

Extrapyramidal effects of neuroleptics

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SYNOPSIS A study was conducted on 66 psychiatric inpatients who took major tranquillizers for periods of four to 16 years. The frequency of signs of Parkinsonism and the effects of orphenadrine on these were studied in a double-blind crossover method. Sixty-one per cent of the patients showed signs of Parkinsonism. Female patients and those with organic brain pathology more frequently exhibited Parkinsonism (although the difference was not statistically significant). No correlation was found between duration of treatment and extrapyramidal effects. Of the 40 patients who developed Parkinsonism, 25 responded favourably to orphenadrine, while six (15%) had more marked manifestations on orphenadrine than on placebo.

Although phenothiazines have been widely used in psychiatry for approximately 20 years, there is relatively little information concerning many aspects of their chronic administration. The recognition of persistent orofacial dyskinesia as a syndrome connected with prolonged treatment with these drugs raises the possibility of irreversible toxic effects on the brain, particularly the extrapyramidal system (Korczyn, 1972). There have been suggestions that the Parkinsonism effects, frequently observed with these drugs, might become irreversible after prolonged treatment (McGeer *et al.*, 1961) or, conversely, disappear (Cahan and Parish, 1960; Mandell and Oliver, 1961). The ideal way to answer this question—that is, to follow up patients maintained on the same dosage of neuroleptic drugs for several years—is not practical, and available information in the literature deals almost exclusively with the effects of relatively short periods of treatment. We have tried to approach the problem by measuring the extrapyramidal side-effects in patients treated with antipsychotic drugs for long periods, and correlating these manifestations with various parameters. In addition we have measured the protection offered by

orphenadrine against the extrapyramidal manifestations. It has been claimed that with prolonged treatment in Parkinson's disease orphenadrine loses efficacy (Strang, 1965), but there is no information concerning the effects of prolonged treatment in drug-induced Parkinsonism.

METHODS

The population under study consisted of 66 psychiatric patients. These were among the 228 patients in seven long-stay wards at Goodmayes Hospital, Ilford, Essex. The rest of the patients in these wards had not been on major tranquillizers at the time of examination, or the dosage was not kept constant for any length of time before initiation of the study. The drugs used were chlorpromazine, thioridazine, trifluoperazine, fluphenazine, and haloperidol. The most common diagnosis was schizophrenia, either simple or paranoid.

The patients were examined carefully neurologically, and special attention was given to the following signs and symptoms: hypokinesia, rigidity, tremor, facial mask, excessive salivation, extrapyramidal disturbances of gait, and micrographia. Each of these parameters was rated on a 0–3 arbitrary scale according to severity. The Parkinsonism score consisted of the sum of the various rates. Persistent or intermittent orofacial dyskinesias and choreoathetoid movements as well as akathisia were also specifically looked for and rated separately.

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As all patients were receiving anticholinergic drugs as a prophylactic measure, it was thought that the occurrence of extrapyramidal signs could be assessed more accurately if they were discontinued. Most of the patients were receiving orphenadrine 50 mg three times daily, and the few who were taking benzhexol were switched to orphenadrine at least one month before the study began. The trial was conducted on a double-blind basis. The orphenadrine was discontinued after initial neurological assessment and the patients were given unmarked identical tablets containing either 50 mg orphenadrine or placebo three times daily for two weeks. They were then switched over from the active drug to placebo or *vice versa* for another two weeks. Extrapyramidal effects were noted throughout this four-week period. Other medications, particularly the psychotropic drugs, remained unchanged throughout the trial period.

RESULTS

Of the 66 patients, 26 were without features of Parkinsonism throughout the study, making the incidence of Parkinsonism in our population 61%. Most of the patients with extrapyramidal signs had mild asymptomatic Parkinsonism (28 patients) and only 12 had more obvious reactions, none of which were severe. This is presumably because neuroleptic medication would have been discontinued in patients showing serious side-effects.

Analysis showed that there was no correlation between the length of treatment with phenothiazines and the frequency of occurrence of Parkinsonism (Table 1). Similarly, severe Parkinsonism was not related to longer treatment.

When patients were grouped according to their age and sex (Table 2), more women were

found among those with Parkinsonism, particularly among those with severe reactions. Interestingly, the older patients showed severe Parkinsonism less frequently. However, none of these trends was statistically significant ($P > 0.05$).

TABLE 2
NUMBER OF PATIENTS WITH PARKINSONISM IN VARIOUS AGE GROUPS BY SEX

Parkinsonism	Age (yr)							
	Under 40		41-50		Over 51		Total	
	M	F	M	F	M	F	M	F
Absent	5	2	6	5	5	3	16	10
Mild	5	5	6	2	1	9	12	16
Moderate	2	4	0	4	1	1	3	9
Total	12	11	12	11	7	13	31	35

ORGANIC BRAIN PATHOLOGY Organic brain pathology was present in 53 of the 66 patients as evidenced by minor, not extra-pyramidal, neurological deficits (such as pyramidal tract signs or politico-mental reflex), or by an abnormal EEG. As seen in Table 3, the patients with organic damage were more likely to develop Parkinsonism. This difference, however, does not reach statistical significance ($P > 0.05$).

TABLE 3
PARKINSONISM RELATED TO ORGANIC BRAIN PATHOLOGY*

Organic brain pathology	Parkinsonism		
	Present (no.)	Absent (no.)	Present (%)
Present	33	20	61
Absent	7	6	54

*For details see text.

