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Differential Effects of Amphetamine and Neuroleptics on Negative Vs. Positive Symptoms in Schizophrenia

B. Angrist[1], J. Rotrosen[1], and S. Gershon[2]

[1] Department of Psychiatry, New York University Medical Center, 550 First Avenue, New York, New York 10016, USA, and Psychiatry Service, New York Veteran's Administration Medical Center, 1st Avenue and 24th Street, New York, New York 10010, USA
[2] Department of Psychiatry Wayne State University, Detroit, Michigan, USA

Abstract. Positive symptoms of schizophrenia were diminished by neuroleptics and increased by amphetamine and accounted for most of the change seen in the total Brief Psychiatric Rating Scale (BPRS). Negative symptoms in the same subjects were not affected by neuroleptics but increased after amphetamines to a degree that just attained statistical significance. This increase was due to one item (emotional withdrawal) of the negative symptom factor which responded to neuroleptics and amphetamines as did positive symptoms. These findings are discussed with respect to new ideas about the role of dopamine in schizophrenia.

Key words: Amphetamine – Neuroleptics – Dopamine – Schizophrenia – Negative schizophrenic symptoms

In 1975, Itil et al. reported:

> "Therapy resistant' schizophrenic patients were characterized by a lesser degree of very fast beta activity, more alpha waves and slow waves, higher amplitudes in computer EEG, and a lesser degree of acute (florid) psychotic symptomatology but more 'negative' symptoms such as motor retardation and blunted affect."

In 1976, Meltzer and Fang noted that clinical change in schizophrenics after neuroleptic administration or discontinuation occurred more slowly than prolactin elevation or decline. The same group (Meltzer and Stahl 1976) then suggested that 'dopaminergic hyperactivity' (in schizophrenia) 'is probably due to some other basic defect'.

Johnstone et al. (1976) reported that a group of chronically institutionalized schizophrenic patients showed an increase in cerebral ventricular size over age-matched controls as assessed by computerized axial tomographic (CAT) scans. Furthermore, increased ventricular size was correlated with poor performance in tests of cognitive function. The same group (1978a) showed that the therapeutic effect of α-flupenthixol was confined to positive symptoms of schizophrenia; and in a separate study (1978b) showed not only a correlation between increased ventricular size in schizophrenics and intellectual impairment, but also a relationship between impaired cognitive function and negative schizophrenic symptoms ('affectual flattening, retardation, poverty of speech'). Weinberger et al. (1980) confirmed that some chronic schizophrenic patients had enlarged cerebral ventricles and demonstrated that these patients had a poorer response to neuroleptic treatment than a matched group of schizophrenic patients without ventricular enlargement.

Recently Crow (1980) has synthesized these findings in a formulation regarding etiopathogenic mechanisms in schizophrenia which can be summarized:

In schizophrenic disorder two syndromes can be distinguished, each of which may be associated with a specific pathological process. The Type I syndrome or 'acute' schizophrenia is characterized by positive symptoms, delusions, hallucinations, and thought disorder, and is in some way associated with a change in dopaminergic transmission. In contrast the Type II syndrome or 'defect state', marked by affective flattening and poverty of speech, is unrelated to dopaminergic transmission but may be associated with intellectual impairment and, perhaps, structural changes in the brain. Type I symptoms are reversible, but Type II are more difficult to define and may be partly irreversible. The former are likely to respond to neuroleptics whereas the latter may have a poor long-term prognosis. Episodes of Type I symptoms may be followed by Type II symptoms and both may coexist. However, Type II symptoms define a group of disorders with a graver prognosis.

We have recently studied correlations between changes in psychopathology after a single dose of amphetamine and after neuroleptic treatment (Angrist

Offprint requests to: B. Angrist, New York University Medical Center

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et al. 1980). By reanalyzing these data, we could not only assess the effect of neuroleptics on 'positive vs. negative' schizophrenic symptoms, but also determine the response of these types of symptoms to amphetamine as well. We postulated that positive symptoms should increase after amphetamine and decrease after neuroleptics, while negative symptoms should not change after either intervention. These new data are the subject of this report.

