Am J Psychiatry 136:1, January 1979

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BRIEF COMMUNICATIONS

Factors Related to Tardive Dyskinesia

BY GUY CHOUINARD, M.D., M.SC.(PHARMACOL.), LAWRENCE ANNABLE, DIP.STAT., ANDRÉE ROSS-CHOUINARD, M.D., AND JOANNIS N. NESTOROS, M.D.

The authors found a 31% incidence of tardive dyskinesia among 261 schizophrenic outpatients treated with neuroleptics. Multiple linear logistic regression analysis revealed a higher incidence of tardive dyskinesia among elderly patients, those with longer records of hospitalization, those for whom neuroleptic medication had little therapeutic effect, and those treated with fluphenazine. Patients manifesting tardive dyskinesia tended to have fewer parkinsonian symptoms than those without the disorder, especially when tremors and akathisia were excluded from consideration. Multiple linear regression analysis indicated that brain-damaged patients and male patients were more susceptible to severe forms of the disorder, even though these factors were not implicated in its initial appearance.

TARDIVE DYSKINESIA is a hyperkinetic syndrome of extrapyramidal nature associated with neuroleptic drug use (1–3). It is characterized by involuntary repetitive and purposeless movements varying in localization and form but commonly involving the mouth, lips, tongue, and jaw (bucco-linguo-masticatory dyskinesia) and at times by choreoathetoid movements of the neck, trunk, or limbs. These movements are usually intensified by emotional tension or by voluntary movements of other muscle groups. They are reduced in intensity by sleep or drowsiness. Neuroleptic drugs that are causing the syndrome can temporarily reduce the dyskinesia, and the abnormal movements may become more severe or appear for the first time after drug withdrawal or dose reduction (4). Antiparkinsonian drugs fail to reduce the dyskinetic movements and can aggravate or uncover the tardive dyskinesia (5). In many patients the syndrome is irreversible; in others it can sometimes be reversed by discontinuing the neuroleptics (6). When the condition is life-threatening, as in rare cases of dyskinesias of the esophagus or diaphragm, piperazine-like neuroleptics (fluphenazine or haloperidol) can be given and anticholinergic drugs (antiparkinsonian or others) avoided.

Recent studies have shown that tardive dyskinesia occurs with alarming frequency among patients treated with neuroleptics (7, 8). Fann and associates (7) found that 36% of a sample of 204 patients treated with neuroleptics manifested the syndrome. At the present time, there is no treatment of tardive dyskinesia that is effective over a long period of time; most efforts are directed toward its prevention.

The Allan Memorial Institute maintains a special follow-up clinic for the long-term maintenance treatment of schizophrenic outpatients. The present study was designed to evaluate the incidence and severity of tardive dyskinesia among 261 patients from this population and to determine the relationship of the syndrome to various other factors. Whereas most previous surveys of tardive dyskinesia were conducted in long-term wards of mental hospitals, this study dealt with a population of schizophrenic outpatients.

Presented at the 130th annual meeting of the American Psychiatric Association, Toronto, Ont., Canada, May 2–6, 1977. Received July 7, 1977; accepted Jan. 10, 1978.

Dr. Chouinard is Assistant Professor, Department of Psychiatry, McGill University, Allan Memorial Institute, and Psychiatrist and Pharmacologist, Research Department, Hôpital Louis-H. Lafontaine, 7401 Rue Hochelaga, Montreal, Que., Canada H1N 3M5. He is also Professor, Institut National de la Recherche Scientifique-Santé, Montreal. Mr. Annable is Assistant Professor, Department of Psychiatry, McGill University, and Biostatistician, Institute National de la Recherche Scientifique-Santé, Hôpital Louis-H. Lafontaine. Dr. Ross-Chouinard is Neurologist, Hôpital Hôtel-Dieu de Montréal, and Lecturer, McGill University. When this work was done Dr. Nestoros was a resident in psychiatry, Allan Memorial Institute. He is now Assistant Psychiatrist, Allan Memorial Institute.

The authors gratefully acknowledge the help of M. Kropsky, M.D., T. Petitjean Roget, who performed the computations, and Diane Ross and Marilyn E. Levy.

