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The Neuroleptic Hypothesis: Study of the Covariation of Extrapyramidal and Therapeutic Drug Effects

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SUMMARY A therapeutic trial with chlorpromazine was conducted with a homogeneous (for age and sex) group of recently admitted schizophrenic patients. Extrapyramidal effects were measured through quantitative analysis of digital tremor, after four days of fixed-dose treatment. Assessment of treatment efficacy was based on Brief Psychiatric Rating Scale ratings, done at the end of four weeks' treatment. Those patients whose tremor was least affected by drug were most likely to benefit from the treatment. Implications of this negative correlation for our understanding of the neuroleptic hypothesis and the closely associated dopamine hypothesis of schizophrenia are discussed.

Introduction

Delay *et al* (1955) assumed that the pharmacotherapeutic action of antipsychotic drugs was associated with their tendency to produce extrapyramidal side-effects (EPSE) and suggested that this class of drugs be designated as neuroleptics in recognition of this joint action. Study of this association has been the focus of a series of investigations around what might be termed the neuroleptic hypothesis that '. . . the production of extrapyramidal symptoms and the reduction of schizophrenic psychopathology are closely related pharmacological properties and that these drug effects may be elicited at a single site of action in the central nervous system' (Cole and Clyde, 1961, p 565).

Although the neuroleptic hypothesis would lead to a direct (positive) correlation between the two drug effects, evidence from clinical studies has been ambiguous or contradictory and the relation between the two classes of action is still not established. Positive relations between EPSE and therapeutic effects were reported by Freyhan (1957), Denham (1961), and Brune *et al* (1962), while positive but curvilinear results were reported by Haase and Janssen (1965). Curvilinear results were also reported by Simpson and Kunz-Bartholini (1968). Curvilinear and null results were reported by Bishop, Gallant and Sykes (1965). Null results were reported by Karn and Kasper (1959), Hollister, Caffey and Klett (1960) and Goldman (1961). A negative correlation between EPSE and therapeutic response was reported by Simpson *et al* (1964).

Recent biochemical and pharmacological insights have suggested experimental controls which have not been included in the past. We here report results from a study, utilizing these controls, which indicates that there is a negative correlation between the two classes of neuroleptic action. These observations have implications for the neuroleptic hypothesis and the closely associated dopamine hypothesis of schizophrenia (e.g. Meltzer and Stahl, 1976).

The experimental controls which must be considered have three main areas. Firstly, drug factors: drugs differ in their tendency to provoke EPSE and two independent mechanisms have been identified as influencing them —a positive relation with the compound's dopamine receptor blockage potency (Creese,

Burt and Snyder, 1975), and a negative relation with the same compound's anticholinergic potency (Snyder, Greenberg and Yamumura, 1974). The two mechanisms vary independently in different drugs so that clinical studies based on several drugs would be difficult to interpret (as would studies permitting supplemental use of anticholinergics, which counteract the EPSE but do not alter outcome). The two factors may also vary independently and non-linearly, even in the same drug, if a wide dose range is used. In relation to the paradoxical observation that higher doses of a neuroleptic drug can produce fewer EPSE than lower doses, Hollister (1976) suggested that dopamine receptors may saturate at a lower dose than cholinergic receptors. Thus, increasing the dose of a neuroleptic beyond a certain point would be equivalent to adding an anticholinergic agent. The study to be reported here involves use of a single neuroleptic drug at fixed doses, at least during the period of measurement of EPSE. Some variation in dose and the supplemental use of anticholinergic drugs was permitted during the treatment phase, after measurement of EPSE vulnerability, because of the clinical impression that optimal results depend on individuation of treatment parameters. Secondly, there are subject factors: age, sex and previous drug exposure have been identified as affecting vulnerability to EPSE (Ayd, 1961). These factors, as well as diagnosis, may also affect prognosis. This study, however, utilized a subject population which was as homogeneous as possible.