Materials and Methods

The methods used are detailed in the previous study (Angrist et al. 1980). Briefly, 21 schizophrenic patients who consented to participate after extensive discussion of the procedure, were transferred to our ward and remained neuroleptic-free for 6–15 days or more (mean 9.9 ± 0.7 days) before testing. These subjects were 20 males and 1 female, 20–44 years of age (mean 27.9 ± 1.3 years). All met the research diagnostic criteria (RDC) of Spitzer et al. (1978) for schizophrenia: 10 were acute or subacute, and 11 were chronic or subchronic.

Subjects received 0.5 mg/kg of *d*-amphetamine orally. Unstructured clinical interviews were done before and every hour after drug was given. The BPRS and clinical global impressions (CGI) were administered before and 3 h after amphetamine administration.

After rating amphetamine-induced changes in psychopathology, subjects were treated with neuroleptics in individualized, but generally large doses. Haloperidol was most commonly used. Treatment duration ranged from as little as 7 days (in rapid responders who could be discharged) to 5–6 weeks of high dose treatment. All but one subject were able to be discharged at the end of the study. Psychopathology was rated with the BRPS and CGI weekly during neuroleptic treatment and at termination of the study.

In this data analysis, changes in psychopathology after amphetamine and after neuroleptics were compared with baseline levels via paired *t*-tests. Comparisons of change were made for:

1. Total psychopathology.

2. 'Positive' schizophrenic symptomatology consisting of factors 3, 4, and 5 of the BPRS. These factors are: No. 3 thought disturbance (conceptual disorganization, grandiosity, hallucinatory behavior, and unusual thought content); No. 4 activation (tension, mannerisms and postering, and excitement); No. 5 hostile suspiciousness (hostility, suspiciousness, and uncooperativeness).

3. Negative schizophrenic symptomatology consisted of the withdrawal-retardation factor (emotional withdrawal, motor retardation, and blunted affect; Guy 1976).

In addition, for reasons that will be discussed below, separate analyses were done for changes in the emotional withdrawal vs. the motor retardation and blunted affect items of this factor.

Results

Changes in total BPRS psychopathology and both positive and negative schizophrenic symptoms (as defined above) are given in Table 1. A further subdivision in the cluster of negative symptoms (emotional withdrawal vs. motor retardation and blunted affect) is also indicated.

Table 1. The effects of amphetamine and neuroleptics on two different types of schizophrenic psychopathology

	Baseline	Post-amphetamine	Postneuroleptic treatment
Total BPRS	36.5 ± 2.05	42.8 ± 2.6 $P < 0.01$	29.8 ± 1.5 $P < 0.01$
'Positive' symptoms	21.3 ± 1.7	26.6 ± 2.3 $P < 0.001$	15.4 ± 1.05 $P < 0.001$
'Negative' symptoms	8.09 ± 0.42	8.85 ± 0.43 $P < 0.05$	7.66 ± 0.55 NS
Emotional withdrawal	3.47 ± 0.28	4.38 ± 0.33 $P < 0.001$	2.85 ± 0.26 $P < 0.02$
Motor retardation and blunted affect	4.66 ± 0.36	4.47 ± 0.37 NS	4.85 ± 0.40 NS

P refers to change from baseline (paired *t*-test, two tailed)

Discussion

Total psychopathology scores were significantly increased by amphetamine and diminished by neuroleptic treatment. Consistent with our hypothesis (based on Crow's formulation), most of this could be accounted for by changes positive schizophrenic symptoms. The lack of significant effect of neuroleptic treatment on negative schizophrenic symptoms was also consistent with the above hypothesis. The finding that negative symptoms were increased by amphetamine at a level just reaching significance was unexpected.

