Schizophrenia: A Multidimensional Disorder

Positive symptoms are active processes such as hallucinations and delusions, whereas negative symptoms are absences of normal function such as blunted affect and emotional withdrawal.

by LEWIS A. OPLER, MD, PhD, and MICHAEL Y. HWANG, MD

In the 1970s, one of us (LAO) was involved in administering L-dopa to chronic schizophrenic inpatients as a putative treatment for tardive dyskinesia. Since L-dopa, the precursor of dopamine, had been reported to exacerbate psychosis in acute schizophrenia, only patients with severe tardive dyskinesia were offered this treatment. Surprisingly, many chronic schizophrenics placed on L-dopa showed improvement in symptoms of blunted affect and emotional withdrawal, as opposed to improvement in symptoms such as hallucinations and delusions.

Crow's 1980 publication, "Molecular Pathology of Schizophrenia: More Than One Disease Process?" offered a conceptual framework for explaining these observations. Crow argued that Type I (positive symptoms) and Type II (negative symptoms) reflected independent pathological processes, suggesting that perhaps L-dopa was targeting what Crow called the Type II or negative syndrome.

As articulated in an earlier publication by Strauss, Carpenter, and Bartko, positive or productive symptoms are active processes such as hallucinations and delusions, whereas negative or deficit symptoms are absences of normal function such as blunted affect and emotional withdrawal.

Our research group was eager to test Crow's hypothesis. But how should negative symptoms be measured? The widely used 18-item Brief Psychiatric Rating Scale (BPRS) contained, at most, three items that could clearly be conceptualized as primary negative symptoms (blunted affect, emotional withdrawal, and motor retardation); even these, given the lack of clear definitions and operational criteria, were likely to be secondary negative symptoms. Secondary negative symptoms are disruptions in normal functioning due to factors such as positive symptoms (e.g., autistic withdrawal as a reaction to auditory hallucinations or persecutory delusions), depression, or drug side effects. While secondary negative symptoms mimic primary negative symptoms, their etiology is by definition entirely different. Angrist et al had used the BPRS in a study of the differential effects of amphetamine and neuroleptics on negative versus positive symptoms in schizophrenia and had found the following as regards the BPRS emotional withdrawal item:

Dr. Opler is Clinical Professor of Psychiatry at Columbia University College of Physicians and Surgeons, and Medical Director, New York City Regional Office, New York State Office of Mental Health. Dr. Hwang is Staff Psychiatrist at Manhattan Veterans Affairs Medical Center.

Address reprint requests to Lewis A. Opler, MD, PhD, New York City Regional Office, New York State Office of Mental Health, 275 Seventh Avenue, 15th floor, New York, NY 10001.

Psychiatric Annals 24:9/September 1994 491
But how should negative symptoms be measured?

Interview. (Pervasive anger, for example, in response to persecutory delusions or degrading auditory hallucinations, regardless of the interviewer's demeanor, would still be scored as a "failure to be in emotional contact.")

Convinced that the BPRS was inadequate for assessing a broad range of schizophrenic symptoms, and in particular for studying the negative syndrome, Opler and colleagues carried out a series of studies utilizing a special adaptation of the 18-item BPRS supplemented with 12 selected items from the Psychopathology Rating Schedule (PRS) of Singh and Kay.

Items were selected from the PRS if they were not represented in the BPRS, and particularly if they allowed assessment of deficits in affective, cognitive, and social realms. Seven items that could be conceptually linked as reflecting active symptoms were summed to provide a Positive Scale. Seven items that could be conceptually linked as tapping deficits were summed to provide a Negative Scale. These items were selected as primary negative symptoms, and parameters likely to be secondary to positive symptoms (e.g., poor attention, disorientation) or to depression (e.g., guilt feelings, motor retardation) were not included. The remaining 16 items not used to generate positive or negative scales were summed to provide the General Psychopathology Scale, a measure of general severity of illness.

As other features were introduced (e.g., anchoring points for each item), the Positive and Negative Syndrome Scale (PANSS) emerged as a new scale. Recently, the Structured Clinical Interview for the PANSS or SCI-PANSS was developed to assure the gathering of clinical data in a consistent manner. When 101 chronic schizophrenic inpatients were rated on the PANSS, a coefficient alpha of 0.73, 0.83, and 0.79 was obtained for the Positive, Negative, and General Psychopathology Scales, respectively. In other studies, severity of negative symptoms to prefrontal cortical dysfunction was demonstrated.

THE PANSS: ASSESSMENT OF POSITIVE, NEGATIVE, AND DEPRESSIVE SYMPTOMS

The Positive Scale is obtained by summing the following seven items: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility. The Negative Scale is obtained by summing the following seven items: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking. Since each item can receive a rating from 1 to 7 inclusive, both the Positive Scale and the Negative Scale have a potential range of 7 to 49.

While the PANSS was developed primarily to provide a focused assessment of positive and negative syndromes, Lindenmayer and Kay demonstrated predictive validity of a PANSS Depression Cluster, attained by summing the following four items: somatic concern, anxiety, guilt feelings, and depression. Since each item can receive a rating from 1 to 7 inclusive, the PANSS Depression Cluster has a potential range of 4 to 28.

