BRIEF REPORTS

Mutability and Relationship Between Positive and Negative Symptoms During Neuroleptic Treatment in Schizophrenia

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Introduction

The positive/negative symptom dichotomy is being increasingly utilized to explain the heterogeneity of schizophrenia, and poor response to neuroleptic treatment has traditionally been considered to be one of the characteristic features of the negative syndrome. This issue was emphasized by Crow (1980), who principally based this conclusion on the study by Johnstone et al. (1978), which found that *cis*-flupenthixol, a dopamine (DA) receptor blocker, significantly reduced positive symptoms, but was no more effective on negative symptoms than *trans*-flupenthixol, an isomer of *cis*-flupenthixol without DA antagonist properties. Crow suggested that increased dopaminergic activity was the basis of the neuroleptic-responsive positive symptoms which were predominant in the so-called type I syndrome, whereas structural brain abnormalities marked by ventricular enlargement were the basis of the neuroleptic-nonresponsive negative symptoms that characterized the type II syndrome. The association between negative symptoms, poor response to neuroleptics, and ventricular enlargement was confirmed in several later studies (Andreasen et al. 1982; Angrist et al. 1980; Pearlson et al. 1984; Weinberger et al. 1980).

The National Institute of Mental Health and Veteran's Administration collaborative studies completed 25 years ago (Cole et al. 1966), however, had noted significant improvement in individual negative symptoms in schizophrenic patients as a consequence of neuroleptic treatment. This finding of improvement in negative symptoms has been confirmed in several recent studies (Breier et al. 1987; vanKammen et al. 1987; Kay and Singh 1989). One of these studies noted that improvement in negative symptoms was significantly correlated to the improvement in positive symptoms (vanKammen 1987), but another observed no such relationship (Breier et al. 1987).

In an effort to study the question of whether negative symptoms change with neuroleptic treatment and to evaluate the covariance of positive and negative symptoms, we assessed positive and negative symptoms in 40 schizophrenic inpatients at drug-free baseline and 4 weeks after neuroleptic treatment.

Materials and Methods

The sample consisted of 40 consecutively hospitalized patients who were admitted to the Inpatient Schizophrenia Program at the University

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of Michigan. 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 DSM-III-R (American Psychiatric Association 1987) and Research Diagnostic Criteria (RDC) (Spitzer et al. 1978) criteria for schizophrenia and give informed consent for participation in the study. The sample consisted of 27 men and 13 women with a mean ± SD age of 30 ± 6 years and a mean duration of illness of 6 ± 4 years. Twelve of the patients had never previously received any psychotropic medication, and 28 had previously received neuroleptics.

Baseline clinical ratings were performed after patients were medication free for at least 2 weeks. Patients were then placed on clinically determined doses of haloperidol or thiothixene singly, or in combination with 2–6 mg of trihexyphenidyl if they developed extrapyramidal side-effects. After about 4 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 seven BPRS items: conceptual disorganization, mannerisms and posturing, hostility, suspiciousness, hallucinatory behavior, unusual thought content, and excitement. Negative symptoms were assessed by the SANS, with the sum of global scores being used for analysis.

Paired two-tailed *t*-tests were performed to compare the symptom ratings at baseline to those in the posttreatment 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 were found to improve significantly ($p < 0.001$) with neuroleptic treatment (Table 1). Although positive symptoms improved to a greater extent than negative symptoms (Figure 1), this difference was not statistically significant. Drug-naive and previously treated patients showed the same pattern of improvement (Figure 1). Use of the BPRS "THOT" factor (consisting of conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content) to define positive symptoms or the BPRS "ANER" factor (consisting of emotional withdrawal, motor retardation, and blunted affect) to define negative symptoms did not alter the findings.

Change in positive symptoms was significantly correlated to change in negative symptoms ($r = 0.63$, $p < 0.001$). Even if a narrower definition of positive symptoms (the BPRS "THOT" factor) was employed, change in positive symptoms continued to be significantly correlated to change in negative symptoms ($r = 0.60$, $p < 0.001$).