TABLE 1

PARKINSONISM IN PATIENTS ON PROLONGED ANTIPSYCHOTIC DRUG MEDICATION

Duration of treatment (yr)	Patients (no.)	Patients with Parkinsonism (no.) (%)
4-10	22	14 64
11-14	24	14 58
15-16	20	12 60
Total	66	40 61

DYSKINESIA This was seen in five patients. All had organic brain pathology. Although the numbers are small, there seems to be an inverse relationship between dyskinesias and

Parkinsonism. Whereas only one of the 40 patients with Parkinsonism had abnormal movements, four of 26 patients without Parkinsonism had them.

AKATHISIA Akathisia was not seen in any patient at any period.

EFFECTS OF DIFFERENT PSYCHOTROPIC DRUGS

The patients in the present study had been on different antipsychotic drugs, in various dosages, frequently on combined drug regimes. Moreover, drugs had been changed in the past. The number of patients on any single drug was therefore small. However, no drug (chlorpromazine, thioridazine, trifluoperazine, fluphenazine, or haloperidol) seemed more likely than another to produce Parkinsonism or to cause more severe reactions. The comparison is complicated by the fact that patients on chlorpromazine or thioridazine tended to have high doses—that is, about 500 mg daily—while the doses of the other drugs tended to be relatively small—for example, 3 mg haloperidol daily.

BENEFIT FROM ANTICHOLINERGICS This was calculated by using the formula $X - Y/X \times 100$, where X is the Parkinsonism score on placebo and Y is that while taking the (active) orphenadrine. A value of 100% therefore shows complete protection by orphenadrine against the extrapyramidal signs, a value of 0 no protection, and a negative value signifies that the patient is worse on orphenadrine than on placebo. These values were calculated for the 40 patients with Parkinsonism: 12 had a score of 60% or above (defined by us as 'good protection'); 13 had scores of 20–59% ('some protection'); nine had scores of –20 to +19% ('insignificant effects'); and six had values lower than –20 (the lowest being –110%) implying an adverse reaction of these patients' extrapyramidal signs to anticholinergic drugs. Thus, orphenadrine was better than placebo in 25 and worse in six patients. This difference is statistically significant ($\chi^2 = 16.08$, $P < 0.01$). The effectiveness of orphenadrine did not correlate with the duration of treatment (either with phenothiazines or anticholinergics), age, sex, or organic brain pathology, or with the

severity of extrapyramidal manifestations on placebo.

DISCUSSION

Sixty-one per cent of the cases in our series had significant Parkinsonism. This value is higher than the 40% reported by Ayd (1961) and very close to that reported by Klett and Caffey (1972). Part of the discrepancy between our study and the earlier work can be attributed to methodological differences. Ayd's study was probably a retrospective one, and it is possible that mild extrapyramidal signs were not recognized. An additional and possibly more important factor is the introduction during the 1960s of psychotropic drugs which are more likely to produce Parkinsonism. For the reasons discussed above, we could not demonstrate this increased neuroleptic activity in our patients.

The relative vulnerability of females and of those with pre-existing brain damage to extrapyramidal signs produced by phenothiazines has been known (Editorial, *British Medical Journal*, 1964). Although a trend in this direction exists in our material, it did not reach statistical significance. Moreover, we could not confirm the impression (Editorial, *British Medical Journal*, 1964), of a correlation between Parkinsonism and age. Older patients are more likely to have organic brain damage and this may be a factor in their alleged vulnerability. Nor could we support the view (McGeer *et al.*, 1961) that Parkinsonism occurs more frequently after prolonged use of the drug. It must be noted that patients studied by us were on antipsychotic medications for periods exceeding those in preceding studies.

The inverse relationship between features of Parkinsonism and dyskinesias ascribed to prolonged use of phenothiazines is not surprising. It has been suggested (Korczyn, 1972) that these dyskinesias result from excessive concentrations of dopamine at receptor sites in the basal ganglia. This is the opposite situation to the Parkinsonian state where the receptors are not affected by dopamine, either because of failure to release the transmitter in a suitable amount, as in Parkinson's disease, or to re-

ceptor blockade as produced by anti-psychotic drugs.

Many physicians tend to prescribe anticholinergic drugs prophylactically with phenothiazines. According to our results, this does not seem to be justified. Many patients will never develop Parkinsonism, and they will therefore be subjected unnecessarily to an additional drug, frequently for many years. Morpurgo (1965) was among the first to warn against indiscriminate use of anticholinergics in these patients. Information is meagre on possible unwanted effects after many years of drug treatment. It has been reported that some anticholinergics (not orphenadrine) produce toxic delirious states which can be misleading, especially in a psychiatric setting. Moreover, the question is not yet settled whether or not anti-Parkinsonism medication can interfere with the therapeutic effect of neuroleptics (Haase *et al.*, 1974). It has been suggested (Strang, 1965) that prolonged use of orphenadrine gradually decreases its efficacy in Parkinson's disease, so that after two years only 40% of the original patients will benefit from the drug. In our patients we could not show any correlation between the efficacy of orphenadrine and the duration of its use. It is likely that the decline reported by Strang (1965) is related to the progressive nature of Parkinson's disease, rather than to a change in the efficacy of orphenadrine.

Six patients (15%) reacted adversely to orphenadrine and their manifestations of Parkinsonism were more severe while taking orphenadrine than the placebo. A paradoxical response to anticholinergics cannot easily be explained, but it is not unrecognized. Thus, Marshall and Schnieden (1966) demonstrated that the tremor of Parkinsonism was increased by intravenous atropine. Certainly such a response is an argument against the routine prophylactic use of anticholinergics with anti-psychotic drugs. However, it is significant that 30% of our patients with Parkinsonism (or

18% of all patients) gained 'good protection' by orphenadrine and, when the patients with 'some protection' were included, the percentage increased to 63%. Thus, orphenadrine is a valuable tool in the treatment of drug-induced Parkinsonism even after several years.

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