0002-953X/79/01/0079/05/$00.50

METHOD

Patients are accepted in the special follow-up clinic after the primary hospital diagnosis of schizophrenia is confirmed by the psychiatrist in charge of the clinic. The diagnostic criteria used are similar to those of the National Institute of Mental Health–Psychopharmacology Service Center Collaborative Study (9). Schizophrenic patients who are not likely to need long-term pharmacotherapy are not accepted in the clinic. During the two years before this study pharmacotherapy was under strict control, and the following principles were applied: the minimum therapeutic dose was given; a single neuroleptic was prescribed whenever possible; drugs were administered in a single daily dose or twice-daily regimen; procyclidine (Kemadrin) was the only antiparkinsonian drug used; attempts were made to withdraw the antiparkinsonian after three months of treatment; fluphenazine enanthate, an injectable long-acting drug, was given to patients who were resistant to other neuroleptics, those who could not be relied upon to take medication, and those with frequent relapses; fluphenazine hydrochloride was the only piperazine-type drug given orally; polypharmacy was avoided and antidepressant drugs, minor tranquilizers, and hypnotics were not prescribed; and, finally, medication was reviewed each time the patient came to the clinic.

The patients were examined by a neurologist who had not seen them before in random order on the day they came for their regular visit to the clinic. All patients were examined except for a small percentage (less than 5%) who repeatedly failed to keep appointments. The neurologist completed a structured medical questionnaire,[1] carried out a complete neurological examination, and rated each patient for the presence and severity of tardive dyskinesia and other extrapyramidal symptoms. The presence of tardive dyskinesias was assessed according to a standard procedure that included the following routine neurological tests: 1) the patient's spontaneous behavior was observed while seated, standing, or walking, 2) since abnormal movements are increased by voluntary movements of other muscle groups, the oral-facial region was observed while the patient carried out the pronation-supination tests of both hands as fast as possible and performed rapid alternate movements of both wrists and the finger-nose-finger test, 3) the patient was asked to walk without shoes so that any choreoathetoid movements of the limbs could be noted, and 4) the patient was asked to copy a spiral with both hands and to sign his or her name (since the test is performed under emotional tension, this procedure may activate dyskinetic movements and thus sometimes uncover covert dyskinesias). In doubtful cases, the patient was asked to open his or her mouth while performing the pronation-supination and alternate movement tests so that the tongue could be observed. Questionable cases of tardive dyskinesia were not considered to be positive.

Dyskinetic movements were rated according to frequency and amplitude on a 4-point scale (0–3) as follows: 0=absent, 1=mild but clearly present, 2=moderate, and 3=severe. Abnormal movements in the lingual, masticatory, and facial-labial areas and the trunk and extremities were rated separately.

Other extrapyramidal symptoms were also rated on a modified version of a specially designed extrapyramidal rating scale (10). The following items were evaluated: expressive automatic movements (facial mask and speech), bradykinesia, rigidity of limbs, gait and posture, tremor (of limbs, head, chin, and tongue), akathisia, increased salivation, and dystonia. Both spontaneous tremors and those manifested when the patient extended both arms forward with palms down and eyes closed or performed the spiral test and handwriting were evaluated. Each item was rated on a 6-point scale ranging from normal to extremely severe.

In the same visit the patient was seen by one of three psychiatrists who rated the therapeutic response to treatment on a 5-point scale (11) and overall severity of illness on a 7-point scale (11). The neurologist and psychiatrists did not have access to each others' findings.

RESULTS

The study population consisted of 261 schizophrenic outpatients, 138 male and 123 female, ranging in age from 19 to 67 years. Table 1 shows the mean and standard deviation for the age, length of neuroleptic treatment, neuroleptic dose (converted to chlorpromazine units [12]), clinical global impression (CGI) of overall severity of illness, and CGI therapeutic effect for male and female patients separately and for both sexes combined. Table 2 shows the percentages of patients with tardive dyskinesia and parkinsonian symptoms, those being treated with antiparkinsonian medication and fluphenazine, and those with a history of ECT treatment, insulin treatment, brain damage, alcoholism, antidepressant treatment, and hospitalization.

