Negative and Deficit Symptoms in Schizophrenia Do Respond to Neuroleptics

by Solomon C. Goldberg

Abstract

Five large-scale placebo-controlled studies are cited to show that, contrary to the contention of Johnstone et al. (1976) and Crow (1980), negative and/or deficit symptoms in schizophrenia do indeed respond to neuroleptic treatment. Further evidence is given that it is the "organic-like" symptoms (visual and olfactory hallucinations, disorientation, and memory deficit) that do not respond to neuroleptics. This would more sensibly reformulate the hypothesis of Johnstone et al. (1976) and Crow (1980) to state that schizophrenic patients with enlarged ventricles tend to show symptoms of organicity and tend not to respond to neuroleptics.

The issue under discussion is based on an assertion by Johnstone et al. (1976) and Crow (1980) to the effect that schizophrenic patients with negative symptoms show structural brain abnormalities in the form of enlarged ventricles on computed tomography (CT), and tend to be poor responders to neuroleptics. Their statement was exciting because they showed a relationship between three different classes of variables: (1) phenomenology of symptomatology before treatment, (2) response to neuroleptics, and (3) structural abnormalities in the brain.

Since the publication of their results, there has been some replication—for example, by Andreasen and Olsen (1982), who contributed further by more systematic measurement and construct validation of negative symptoms. There has been more recent controversy as to whether "deficit" symptoms rather than negative symptoms were more crucial since some symptoms of schizophrenic deficit, such as inappropriate affect, are residual late-stage symptoms that are not necessarily negative. Thus, the original hypotheses have been broadened to say that negative and/or deficit symptoms in schizophrenia do not respond to neuroleptics and are associated with enlarged ventricles.

Although it will be one of our purposes in this commentary to show that Johnstone, Crow and their associates are mistaken about the symptoms variable, we still believe that they should be credited with an otherwise valid formulation of substantial heuristic value. There are now at least two other studies (Weinberger et al. 1980; Schulz et al. 1983) showing that enlarged ventricles on CT scan are associated with poor response to neuroleptic medication.

The point in contention is whether negative and/or deficit symptoms in schizophrenia respond to neuroleptics. Unfortunately, there is a tendency to disregard some of the earlier studies of neuroleptic effects in schizophrenia. The major features that commend the earlier studies are that they were done in a day when it was possible to have a placebo control group and they were based on sizable samples. The earlier studies might not pass the Institutional Review Board of the majority of institutions today because of the inclusion of placebo. Hence, it is of more than passing value to inspect the handful of large-sample studies done in the 1960s by the Veterans Administration, the National Institute of Mental Health (NIMH), and a few private and State hospitals. In the NIMH study reported by Goldberg, Klerman, and Reprint requests should be sent to Dr. S.C. Goldberg at Department of Psychiatry, Medical College of Virginia, Box 710, Richmond, VA 23298.
Cole (1965), highly significant drug-placebo differences were shown in a variety of positive, negative, and deficit schizophrenic symptoms. Included in the latter two categories are indifference to environment or apathy, hebephrenic symptoms or inappropriate affect, slowed speech and movements, poor social participation, poor self-care, and confusion (see table 1). Indeed, the greater drug effects were in hebephrenic symptoms, poor social participation, confusion, and poor self-care rather than positive symptoms. It was for this reason that we called attention to the fact that phenothiazines had more than a tranquilizing property. While the drugs did calm excitement, ideas of persecution, and incoherent thoughts, they appear to have had greater effects on symptoms that could be classified as negative, deficit, or Bleulerian fundamental. All of this was discoverable only because it was possible to have a placebo group in that study. If one looks at the amount of change under the drug condition without subtracting placebo effect, the negative and deficit symptoms do not change as much as the positive symptoms.

Another analysis in that study that brings out the same point was a drug-placebo comparison on that part of the sample which did not show a particular symptom before treatment. As shown in table 2, we demonstrated that there was a greater development of symptomatology in the placebo group than there was in the drug group when the symptom was initially absent. This occurred on the symptoms of auditory hallucinations, poor self-care, incoherent speech, hebephrenic symptoms, slowed speech and movements, and indifference to the environment. All of these symptoms except auditory hallucinations and incoherent speech could be regarded as either negative or deficit symptoms. Here again was a demonstration that the effects of the phenothiazines were primarily on negative and deficit symptoms.