Discussion

The observed improvement in negative symptoms with neuroleptic treatment is consistent with the findings of other recent studies (Breier et al. 1987; vanKammen et al. 1987; Kay and Singh 1989) that have documented such improvement. Similar to the findings of these studies, we observed that positive symptoms improved to a somewhat greater extent than negative symptoms. The significant correlation between change in positive and negative symptoms noted in this study is in agreement with the findings of vanKammen et al. (1987), but inconsistent with Breier et al. (1987), who did not find such a relationship. The failure of Breier et al. to find this relationship may have been related to their relatively smaller sample size (n = 19).

The covariance of positive and negative symptoms with reference to neuroleptic treatment indicates that common or related pathophysiological mechanisms may underly positive and negative symptoms in the psychotic phase of the illness. In an effort to reconcile discrepant findings with regard to neuroleptic responsiveness of negative symptoms, Meltzer (1985, in

Table 1. Positive and Negative Symptom Ratings at Baseline and Following 4 Weeks of Neuroleptic Treatment

Symptom measures	Baseline	Posttreatment	Significance		
			t	df	*p*
Global severity (BPRS total)	49.3 ± 8.0	35.0 ± 7.3	11.0	39	<0.001
Positive symptoms (BPRS subscale)	21.6 ± 4.9	13.4 ± 4.0	9.8	39	<0.001
Negative symptoms (SANS sum of global scores)	13.3 ± 4.1	8.7 ± 3.7	10.7	39	<0.001

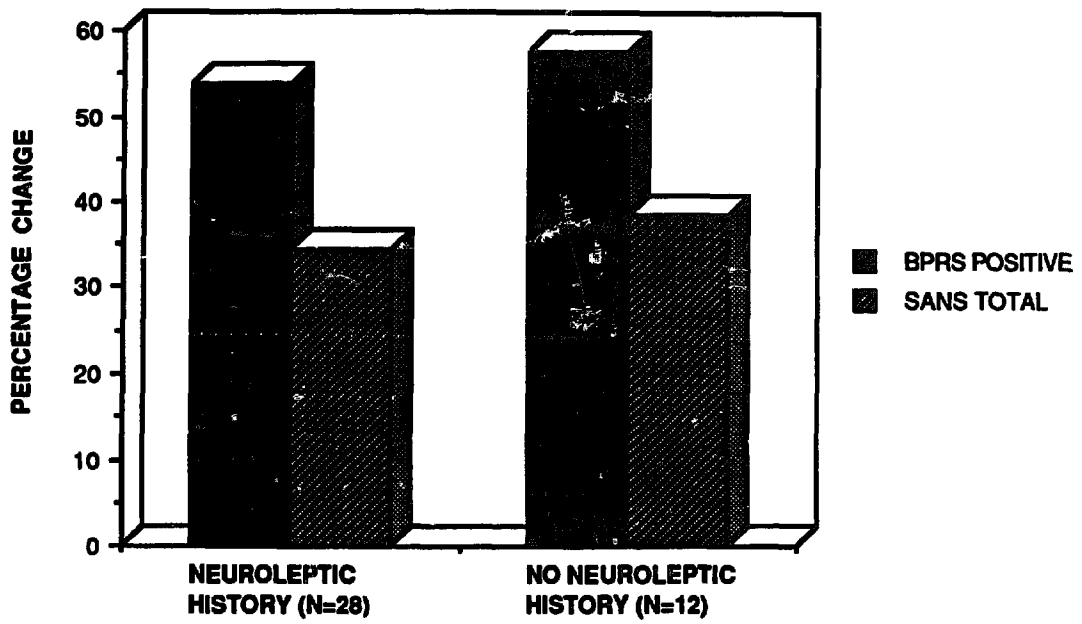

Figure 1. Degree of symptom improvement from baseline to posttreatment.

press) suggested that the effect of treatment on negative symptoms is dependent on positive symptom improvement; our findings are consistent with this contention. Alternatively, the concurrent improvement in positive and negative symptoms observed in our study is also consistent with the recently proposed model of dopaminergic/cholinergic interactions in schizophrenia (Tandon and Greden 1989) which suggests that distinct but related pathophysiological mechanisms underly positive (dopaminergic hyperactivity) and negative (muscarinic cholinergic hyperactivity) symptoms in this phase of the illness.

Though the validity of these inferences can be determined only through further study, these data are inconsistent with the characterization of negative symptoms as always being neuroleptic nonresponsive and suggest that common or related mechanisms may underly positive and negative symptoms in the psychotic phase of the illness.

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