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40 - 50% Prevalence
out patients

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The Prevalence of Tardive Dyskinesia in Fluphenazine-Treated Patients

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One hundred thirty-five outpatients were evaluated for tardive dyskinesia (TD). Of the fluphenazine-treated patients (N = 63), 32 were found to have TD as compared with 29 of 72 non-fluphenazine-treated patients. This difference was not statistically significant. There was no difference in duration and total dose of fluphenazine injections between TD and non-TD patients. However, patients receiving fluphenazine injections were found to require fewer hospitalizations after fluphenazine therapy was started.
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THERE is essentially universal agreement that neuroleptics cause tardive dyskinesia (TD). However, the contribution of each neuroleptic to the prevalence of TD still remains anecdotal[1] as no prospective, large studies have been conducted to date to indicate that a particular neuroleptic is more responsible for the development of TD than another. Some studies, however, have indicated that fluphenazine-treated patients are more prone to develop TD than are non-fluphenazine-treated patients.[2–10] An equal number of studies have also indicated that the reverse is true.[11–16] Thus, at present, there is no firm indication that fluphenazine treatment increases the prevalence of TD.

We undertook a study in our outpatient department to determine the prevalence of TD in a group of patients treated with fluphenazine and compared them with another group receiving other neuroleptics.

Patients and Methods

The patient population was drawn from the Adult Outpatient Services of Douglas Hospital Centre during 1985. Each consecutive patient was examined blind to his intake of fluphenazine or oral medication using the Abnormal Involuntary Movement Scale developed by the National Institute of Mental Health.[18] To diagnose TD, a score of 2 or more in any body area was considered as TD. Many of these patients had been evaluated 5 years earlier.[12] A total of 154 patients was evaluated. Each patient was then allocated to whether they were receiving fluphenazine injectable or oral medication. Fluphenazine decanoate has been the only fluphenazine injectable preparation used in our hospital since 1983.

To be included in the final analysis, the patients should: (1) have received fluphenazine decanoate for 2 years or more before the present assessment; this criterion excluded four patients; (2) have all their illness (from the time of onset to the present) treated in our hospital; this criterion excluded nine patients; and (3) have not received any fluphenazine or injectable medication at any time during their past psychiatric history when thorough review of their files was done; this criterion excluded six patients.

Thus, a total of 135 patients (63 fluphenazine- and 72 non-fluphenazine-treated patients) constituted the present study. The files of each patient were reviewed for the following information: (1) age at onset of psychosis and neuroleptic intake; (2) number and duration of hospitalisations; (3) current dose of neuroleptic; (4) in the case of fluphenazine-treated patients, duration, dose (maximum, minimum, and current dose), and total amount of fluphenazine; (5) record of the onset of TD if mentioned in the charts.

Of the 63 patients receiving fluphenazine, one was diagnosed as suffering from mental retardation, two each from alcoholic psychosis and bipolar disorder and 58 from schizophrenia, using the DSM-III criteria.[20] Of the 72 receiving treatment other than fluphenazine, six each were diagnosed as suffering from bipolar disorder and mental retardation and 60 as suffering from schizophrenia.

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Results

Prevalence of TD

Of the fluphenazine-treated patients 32 of 63 (50.8%) showed evidence of TD, as compared with 29 of 72 (40.3%) non-fluphenazine-treated patients (χ^2 [2 *df*] = 1.5, not significant). As noted in Table 1, TD patients in both groups were significantly older than non-TD patients. However, duration of neuroleptic treatment and current dose of neuroleptics were not significantly different. Fluphenazine injections were converted according to a formula suggested by Nestoros and colleagues[21] where 25 mg intramuscularly every 2 weeks = 300 mg chlorpromazine daily, although some authors[22] suggested that this dose would be equivalent to 2,000 mg chlorpromazine daily. Other medications were converted according to Davis' formulae.[23]

TD severity and onset

Of the fluphenazine-treated patients, 17 were considered as showing mild and 15 moderate TD, when the global rating was considered, as compared with 14 mild, 13 moderate, and two severe TD in non-fluphenazine-treated patients. TD was described in three patients before fluphenazine therapy was started and in 18 after fluphenazine therapy, while it was not noted in 11 patients. Of the non-fluphenazine-treated patients, TD was noted in 15 of 29 patients.

Sex distribution

More men than women were receiving fluphenazine injections (54% versus 46%) as compared with 33.3% and 66.7%, respectively, in non-fluphenazine-treated patients. TD was equally distributed in men and women (45.5% versus 44.8%, respectively).

Current medication

Of the non-fluphenazine-treated patients, chlorpromazine was prescribed to 23 women and four men, trifluoperazine to 13 women and three men, haloperidol and methotrimeprazine to seven women and six men, perphenazine to five women and three men, thioridazine to four women and two men, and prochlorperazine to one woman and three men. In addition, lithium was given to one woman and two men and carbamazepine to one woman and one man. Two or more neuroleptics were prescribed to 15 patients.

Of the fluphenazine-treated patients, two women and four men were also prescribed chlorpromazine; two men, haloperidol; a man and a woman, methotrimeprazine; one man, perphenazine; and one man, trifluoperazine. Thus, 51 patients were receiving fluphenazine only.

Concurrent antiparkinsonian drugs

Of the non-fluphenazine-treated patients, 27 (37.5%) were receiving antiparkinsonian drugs as compared with 40 (63.5%) in fluphenazine-treated patients (χ^2 [2 *df*] = 9.06, $p < 0.005$). Of the TD non-fluphenazine-treated patients, 10 (34.5%) were receiving antiparkinsonian drugs as compared with 22 of the fluphenazine-treated patients (68.8%; χ^2 [2 *df*] = 7.2, $p < 0.01$).

