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Depot Injections and Tardive Dyskinesia

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SUMMARY A prospective study was undertaken on 374 out-patients receiving depot fluphenazine or depot flupenthixol to determine the incidence of tardive dyskinesia. In three years the percentage showing the bucco-linguo-masticatory syndrome rose from 8 per cent to 22 per cent, though patients had received various neuroleptics for a mean of 13 years previously. Fluphenazine and flupenthixol were equally involved though 75 per cent of affected patients had the condition in mild degree. Six additional cases of generalized chorea were all receiving flupenthixol. Reduction of dose or the substitution of pimozide produced marked improvement, but results suggest that it is unlikely that this will be permanent. Substitution of depot fluspirilene also produced favourable results. Careful monitoring, minimal neuroleptic dosage, and periods of neuroleptic abstinence are recommended.

Introduction

Tardive dyskinesia (TD), first described by Schonecker (1957), is a condition of hyperkinetic movements usually restricted to the lower face and tongue. However, it may occur in diverse forms, chorea of the extremities being the commonest, though generalized choreiform athetoid movements may occur, with abnormalities of gait and trunk posture. Tremor is not part of the syndrome, and chronicity and lack of response to anticholinergic drugs are the rule. Since Sigwald *et al* (1959) related the condition to prolonged neuroleptic drug taking thousands of cases have been recorded, the majority since 1966. Although the evidence that TD is caused by neuroleptics is mainly epidemiological (Crane, 1973), it is sufficient to convince most investigators.

The writer has been involved in a programme of rehabilitating chronic patients. Of the schizophrenic patients maintained in the community, 450 were receiving depot neuroleptic injections, and a prospective study was undertaken on these patients from 1974 to 1977 to record the incidence of TD. Previous reports of this condition relate to institutionalized chronic populations, and Brandon *et al* (1971) raise the question as to whether length of stay in hospital could be contributory to the disorder. In the present survey a low incidence was expected, but a yearly increase was actually observed. Possible reasons for this will be considered.

Patients and Method

By the end of the study, the 450 schizophrenic patients originally examined had been reduced to 374, 261 females and 113 males. Two hundred and seventeen of these had received depot fluphenazine for a mean of 4.4 years, and 157 had received depot flupenthixol for a mean of 2.8 years. All had received oral medication before being placed on injections, the mean time for the fluphenazine group being 11 years (SD $\pm$ 10.8) and for the flupenthixol group 10 years (SD $\pm$ 9.4). The majority of patients on flupenazine received 25 mg every three weeks and those on flupenthixol 40 mg every two weeks. The mean age of patients receiving fluphenazine was 51 years and flupenthixol 48 years.

The patients were examined mentally and physically, with particular reference to extrapyramidal signs. Mouth and tongue movements, blepharospasm, choreiform movements of the extremities, in particular twisting movements, 'piano playing' and spreading movements of the

fingers, dorsiflexion of the toes, foot tapping, shoulder shrugging, rocking movements of the pelvis and interruption of respiratory rhythm being sought. The author personally examined all the patients at yearly intervals from the beginning of 1974 to the beginning of 1977.

The patients were visited in their homes by community nurses at intervals varying from two to four weeks, and referred for reappraisal by the writer if they were concerned about their state. As the study progressed the nurses became expert at recognizing early TD, so that cases were referred and identified between the yearly examinations. For the sake of simplicity, they are presented here as if they arose year by year.

The incidence of the bucco-linguo-masticatory (BLM) syndrome was recorded, and from the beginning of 1975 the severity of these movements was classified as follows:

1. (Mild) Infrequent lateral jaw movements, smacking movements of the lips, puckering and pouting and slight tongue movement as evidenced by the tongue occasionally distending the cheek.
(Movement of the tongue alone as visible in the open mouth was not included.)

2. (Moderate) Almost constant movements as described above.

3. (Severe) Constant movements of the lower face and tongue associated with mouth opening, and protrusion of tongue. Tongue movements alone with the mouth open were not included, as patients may try and use their tongues to re-position a loose upper denture.