A review by Cole, Goldberg, and Davis (1966) of other prominent controlled studies of phenothiazines and schizophrenia showed similar results. The other major studies were done primarily by the Veterans Administration, but also by Kurland et al. (1961) at the Spring Grove State Hospital in Maryland and by Klein (1967) at Hillside Hospital. VA Studies #1 and #2, reported by Casey et al. (1960a), were done on 805 acute and chronic schizophrenic men, and compared chlorpromazine,

Table 1. Greater reduction of negative and/or deficit symptoms under drug than placebo

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Placebo pre-post change standard scores</th>
<th>Drug pre-post change standard scores</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indifference to environment (n = 214)</td>
<td>.353</td>
<td>1.234</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Slowed speech &amp; movements (n = 245)</td>
<td>.114</td>
<td>.849</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Social participation vs. withdrawal (n = 302)</td>
<td>.788</td>
<td>1.776</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Hebephrenic symptoms (n = 150)</td>
<td>.247</td>
<td>1.437</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Confusion (n = 276)</td>
<td>.620</td>
<td>1.600</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Poor self-care (n = 224)</td>
<td>.349</td>
<td>1.283</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Table 2. Greater development of negative and/or deficit symptoms under placebo than drug among initially asymptomatic patients

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Placebo pre-post</th>
<th>Drug pre-post</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor self-care (n = 94)</td>
<td>-.656</td>
<td>-.192</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Slowed speech &amp; movements (n = 80)</td>
<td>-1.087</td>
<td>-.257</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Hebephrenic symptoms (n = 175)</td>
<td>-.865</td>
<td>-.204</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Indifference to environment (n = 111)</td>
<td>-1.261</td>
<td>-.572</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>
promazine, phenobarbital, and placebo. VA Study #3, also reported by Casey et al. (1960b), was done on 640 newly admitted schizophrenic men and compared a variety of phenothiazines with a phenobarbital control group. The study of Kurland et al. (1961) at Spring Grove State Hospital was done on 238 new admissions, most of whom were schizophrenic, and compared a variety of phenothiazines with placebo. The study by Gorham et al. (1964) compared phenothiazines with group psychotherapy. As pointed out in the review by Cole, Goldberg, and Davis (1966), all five studies find a strong drug effect on thought disorder; two of the studies show an effect on blunted affect and indifference; four of the studies show an effect on withdrawal-retardation, and four of the studies show a drug effect on autistic behavior and mannerisms. Thus, there seems to be more than ample evidence in placebo-controlled studies that phenothiazines at least have an effect on negative symptoms as well as positive symptoms and on what many consider residual deficit symptoms in schizophrenia, e.g., inappropriate affect, and autistic behavior and mannerisms.

Aside from the review by Cole, Goldberg, and Davis, there is the very early work of Klein (1967) in which one of his main points was that compared to placebo, a neuroleptic not only calms excitement, but also tends to normalize underactivity and retardation.

The more recent studies showing a relationship between negative symptoms and poor outcome are possibly an artifact of not having a randomized placebo group for comparison.

What, then, in the way of symptomatology does not respond to neuroleptics? In the study of Goldberg, Klerman, and Cole (1965), some of these nonresponsive symptoms—for example, nonauditory hallucinations (visual and olfactory), disorientation of time, place, and person, and memory deficit for recent events—might alert a diagnostician to the possibility of organicity. Of course, one would not rely on the interview for diagnosing organicity, but might instead employ one of the better standardized neuropsychological performance batteries such as the Luria or the Halstead. Indeed, there is another literature already showing that a pathognomonic index of organicity, in both the Halstead-Reitan (Donnelly et al. 1980) and the Luria-Nebraska (Golden et al. 1980) is associated with enlarged ventricles on CT scan. It stands to reason that if one is then looking for the phenomenological behavior associated with enlarged ventricles, one might look for organic signs rather than negative or deficit symptoms in schizophrenia.

Further, it seems that the field has gone as far as it is able in advancing theoretical formulations on the basis of rated behavior as observed in an interview. More precise theoretical formulations will require behavioral responses to standard stimulus conditions. Ratings have improved enormously over the years of research and have been shown to be highly reliable and to have some predictive and construct validity. Nonetheless, these retrospective judgmental observations must now be compared with regard to their reliabilité validity with the more precise standard stimulus performance measures.

In providing evidence against the importance of negative and deficit symptoms in the hypothesis of Johnstone et al. (1976) and Crow (1980), I would like to offer a reformulation for which there appears to be more than ample evidence. The reformulation would state that schizophrenic patients with enlarged ventricles on the CT scan are those who show signs of organicity by a variety of observational systems and respond poorly to neuroleptics. As modified, this formulation remains one of the more heuristic ones in schizophrenia research since it stimulated a number of seemingly unrelated questions. For example, the work by Murray et al. (in press) in England shows that the more organic schizophrenic patient tends to have less genetic loading for schizophrenia, is more likely to have had severe birth complications, and is more likely to have been born in a winter month, thus implicating the possibility of viral infection. Their results do not deny the validity of genetic transmission in many schizophrenic patients, but only point out that many other validly diagnosed schizophrenic patients are more likely to be a product of environmentally induced structural brain damage.

References


The Author

Solomon C. Goldberg, Ph.D., is Director of Psychiatric Research, Medical College of Virginia, Richmond, Virginia.