Definition and measurement of EPSE: Thirdly, Chien and DiMascio (1967) have reviewed problems in the description and classification of EPSE and concluded that a good deal of the ambiguity in the study of neuroleptic hypothesis may be attributable to methodological inadequacies. They urged the use of quantitative measuring instruments and experimental rigour. Our measure of EPSE is based on a quantitative analysis of digital tremor, recorded bilterally from each index finger (Alpert, Lomask and Friedhoff, 1966) and then analyzed for amplitude and spectrum of the tremor wave form (Alpert, 1975). We have found tremography to be repeatable, quantitative and a good correlate of clinical ratings. In addition, because of the sensitivity of the system, it is possible for it to detect neuroleptic effects below their threshold for clinical expression.

We have recently reported results from a pilot study, incorporating the methods described above (Alpert, Diamond and Kesselman, 1977). In this, we studied ten recently admitted premenopausal female schizophrenics treated with fixed doses of trifluoperazine, and found that those patients showing the least tremor changes during the first week of treatment tended to show better responses to treatment three weeks later—a negative correlation between EPSE and treatment outcome. The present study was designed to replicate and extend this previous report. In addition to our tremographic measure of EPSE, we also studied sedation because it is a frequent side-effect of antipsychotic compounds and might provide a control for any non-specific tendency of patients to show side-effects. This tendency could, in itself, be related to outcome, so that inclusion of a measure of sedation might serve as a control for the specificity of a relation between EPSE and outcome.

Method

Twenty-one female schizophrenics, newly admitted to Bellevue Psychiatric Hospital, volunteered for the study, providing signed, informed consent. Only patients in good physical health, without history of hepatic, CNS or other major disease or substance abuse and who had not received neuroleptic medication for more than two days in the previous week, or more than seven days in the previous three months, were accepted for study. Four patients were lost to study: one due to absconding; two because they changed their minds and withdrew from the study and one patient because of a charting error, which led to a departure from the medication schedule. The age-range of the patients (N = 17) was 17 to 34 years and the mean age was 26.0 years. All patients were diagnosed independently by two psychiatrists as schizophrenic, using DSM II criteria (American Psychiatric Association, 1968). Although many of the patients had been hospitalized previously, all had been out of

hospital and had shown a recent exacerbation of their illness, requiring admission to our acute receiving hospital.

There was a baseline placebo period of four to seven days, followed by four weeks of chlorpromazine (CPZ) treatment. Chloral hydrate was permitted during the baseline period. Starting dose of CPZ was 200 mg/day at bedtime. This was increased daily in 200 mg/day increments for five days, always in a single bedtime dose. Two patients developed side-effects and were held on 600 mg/day on days four and five. After the dose-range period, medication was adjusted at doctors' choice to attempt to achieve an optimum therapeutic dose. Anticholinergic drugs could be added and five patients received them during the three-week adjusted dose period. The average daily dose of CPZ in the last week of treatment was 996 mg.

Tremor was recorded in the morning at base-line and during the week of fixed dose increments. To measure sedative effects, we used a clinical scale—the Stanford Sleepiness Scale (SSS) (Hoddess, Dement and Zarcone, 1973)—and a psychometric measure—the Digit Symbol Substitution Test (DSST) (Wechsler, 1958). The measure of treatment response was based on the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). The SSS and DSST were administered following each tremor recording. Two psychiatrists independently rated each patient at base-line and termination of treatment, using the BPRS. BPRS inter-rater reliabilities were above .9 and the two ratings were averaged in the results.

Results

At base-line, the average BPRS total score was 48.0, with a standard deviation of 11.04. At termination, these figures were 31.9 and 9.33 respectively. The range of changes was from +3 (one patient had a higher BPRS at termination) to −49, and it is the association of this range of therapeutic responses with the measures of side-effects that were examined.

There was a monotonic increase in sleepiness scores over the five dose-increment days, but no suggestion of such a trend for the DSST scores. The two measures of sedation were uncorrelated and were unrelated to either the tremographic measures or the BPRS measures. The sedation results will not be described further here.

