 1990; Meltzer 1990) or occurs independently of such improvement (Breier et al 1987; Serban et al 1992) is unresolved. This issue has obvious pathophysiological and therapeutic relevance.

In a previous study (Tandon et al 1990), we had observed a significant improvement in negative symptoms with four weeks of neuroleptic treatment in a sample of forty schizophrenic inpatients; a significant correlation between change in positive and negative symptoms was also noted. In an effort to replicate these findings and further evaluate to covariance of positive and negative symptoms in the course of initial neuroleptic treatment, we assessed positive and negative symptoms in another nonoverlapping sample of 80 schizophrenic inpatients at drug-free baseline and four weeks after clinically determined neuroleptic treatment.

Materials and Methods

The sample consisted of 80 consecutively hospitalized patients admitted to the University of Michigan Schizophrenia Program. Diagnostic evaluation included a structured interview using the Schedule of Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer 1978) as well as all available history and clinical observations. Patients had to meet both Research Diagnostic Criteria (RDC) (Spitzer et al. 1978) and DSM-III-R criteria (American Psychiatric Association 1987) for schizophrenia and give informed consent for participation in the study. The sample consisted of 50 men and 30 women with a mean ± SD age of 29 ± 8 years and a mean duration of illness of 8 ± 6 years. Twenty of the patients had never previously received any psychotropic medication.

Baseline clinical ratings were performed after patients were medication free for at least two weeks. Patients were then placed on clinically determined doses of haloperidol or thiothixene singly, or in combination with an anticholinergic agent if they developed extrapyramidal side-effects. After about four weeks of neuroleptic treatment, clinical ratings were repeated. Patients were rated on the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962), and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1983) at both timepoints. Assessment of global severity was made by the 18-item BPRS total score. Positive symptoms were assessed by the sum of the following four BPRS items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content. Negative symptoms were assessed by the SANS, with the sum of global scores being used for analysis.

Paired two-tailed Students *t*-tests were performed to compare the symptom ratings at baseline to those in the post-treatment phase. Correlation analysis between change in positive symptoms and change in negative symptoms was conducted to evaluate the covariance of these symptom clusters.

Results

Both positive and negative symptoms improved significantly ($p < 0.001$) with neuroleptic treatment (Table 1). Positive symptoms improved to a greater extent than negative symptoms. Drug-naive and previously-treated patients showed the same pattern

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Table 1. Positive and Negative Symptoms at Baseline and Following Four Weeks of Neuroleptic Treatment

	Baseline	Post-Treatment	Significance		Degree of improvement (% change from baseline)
			t	p	
Global severity (BPRS Total)	50.2 ± 8.6	36.6 ± 7.9	18.1	<0.0001	27
Positive symptoms (BPRS "THOT")	15.6 ± 2.9	10.1 ± 3.2	17.2	<0.0001	35
Negative symptoms (BPRS "ANER")	11.3 ± 2.9	8.4 ± 2.2	14.0	<0.0001	26
Negative symptoms (SANS sum of global scores)	12.5 ± 4.2	8.6 ± 3.4	13.3	<0.0001	30
Individual SANS scales					
Affective flattening	2.6 ± 0.97	1.9 ± 0.83	9.5	<0.001	27
Alogia	2.1 ± 1.04	1.4 ± 0.80	9.0	<0.001	32
Avolition-apathy	2.6 ± 1.01	1.7 ± 0.76	10.3	<0.001	33
Anhedonia-asociality	3.1 ± 0.82	2.3 ± 0.74	10.7	<0.001	26
Attention	2.2 ± 0.90	1.3 ± 0.79	11.7	<0.001	38

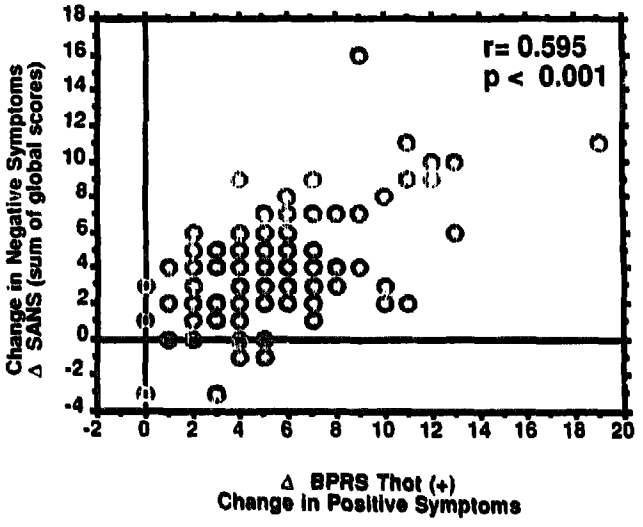

Figure 1. Relationship between change in positive and negative symptoms with neuroleptic treatment (N = 80).

of improvement. Use of the BPRS "ANER" factor (emotional withdrawal, motor retardation, and blunted affect) instead of the SANS sum of global scores to define negative symptoms did not alter the findings. There was a significant reduction in global scores on all five subscales of the SANS.

Change in positive symptoms was significantly correlated to change in negative symptoms ($r = 0.60$, $p < 0.001$) (Figure 1). Change in positive symptoms was also significantly correlated to change in each of the individual SANS global scales (affective flattening: $r = 0.37$, $p < .01$; alogia: $r = 0.49$, $p < 0.01$; avolition-apathy: $r = 0.48$, $p < 0.01$, anhedonia-asociality: $r = 0.39$, $p < 0.01$; attention: $r = 0.56$; $p < 0.01$).

Discussion

In agreement with the findings of other recent studies (Breier et al 1987; vanKammen et al 1987; Kay and Singh 1989; Tandon et al 1990; Meltzer, 1990; Serban et al 1992), these data confirm that both positive and negative symptoms improve significantly with neuroleptic treatment. Similar to the findings of these studies, we observed that positive symptoms improved to a greater extent than negative symptoms. The significant correlation between change in positive and negative symptoms noted in this study is in agreement with our previous study and the findings of vanKammen et al (1987) and Meltzer (1990), but inconsistent with Breier et al (1987) and Serban et al, (1992), who did not find such a relationship. Breier et al's inability to find this relationship may have been related to their relatively small sample size (19). Serban et al (1992) studied a sample of "negative schizophrenics" and excluded patients with more than moderate positive symptoms; their ability to detect covariance between positive and negative symptoms may have been limited by the restricted range of positive symptoms in their sample. Meltzer (1990) noted covariance of positive and negative symptoms in the course of treatment of schizophrenic patients with typical neuroleptics but not with clozapine.

The covariance of positive and negative symptoms in the course of initial neuroleptic treatment indicates that common or related pathophysiological mechanisms may underlie positive and negative symptoms in the psychotic phase of the illness. These data are consistent with the notion that only secondary negative symptoms (secondary to positive symptoms; Carpenter et al 1985) are responsive to treatment with typical neuroleptics. Alternatively, the concurrent improvement in positive and negative symptoms observed in our study can also be explained by the recently proposed model of dopaminergic/cholinergic interactions in schizophrenia (Tandon and Greden 1989), which suggests that distinct but related pathophysiological mechanisms

underlie positive (dopaminergic hyperactivity) and negative (cholinergic hyperactivity) symptoms in the psychotic phase of the illness.

These data are inconsistent with the characterization of negative symptoms as always being neuroleptic nonresponsive and suggest that common or related mechanisms may underlie positive and negative symptoms in the psychotic phase of the illness. The question of whether clozapine differs from typical neuroleptics with regard to the covariance of positive and negative symptoms during treatment requires further study.

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