Results

The Table indicates the incidence of the BLM syndrome and of accompanying chorea when it arises. In all but four cases the chorea affected the extremities only.

It is not known how long patients suffering from TD in 1974 had been affected. The proportion of patients developing the BLM syndrome did not differ significantly whether they received fluphenazine or flupenthixol. Seven of the cases of chorea received fluphenazine, and 11 flupenthixol: these 11 included the four more severely affected cases with involvement of the shoulder girdle and trunk in one of whom the respiratory muscles were also involved.

In addition to this group of 84 cases, there were six patients, all receiving flupenthixol, who developed chorea affecting the extremities, shoulders and trunk, without involvement of the lower face and tongue; all developed chorea within one year of starting their injections. This group comprised three men and three women, with a mean age of 46 years. Four responded to a change in neuroleptic medication, one recovered after refusing injections, but one, a male of 29 years, despite a change of medication is now severely affected with gross choreoathetoid movements of the whole body, a bizarre gait with lumbar lordosis and involvement of his mouth and tongue. His family history reveals no suspicion of Huntington's chorea.

The ratio of females to males affected was five to two, which was the same as the sex ratio of the whole group of patients. The mean age of patients with TD was 58 years as against 52 years of the unaffected individuals.

TABLE

Numbers out of 374 patients receiving depot neuroleptic injections who developed tardive dyskinesia

Year	Patients showing BLM syndrome			Total	Patients showing chorea as well as BLM syndrome
	Grade I	Grade II	Grade III		
1974	25 (6.7%)		6 (1.6%)	31 (7%)	0
1975	32 (7%)	10 (2.7%)	6 (1.6%)	48 (12.6%)	4 (1.1%)
1976	52 (14%)	12 (3.3%)	6 (1.6%)	70 (18.7%)	10 (2.7%)
1977	63 (17%)	15 (4%)	6 (1.6%)	84 (22%)	18 (5%)

The longer patients had received depot injections, the more likely they were to develop TD. Over one-third of patients who had had fluphenazine for ten years or more were affected, but this may only mean that they had reached an age where they had become more vulnerable. Twenty other patients showed slight jerky movements of the limbs or foot tapping, but they will not be considered here due to the difficulty in deciding whether they had TD or akathisia.

Patients receiving larger than average doses of depot injection took longer than the affected group as a whole to develop the condition, but larger doses did not confer protection.

Four patients showed concomitant parkinsonism and one had oculogyric crises. Theoretically, on the dopamine hypersensitization theory this cannot occur but has been observed by Fann *et al* (1974).

Discussion

Although 22 per cent of patients developed TD, other studies (Baldesserini *et al*, 1975; Brandon *et al*, 1971; Crane, 1970; Degwitz, 1969; Dynes, 1970; Fann *et al*, 1972; Jus *et al*, 1976; Kennedy *et al*, 1971; Roxburgh, 1970) describe a wide variation in the incidence of TD, from less than 0.5 per cent to over 50 per cent, that such differences must represent different definitions of TD held by different investigators; therefore valid comparisons cannot be made. Marriett (1975) identified TD in 20 out of 380 patients on depot fluphenazine, an incidence of 5 per cent. However, if the mild cases described here are excluded, the remainder give an incidence of 5.2 per cent and it may be that Marriett only included patients whose condition was instantly recognizable. Nevertheless, after 13 years of neuroleptic treatment 8 per cent of cases showed TD, and after 16 years 22 per cent showed TD, this rapid increase coinciding with the prescribing of depot injections.