One possible explanation was that emotional withdrawal (defined on the BPRS as the degree to which the patient gives the impression of failing to be in emotional contact with other people in the interview situation) could be of two clinical types. The first is an inadequate capacity for emotional response (emotional deterioration). In the second type, emotionality is preserved, but is congruent with autistic preoccupations rather than the 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'.) Separating the Withdrawal-Retardation Factor into its components, 'emotional withdrawal' vs. 'motor retardation and blunted affect', supports the clinical interpretation that the increase in negative symptoms seen after amphetamine was largely due to our scoring the incongruent type of emotionality as 'emotional withdrawal'. Motor retardation and blunted affect were not significantly changed by administration of either amphetamine or neuroleptics. Emotional withdrawal, however, showed a pattern of response similar to that of positive schizophrenic symptoms. Mean scores for this item were highly significantly increased by amphetamine ($P < 0.001$) as well as being significantly diminished by neuroleptics.

If the methodologic problems involved in scoring the 'Emotional Withdrawal' item of the BPRS are

taken into account (see Guy 1976, p 162, for further discussion of these problems), we believe that these results rather strongly support the formulation proposed by Crow. Not only is the "Type I syndrome' improved by neuroleptics, but it is also intensified by amphetamine. The 'Type II syndrome', however, is relatively uninfluenced by either of these manipulations of dopaminergic systems.

We believe that Crow's formulation constitutes an important refinement of the 'Dopamine Hypothesis' of schizophrenia. It takes into account both the probable role of dopaminergic mechanisms in the pathogenesis of productive schizophrenic symptoms and the limitations of this concept in explaining all clinical aspects of schizophrenic illness. It is certainly consistent with the very common clinical experience represented by the patient whose florid psychopathology is effectively reduced by neuroleptics, but who remains incapacitated to some degree by a residual schizophrenic 'defect state'.

Further research in this area might specifically address the relationships between positive and negative symptoms' predominance and ventricular enlargement on CAT scan in young schizophrenics with minimal neuroleptic treatment histories. Such subjects' responses to both dopaminergic agonists and neuroleptics should also be investigated. Furthermore, Crow's formulation might influence treatment approaches. Negative symptomatology, the Type II syndrome, might be an important index of poor prognosis. More important, the use of neuroleptics might be reserved specifically for the treatment or prevention of the positive symptomatology of the Type I syndrome.

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References

Angrist B, Rotrosen J, Gershon S (1980) Response to apomorphine, amphetamine and neuroleptics in schizophrenic subjects. Psychopharmacology 67:31–38

Crow TJ (1980) Molecular pathology of schizophrenia: more than one disease process? Brit Med J 280:66–68

Guy W (1976) E.C.D.E.U. assessment manual for psychopathology. Washington D.C.: U.S. Department of Health, Education and Welfare, pp 160, 162, 167

Itil TM, Marasa J, Saletu B, Davis S, Mucciardi AN (1975) Computerized EEG: predictor of outcome in schizophrenia. J Nerv Ment Dis 160:188–203

Johnstone EC, Crow TJ, Frith CD, Carney MWP, Price JS (1978a) Mechanism of antipsychotic effect in the treatment of acute schizophrenia. Lancet 1:848–851

Johnstone EC, Crow TJ, Frith CD, Husband J, Kreel L (1976) Cerebral ventricular size and cognitive impairment in schizophrenia. Lancet 2:924–926

Johnstone EC, Crow TJ, Frith CD, Stevens M, Kreel L, Husband J (1978b) The dementia of dementia praecox. Acta Psychiat Scand 57:304–324

Meltzer HY, Fang VS (1976) Serum prolactin levels in schizophrenia – effect of antipsychotic drugs: A preliminary report. In: Sachar EJ (ed) Hormones, behavior and psychopathology. Raven Press, New York, p 177

Meltzer HY, Stahl SM (1976) The dopamine hypothesis of schizophrenia: a review. Schizophr Bull 2:19–76

Spitzer RL, Endicot J, Robins E (1978) Research diagnostic criteria: Rationale and reliability. Arch Gen Psychiatry 35:733–782

Weinberger DR, Bigelow LB, Kleinman JE, Klein ST, Rosenblatt JE, Wyatt RJ (1980) Cerebral ventricular enlargement in chronic schizophrenia: an association with poor response to treatment. Arch Gen Psychiat 37:11–13

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