QUESTIONNAIRE ON SEVERE TARDIVE DYSKINESIA

DEAR SIR,

While irreversible movements of the lower face and tongue are common in patients receiving long-term neuroleptic treatment, generalized choreoathetosis is a rare complication (by the end of 1975 the Committee on Safety of Drugs had received reports of 12 cases).

In a prospective study of patients receiving depot neuroleptics (Gibson, 1978), 6 out of 167 developed generalized chorea within months of starting flupenthixol. Dr P. Snaith suggested that in view of the rarity of this form of tardive dyskinesia (T.D.) it would be worthwhile asking other psychiatrists if they had had a similar experience. A simple questionnaire was devised which read as follows:—

> Have you any schizophrenic patients receiving antipsychotic medication who have developed generalized body chorea, with or without involvement of the lower face or tongue? If so, could you please indicate the numbers involved, and the drug(s) they were receiving at the time the abnormal movements were first observed?

	Number
Fluphenazine (Modecate)	....
Flupenthixol (Depixol)	....
Fluspirilene (Redeptin)	....
Oral neuroleptic of any kind	....

The questionnaire was sent to 827 consultant psychiatrists: this number included specialists in mental handicap and psychotherapy. It was hoped that in view of the rarity and bizarre nature of the syndrome doctors would be able to recall cases without undertaking research. One hundred and twelve doctors reported 279 cases in all, and a further 263 said they had seen none. One hopes that the positive reports cover the majority of cases that exist in the country. Two doctors said they could not answer the questions as the condition was so common that they had scores of cases. Their diagnostic criteria must differ from the majority, and it is agreed that many patients show slight twitching movements of the extremities without the whole body being affected.

It was then realised that, if the number of doses of all neuroleptic drugs prescribed in a particular year could be discovered, the number of cases receiving each medication might be deduced. The DHSS and all the regional pharmacists but one were extremely helpful and provided the information for 1976. An adjustment was made for the missing one, based on its population. Typical doses and time intervals of injections had to be assumed.

The actual quantities of various drugs prescribed is a commercial secret, but the proportion of cases reported as developing chorea can be disclosed without prejudice.

Depot flupenthixol	1 in 230
Depot fluphenazine	1 in 400
Oral neuroleptics	1 in 1800

Figures concerning fluspirilene were not available from some regional health authorities. These figures assume that every case receiving neuroleptic medication suffers from schizophrenia, and while this may approximate to the truth so far as flupenthixol and fluphenazine injections are concerned, one can only guess at the proportion of oral neuroleptics that are prescribed for schizophrenics. If one assumes that this figure is one-half, the number of cases of treated schizophrenia in England and Wales works out at 150,000, probably a realistic figure, and the incidence of generalized chorea in treated schizophrenics not receiving injections would work out at 1 in 900.

Crane (1973) has emphasized that it is the sum of neuroleptic medication taken over the years that causes T.D. and while Turek (1972) has challenged this point of view the simple investigation reported here, with no information concerning previous medication, use of anticholinergic drugs, age of the patient or duration of illness, can be criticized. Unfortunately, answers to such questions would have involved the persons replying to the questionnaire in a mammoth task. To set up a prospective study with previously untreated patients would take a decade to get results, and psychiatrists need to get all the clues they can to know if depot drugs might be more likely than oral preparations to cause T.D.

Patients receiving injections must adhere to their treatment programme, and injections by-pass the vagaries of intestinal absorption and hepatic destruction, which could make them more prone to produce neurological damage as time goes by. Flupenthixol may be almost twice as likely to produce chorea as fluphenazine, but there is no suggestion that it is more likely to produce the bucco-linguo-masticatory syndrome. Moreover, generalized chorea seems to be a sufficiently rare complication of these medications for it not to be necessary for anybody to change his prescribing habits in the light of the above information. Perhaps all one should do is to emphasize the need to monitor regularly all cases on neuroleptic drugs, particularly injections, for early signs of T.D. and be prepared to discontinue the neuroleptic until the dyskinesia goes, and then give it intermittently.

I would like to thank all those psychiatrists who were kind enough to complete the questionnaire, the

regional pharmacists and their staffs and specially Mrs M. J. Roberts of the DHSS who went to such great trouble to let me know the number of doses of the drugs prescribed. I am also indebted to the Schizophrenia Association of Great Britain for paying for the postal and secretarial expenses involved.

ALAN C. GIBSON

St Ann's Hospital,
Canford Cliffs,
Poole, Dorset

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TARDIVE DYSKINESIA AND DEPOT FLUPHENAZINE

DEAR SIR,

There have been several reports of an increase in tardive dyskinesia with depot fluphenazine treatment (Chouinard *et al*, 1977; Gardos *et al*, 1977; Smith *et al*, 1978). The report by Gibson (*Journal*, October 1978, **132,** 361–5) is an important prospective study which shows a progressive increase in the prevalence of tardive dyskinesia in chronic schizophrenic patients maintained on depot fluphenazine and flupenthixol.

Based on our studies with fluphenazine plasma concentrations following depot injections of fluphenazine decanoate (Nasrallah *et al*, 1978) I would like to propose that the increased occurrence of tardive dyskinesia with depot fluphenazine treatment might be related to the wide fluctuations in plasma concentrations of fluphenazine after an injection of the depot. Our findings show that after a dose of 50 mg i.m. of the decanoate ester in schizophrenic patients with or without ongoing cycles of depot injections, daily fasting plasma levels fluctuated widely between trace and over 100 ng/ml, suggesting an irregular release pattern of fluphenazine from the depot site. For several patients, no plasma fluphenazine could be detected for one or more days after the injection, and higher values (usually between 3–16 ng/ml) could be measured on other days. Different patients achieved different peaks at different times, and no intra- or inter-patient kinetic pattern could be observed.

Given the model of dopaminergic receptor hypersensitivity following the withdrawal of neuroleptic drugs (Tarsy and Baldessarini, 1974), it is possible that chronic fluctuations in fluphenazine plasma concentrations with depot maintenance could have the effect of 'repeated withdrawals', resulting in 'withdrawal' dyskinesia, which may or may not be reversible.

With orally administered neuroleptics, the greatest fluctuation in plasma concentrations occurs with once-a-day dosage schedules. Jeste *et al* (1977) reported that four-times a day administration of chlorpromazine masked the symptoms of tardive dyskinesia, whereas these were clinically evident with once-a-day administration of the same total daily dose.

Obviously, the above 'hypothesis' needs validation with well designed prospective studies, since the implications are important for better maintenance treatment of chronic schizophrenic patients.

HENRY A. NASRALLAH

Department of Psychiatry,
University of California, San Diego,
La Jolla, California 92093, USA

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CANCER IN THE LONG-STAY HOSPITALS

DEAR SIR,

I read with great interest Dr Rice's letter (*Journal*, January 1979, **134,** 128), in which he states that he cannot recall during 35 years of psychiatric practice a single case of a chronic schizophrenic patient dying of bronchial carcinoma.

In our recent survey of 1,125 mentally handicapped patients who died during the past 40 years in four