Fig 1 contains the average tremor spectra

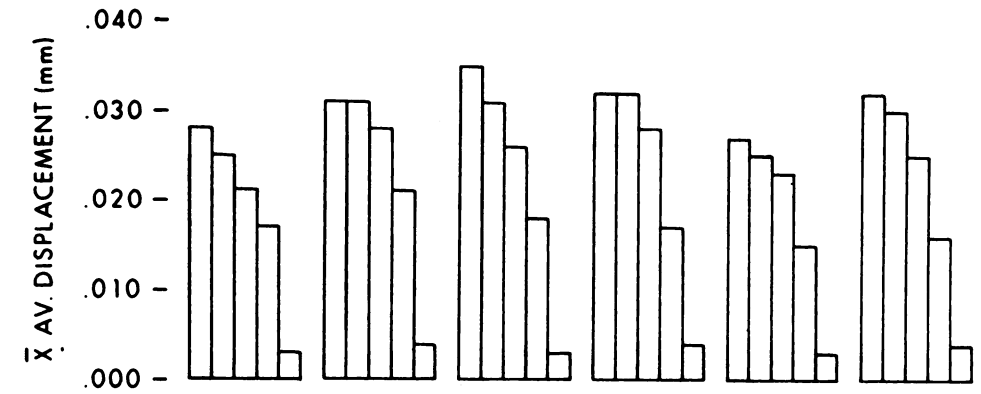

FIG 1.—Average tremor spectra during the dose range period.

during the dose-range period. At base-line, the group was characterized by a relatively homogeneous, low amplitude tremor with some greater than expected energy in the low frequency band. There was a modest increase in amplitude of tremor with the first two doses and it was noted that mean tremor measures for day 4 were very close to the base-line measures. However, patients were differentially affected by the medication so that the base-line and day four tremors were only slightly correlated (see Table 1A).

In previous work, we found that tremor energy in the 2–4 Hz band is most reflective of EPSE, which appear as a shift of energy into this band, with or without an increase in overall amplitude. To investigate the relationship between the EPSE and therapeutic effects of CPZ, we calculated the correlations between 2–4 Hz energy and BPRS score. The relationships to be described hold, at equal confidence levels, for total tremor energy. In Table 1A, the inter-correlations between base-line and termination BPRS scores and 2–4 Hz energy at base-line and on day four are presented. Day four tremor will be discussed because it is the highest dose to which most of the patients were uniformly exposed and because on day three, two patients required diphenhydramine because of side-effects. The relations to be described hold, in a somewhat weaker form, for days three and five.

In Table 1A it can be seen that on day four, 2–4 Hz energy is positively related to termination BRPS; patients who are more affected by neuroleptic on day four tend to do less well at outcome. However, day four 2–4 Hz tremor is also weakly correlated with the base-line BPRS measure and with the base-line tremor measure. To partial out the relations among these predictors, a multiple regression analysis was carried out, relating termination BPRS with base-line BPRS, base-line 2–4 Hz tremor and day-four tremor—with the predictors inserted in that order (Table 1B). Here it may be seen that base-line BPRS explains only 10 per cent of the outcome variance and that base-line tremor is unrelated to outcome. The day-four 2–4 Hz tremor explains over a third of the outcome variance, after the contribution of the base-line

TABLE I

A. Intercorrelations among baseline and termination measures of total BPRS scores, and baseline and day-four measures of tremor (2–4 Hz band) (N 17)

	Base band 2–4 Hz	Day 4, Band 2–4	Post BPRS
Base BPRS	−.11	.33	.31
Base band 2–4		.38	−.11
Day 4, Band 2–4			.58*

* P < .01

B. Summary of multiple regression analysis of date in (A) above

	Cumulative proportion of variance explained	df	F
Base BPRS	.0961	1/15	1.59
Base Band 2–4	.0996	1/14	.05
Day 4, Band 2–4	.4636	1/13	8.81†

† P < .05

measures is removed, yielding an F of 8.8 which, with 1/13 df, is significant at P < .05.

Discussion

Our main finding—that neuroleptic effects are negatively associated with outcome—is a replication and extension of the report of Simpson *et al* (1964) and of our earlier study (Alpert, Diamond and Kesselman, 1977). The null association between sedative side-effects and outcome may reflect measurement difficulties in this area, although neither of our measures was an effective predictor and both are of established reliability. The predictive efficiency of tremography and the null results for sedation, taken together, suggest that these are relatively specific relations and thus consistent with the neuroleptic hypothesis. The inverse nature of the correlation indicates that the finding is not simply an artifact of drug kinetics, since factors such as drug absorption or metabolism would tend to produce positive correlations between two overlapping processes.