The hypothesis that TD is due to hypersensitization of dopamine receptors in the extrapyramidal motor system by years of neuroleptic-induced dopamine blockade is too well-known to need elaboration (Carlsson, 1970; Gerlach, 1977; Klawans *et al*, 1970; Klawans, 1973). Crane (1970) considers the condition to be dependent on the quantity of neuroleptic drug administered over the years. The apparent increase in TD in patients receiving injections might only mean that this group had no choice but to take their treatment. It might mean that the majority had reached an age of between 50 and 70 years, which Jus *et al* (1976) consider to be the most important factor in the development of the disorder. It might mean that the TD group had had larger amounts of oral neuroleptics before they started their injections. This is unlikely; it was not possible to ascertain the quantity of each oral drug taken over the years, and in any case non-adherence was the reason that the patients were changed to injections. Nevertheless the time (11.2 years) that the TD group had had oral medication was not significantly different from the time (10 years) the non-TD group was so treated; their therapy had been in the hands of the same group of psychiatrists and none had received exceptional doses. However, the patients who did develop TD had not received either doses of depot neuroleptics that were larger, or for a longer period, than those patients who did not develop TD.

Is there any other reason why certain individuals could be particularly prone to develop TD on depot neuroleptic? Adamson *et al* (1973) examining 97 schizophrenics considered non-responders to chlorpromazine showed 39 to have low plasma levels of unmetabolized chlorpromazine, and a change to fluphenazine injections produced improvement in their psychosis. It may be that a proportion of persons receiving neuroleptic drugs over a long period develop protection against them by reducing their absorption; such protection is not available when the drug is given by injection.

Many authors (Crane, 1968; Klawans *et al*, 1970; Kiloh *et al*, 1973; Smith, 1974) conclude that the concomitant prescription of anticholinergic drugs with neuroleptics increases the chance of TD developing. This did not appear to be so in the patients described here; this finding is in accord with the work of Jus *et al* (1976).

In the first eighteen months of this study, no change was made in neuroleptic dosage. In this

period six showed worsening of their TD, but 36 did not show any deterioration.

In most cases treatment was instituted as soon as TD became apparent and it was hoped that by eliminating the factor of chronicity, the intractability of the disorder, described in most other studies, could be overcome. Forty-one out of 50 patients whose medication was changed to pimozide (reported by Costall and Naylor (1977) as reversing dyskinesia produced in experimental animals) or the chemically similar fluspirilene, virtually lost their TD, but it has recurred in all BLM cases followed up for more than three years. Cases with chorea only have remained symptom free except for one severely affected case. Similarly, halving the dose of depot fluphenazine or flupenthixol after an initial worsening of TD in a few patients produced remission in all 19 patients so treated but three years later 10 had relapsed.

Reserpine has been reported as causing remission in TD (Villeneuve *et al*, 1970), as has oxypertine (Eckmann, 1968) and these drugs might warrant further study.

It was found that in a period of a year, out of 100 patients without TD, receiving depot fluphenazine in a dose of 25 mg every three weeks, 43 remained symptom free on a dose of 12.5 mg a month, and a further 18 on 18.75 mg a month. The finding of TD and parkinsonism concurrently in four patients, the one condition due to relative dopamine excess and the other due to dopamine lack, supports the view of McLennan and York (1967) that there are two populations of neurones in the caudate nucleus, respectively inhibited or facilitated by dopamine.

After the discovery of chlorpromazine, probably the greatest advance in the treatment of chronic schizophrenia has been the development of depot preparations of neuroleptic drugs, which, by reducing the relapse rate allowed many patients to be permanently discharged from hospital. The presence of TD, though it has appeared in 22 per cent of people included in this study has been mild in three-quarters and has responded, though perhaps temporarily, to a change of treatment in more than two-thirds of them. Nevertheless, it is a condition which may be both irreversible and severe. Moreover, although mild TD may pass unnoticed among the socially handicapped population of a long-stay hospital ward its presence in a patient in the community can be more distressing. Frequent monitoring of patients to identify early cases and consideration as to whether they can be maintained on a lower neuroleptic dose, whether they have TD or not, would seem to be essential in anyone receiving neuroleptics over long periods.

A number of patients refused medication for periods of many months before psychotic relapse, so periods of neuroleptic abstinence would appear to be practical as well as desirable.

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