TD in fluphenazine-treated patients

We compared fluphenazine-treated patients with and without TD on several variables. As noted in Table 2, TD patients were significantly older. However, of the other variables studied, none was statistically significant (Table 2).

The fact that the number and duration of hospitalizations significantly decreased after the introduction of fluphenazine injections is shown in Table 3. It should be noted that only admissions after the start of neuroleptic treatment were considered.

Discussion

Our study indicates that TD was present in 45% of the patients assessed. This high prevalence of TD may be related to the older patient population examined (mean age of patients is 60 years). In a review of the literature, Smith and Baldessarini[24] indicated that the risk of TD increases with age.

Our study also indicates that fluphenazine treatment does not increase the prevalence of TD when compared with patients who do not receive fluphenazine therapy.

Table 1. Demographic characteristics of fluphenazine and non-fluphenazine-treated patients (mean ± SD)

Variables	Fluphenazine-treated patients		Non-fluphenazine-treated patients	
	TD (N = 32)	Non-TD (N = 31)	TD (N = 29)	Non-TD (N = 43)
Age	60.5 ± 10.3[a]	53.1 ± 8.6[a]	63.9 ± 5.1[b]	59.5 ± 10.6[b]
Duration of neuroleptic treatment (months)	291.0 ± 72.2	260.5 ± 84.7	293 ± 60.1	295.5 ± 70.0
Current dose (mg, chlorpromazine equivalent)	390.9 ± 329.4	489.5 ± 562.4	396.9 ± 323.9	303.1 ± 273.9

[a] $t(61\ df) = 3.06$, $p < 0.003$.
[b] $t(66\ df) = 2.349$, $p < 0.02$.

TABLE 2. Comparison between fluphenazine TD and non-TD patients (mean ± SD)

Variables	TD patients (N = 32)	Non-TD patients (N = 31)	*t*-tests
Age	60.5 ± 10.3	53.1 ± 8.8	$t(61\ df) = 3.06, p < 0.003$
Duration of neuroleptic (months)	138.8 ± 81.2	111.9 ± 59.9	$t(59\ df) = 1.5$, NS[a]
Duration of fluphenazine (months)	155.3 ± 67.8	161.6 ± 42.8	$t(54\ df) = 0.44$, NS
Total fluphenazine (g, chlorpromazine equivalent)	1,647.1 ± 1,082.1	2,148.6 ± 1,348	$t(61\ df) = 1.63$, NS
Highest dose (mg)	52.7 ± 29.5	60.5 ± 34.1	$t(61\ df) = 0.85$, NS
Lowest dose (mg)	20.5 ± 16	19.5 ± 16.2	$t(61\ df) = 0.232$, NS
Current dose (mg)	25.8 ± 25.9	28.7 ± 22.2	$t(61\ df) = 0.476$, NS

[a] NS, not significant.

TABLE 3. Number and duration of admissions before and after fluphenazine

	Before fluphenazine		After fluphenazine	
	TD	Non-TD	TD	Non-TD
No. of admissions	3.4 ± 2.1[a]	4.4 ± 3.0[b]	1.0 ± 0.3[a]	1.3 ± 1.6[b]
Months in hospital	49.4 ± 63.2[c]	35.1 ± 39.5[d]	6.0 ± 10.5[c]	7.0 ± 11.8[d]

[a], [b] $t(43\ df, 47\ df) = 5.942, 5.076, p < 0.001$.
[c], [d] $t(33\ df, 36\ df) = 3.832, 3.795, p < 0.001$.

This confirms other studies in which negative results were reported.[11–18] In addition, several recent review articles have come to the conclusion that depot neuroleptics do not increase the risk of TD when compared with oral neuroleptics.[18, 25–29]

Morgenstern and associates[5] have recently reviewed the reasons that depot neuroleptics have been implicated in the development of TD. They believe that depot neuroleptics reduce noncompliance; thus, users of depot medication may be more exposed to more medication. Also, depot and oral neuroleptics may have different pharmacokinetic effects because of variations in drug metabolism or absorption. Jeste and coauthors[30] found that oral neuroleptics increase serum neuroleptic levels in TD patients more than in control subjects. This observation was recently confirmed by Yesavage and colleagues.[31] However, this finding was not confirmed by Tune and associates,[32] Fairbairn and associates,[33] and Kimber and associates,[34] who found no difference in plasma levels of neuroleptics in TD and non-TD patients. It is also possible that depot and oral drugs differentially influence the masking (i.e., suppression) of abnormal movements once the sufficient etiology for TD is complete. Jeste and coauthors[35] found that neuroleptics taken four times a day masked the symptoms of TD more than dosage once a day. Levine and associates[36] found a higher rate of new TD movements after neuroleptic discontinuation in orally treated patients than in depot fluphenazine patients. Thus, oral medication may mask TD more than depot neuroleptics.

We have found that fluphenazine-treated patients received significantly more antiparkinsonian drugs than did non-fluphenazine-treated patients, which confirms other studies.[37] Unfortunately, we did not measure the prevalence of parkinsonian symptoms in both groups; thus we could not indicate whether the use of prophylactic antiparkinsonian drugs is warranted or not, although according to a recent review of the literature, anticholinergic drugs have no effect on the risk of TD.[38]

Several studies have indicated that depot preparations are superior to oral medications in preventing further relapse.[39] This finding is confirmed in our study, where we found that the number and duration of hospitalizations were greatly diminished after the introduction of depot injections.

Thus, in our study, the prevalence of TD was not found more in fluphenazine- than in non-fluphenazine-treated patients. In addition, the results of our study indicate that the benefits of depot injections outweigh the risks in terms of relapse and subsequent stay in hospital.

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