The strength of the neuroleptic correlation is especially impressive when considering the temporal separation between the EPSE and outcome measurement points. It appears that some pharmacological mechanisms, effective by day four, were related to therapeutic processes not yet manifested. Although there are not sufficient data for a direct analysis, it is our impression that the neuroleptic correlation would not have been enhanced by tremor measures taken later, or BPRS measures taken much sooner. The nature of the underlying pharmacological mechanisms, though, is far from clear.

The dopamine hypothesis of schizophrenia is largely based on the observation that therapeutic drugs reduce the action of dopamine at central dopaminergic receptors. As noted above, it has even been shown that the clinically effective dose of different drugs is proportional to measures of the potency of the drug's dopamine receptor blockade. These observations, as well as others, have supported the suggestion that schizophrenia is a hyperdopaminergic state and that reduction of this excess activity is the mode of therapeutic action. Following this reasoning, one would expect that patients most clearly showing evidence of dopamine blockade would be most likely to have a positive therapeutic outcome. Bishop, Gallant and Sykes (1965) suggested clinical mechanisms that might moderate a positive correlation. They noted that sicker patients might appear less sick and recovered patients appear less well if EPSE masked their true condition. In this study, where tremor was used as a measure of EPSE in the absence of overt clinical manifestation, this explanation seems unlikely. Thus, while our results are consistent with the importance of interaction with dopamine in the pharmacodynamics of antischizophrenic drugs, they are contrary to the suggestion that direct dopamine blockade in itself is the pharmacotherapeutic mechanism.

Rather than the reduction in dopamine activity, some consequence of this reduction may be important—perhaps the tendency of anti-schizophrenic drugs to stimulate increased dopamine turnover, or some consequence of this stimulation. There is some biochemical evidence which is consistent with this suggestion, although indirectly. Crowley *et al* (1976, 1977) have reported that patients who develop EPSE have low urinary free dopamine prior to drug administration. Van Praag and Korf (1976) have reported a similar association from measures of premedication HVA collected from spinal fluid (CSF) of probenecid-treated patients who subsequently developed EPSE. Chase, Schnur and Gordon (1970) found that patients who developed EPSE while on drug had lower drug stimulated increases in levels of HVA (and, to a lesser extent, 5 HIAA) in CSF. These findings, taken together, may be interpreted as suggesting that EPSE reflect some failure of drug-stimulated increase in dopamine turnover. In extension of these observations, our inverse correlation between EPSE and outcome might indicate that patients with higher pre-treatment dopamine, or those showing adequate drug-stimulated increases in dopamine turnover, will be less likely to develop EPSE and also tend to have a better therapeutic outcome.

Stimulation of increased dopamine turnover is one of a number of reactive mechanisms which would be consistent with the time course of therapeutic action, since therapeutic response is delayed for days or weeks beyond the point at which dopamine blockade is thought to be established. Such a mechanism is also consistent with the number of recent reports of improvement in therapeutic response, following the addition of l-dopa to a regimen of standard neuroleptic treatment of chronic schizophrenics (Alpert *et al*, 1977). However, such a mechanism would not be consistent with the reported sensitivity of schizophrenics to methylphenidate (Janowsky *et al*, 1973) the amphetamine model of paranoid schizophrenia (Angrist *et al*, 1974) or the report of low MAO in schizophrenics (Wyatt and Murphy, 1976), all of which implicate hyperdopaminergic states in the pathogenesis. Nor is it apparent how increased levels of dopamine, either provoked by neuroleptic drugs or via the addition of l-dopa to neuroleptic drugs, would be therapeutic in the presence of the dopamine blocking drug. However, since insights into the mechanism of action of anti-schizophrenic drugs provide such an important source of information about the

pathophysiology of schizophrenia, further study of these mechanisms, especially in relation to their temporal course, should prove valuable.

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