POSITIVE, NEGATIVE, AND DEPRESSIVE SYMPTOMS OF SCHIZOPHRENIA: RESPONSE TO TREATMENT

Early studies used the PANSS to demonstrate that negative schizophrenic symptoms respond to novel pharmacological interventions, e.g., adjunctive L-dopa and pimozide. Recently, the PANSS has been used to demonstrate that the antipsychotic risperidone ameliorates positive, negative, and depressive symptoms. Risperidone, a combined D2-dopamine and S2-serotonin antagonist, administered to 523 chronic schizophrenic inpatients in a multicenter, randomized, double-blind trial carried out in six Canadian and 20 American cities to assess efficacy and safety. Subjects were randomly assigned to one of six groups, receiving either placebo, 2 milligrams per day of risperidone, 6 milligrams per day of risperidone, 10 milligrams per day of risperidone, 16 milligrams per day of risperidone, or 20 milligrams per day of haloperidol for up to 8 weeks. All subjects were rated on the PANSS, and results were as follows:

Compared to placebo, all five treatment groups showed significantly greater overall clinical improvement as measured both by numbers of patients achieving at least a 20% decrease in total PANSS scores, as well as in terms of mean change in total PANSS scores, with the group receiving 6 milligrams per day of risperidone showing the greatest overall improvement, including achieving significantly greater clinical improvement than the group receiving 20 milligrams per day of haloperidol (see Figure 1).

When the placebo, 6 milligrams per day of risperidone, and 20 milligrams per day of haloperidol groups were compared in terms of the improvement on PANSS Positive Scale, while both medications were significantly better than placebo, the risperidone group showed significantly greater improvement than the haloperidol group as well (see Figure 2).
In terms of improvement on PANSS Negative Scale, the haloperidol group failed to demonstrate statistically superior performance compared to placebo, whereas the 6 milligrams per day of risperidone group showed significantly greater improvement than both the placebo and the haloperidol groups (see Figure 3).

Risperidone at the optimal dose of 6 milligrams per day caused significantly less motor side effects than haloperidol, as rated by the Extrapyramidal Symptom Rating Scale (ESRS).

Focusing on the Negative Scale, across all six groups the score at baseline was in the mid-20s. In the group treated with haloperidol, there was less than a 1-point decrement in the mean Negative Scale score after 8 weeks (from 25.0 to 24.2), which failed to achieve statistical significance as compared with placebo, whereas in the group receiving 6 mg per day of risperidone, the Negative Scale rating dropped by 3.9, representing a statistically significant 15% drop in this rating (from 25.5 to 21.5) as compared with both placebo and haloperidol.

Global improvement was assessed using the Clinical Global Impression (CGI) Severity Score, with the 6 mg per day of risperidone demonstrating significantly greater improvement than both placebo and haloperidol (see Figure 4).

As regards the PANSS Depression Cluster, scores decreased in all six groups. At the optimal therapeutic dose of 6 milligrams per day of risperidone, the decrease in the Depres-
sion Cluster was significantly greater than for the group receiving either placebo ($p<0.05$) or haloperidol ($p=0.01$) (see Figure 5).

**PYRAMIDICAL MODEL OF SCHIZOPHRENIA**

Given that negative and positive dimensions could be independent but not sufficient to explain the entire phenomenology of schizophrenia, Kay and Sevy subjected PANSS symptom ratings on 240 schizophrenic inpatients to factor analysis to identify distinct clusters. Principal component analysis disclosed four components with eigenvalues greater than 2. Each of these four components embraced a substantial set of symptoms (five or more), were statistically unrelated by definition of the principal component analysis, and collectively accounted for 52.3% of the variance. The findings confirmed the presence of unrelated negative and positive factors, which emerged respectively as components 1 and 2 and accounted for the main share of variance (36.1%). The negative and positive syndromes, however, were indeed insufficient to explain the phenomenology of schizophrenia, with independent excited and depressive factors emerging as components 3 and 4, respectively.

When the interrelationship among the syndromes was plotted, the positive, negative, and depressive syndrome formed divergent points of a right triangular base, while the excitement syndrome formed a fourth pole that brought this triangular base into a third dimension. This four-component solution, referred to by Kay and Sevy as the "pyramidal model of schizophrenia," provides validation of Crow's model of independent positive and negative dimensions, while revealing two additional factors—depressive and excited components (see Figure 6).

**THE DIMENSIONAL PERSPECTIVE AND SCHIZOPHRENIC COMORBIDITIES**

Schizophrenic comorbidities are usually conceptualized as reflecting the simultaneous existence of two diagnostic categories (e.g., schizophrenia plus depression, schizophrenia plus obsessive-compulsive disorder). Given that schizophrenia is a multidimensional disorder, an alternative way of conceptualizing schizophrenic comorbidities is as reflecting either prominence of one of the core schizophrenic dimensions (e.g., schizophrenia with depressive features), or as reflecting the existence of an additional prominent dimension of pathology not normally found in schizophrenia (e.g., schizophrenia with obsessive-compulsive features). Recent epidemiological and clinical studies indicate a significant overlap between major psychiatric diagnoses such as schizophrenia, anxiety disorders, OCD, and mood disorders. Furthermore, clinical trials with the pharmacotherapeutic interventions known to alleviate the specific symptomatology have been associated with marked symptom reduction and functional improvements.

Whether schizophrenia with coexisting psychiatric phenomena such as anxiety, depression, or OCD turns out to be better conceptualized as a comorbid condition with two distinct disorders, or as schizophrenia with a prominent and/or added psychopathological dimension requiring focused clinical attention, it is becoming clear that these patients require specific symptom assessments and treatment approaches to optimize outcome. Ongoing work by ourselves and others is examining which of these models (coexisting categories versus prominence and addition of pathological dimensions) best describes schizophrenic comorbidities.

**REFERENCES**

2. Angrist B, Sathananthan G, Gershon S. Behavioral...