Three kinds of statistical analysis were performed on the data. In each analysis the variable for tardive dyskinesia was regressed against the following variables: age, number of years treated with neuroleptics, length of previous psychiatric hospitalizations, current dosage of neuroleptics (converted to chlorpromazine units), current fluphenazine treatment, total score for parkinsonian symptoms, antiparkinsonian dosage, number of ECT treatments, number of insulin treatments, presence of brain damage, alcoholism, history of antidepressant treatment, CGI overall severity of illness, and CGI therapeutic effect.

[1]The medical questionnaire covered the following items: 1) family history of mental disease, epilepsy, abnormal movements or tics, or any neurological disease, 2) history of previous admission for or investigation of neurological disorder, brain surgery, head trauma (with or without skull fracture), meningitis, or coma, and history or presence of abnormal movements, tics, epilepsy, or venereal disease, 3) abnormal laboratory results (VDRL or EEG), 4) history of loss of consciousness, headache, visual trouble (decreased vision), loss of balance or difficulty walking, or difficulty swallowing or talking, and 5) history of alcoholism or drug abuse (LSD, barbiturates, etc.).

TABLE 1
Characteristics of 138 Male Patients and 123 Female Patients in Study Population

Characteristic	Males Mean	Males SD	Females Mean	Females SD	Total Mean	Total SD
Age (years)	38.3	11.0	44.2	11.1	41.1	11.4
Years of neuroleptic treatment	8.8	5.7	10.7	5.8	9.7	5.8
Neuroleptic dose (chlorpromazine units)*	425.0		300.0		400.0	
CGI (in general)	4.6	0.9	4.5	0.9	4.5	0.9
CGI (therapeutic effect)	1.6	0.9	1.7	0.9	1.6	0.9

*Median dose given because the distribution of neuroleptic dosages was skewed (range=0–5500 chlorpromazine units/day). Neuroleptic medications were converted to chlorpromazine units according to the equivalency given by Davis and Cole (12). Fluphenazine enanthate was converted to chlorpromazine units on the basis of an equivalency of a dose of 25 mg I.M. every 2 weeks to 300 mg chlorpromazine daily.

TABLE 2
History and Presence of Tardive Dyskinesia or Parkinsonian Symptoms in 138 Male Patients and 123 Female Patients in Study Population

Factor	Males (%)	Females (%)	Total (%)
Tardive dyskinesia	29.0	32.5	30.7
Parkinsonian symptoms	71.0	59.3	65.5
Antiparkinsonian treatment	60.9	56.9	59.0
Fluphenazine treatment	47.8	30.9	39.9
ECT treatment	47.8	59.3	53.3
Insulin treatment	4.5	8.8	6.5
Brain damage	24.6	17.1	21.1
History of alcoholism	17.4	3.3	10.7
History of antidepressant treatment	23.2	31.7	27.2
Previously hospitalized	86.2	90.2	88.1

ABLE 3
ariables Significantly Related to Presence of Tardive Dyskinesia According to Stepwise Logistic Regression Analysis

'ariable	Significance
ge	p<.001
ays in hospital	p=.03
GI therapeutic effect	p=.05
luphenazine treatment	p=.03
rkinsonism total score (negatively related)	p=.06*

=.03 when score for tremors is excluded from parkinsonism total score; =.02 when scores for tremors and akathisia are excluded from parkinsonism total score.

riables Predicting Incidence of Tardive Dyskinesia

Patients were coded 1 or 0 according to whether tarve dyskinesia was present or not; a regression analy; using the linear logistic model (13) related other riables to the probability of the patient's manifesting dive dyskinesia. This analysis was carried out on all 1 patients by a computerized stepwise inclusion produre (14), which first determines the single most imrtant characteristic in predicting the incidence of dive dyskinesia, then the second most important iable given that the first has been included in the iation, and so on. Table 3 shows the five variables

TABLE 4
Variables Contributing Significantly to Multiple Regression Relationship with Total Score for Tardive Dyskinesia,* As Entered by Stepwise Inclusion

Variable	Significance	Multiple Correlation Coefficient	Partial Correlation Coefficient
All patients included (N=261)			
Age	p<.001	.29	.29
CGI therapeutic effect	p=.003	.34	.19
Parkinsonism total score (negatively related)	p=.026	.37	−.14
Fluphenazine treatment	p=.013	.39	.15
Days in hospital	p=.050	.41	.12
Sex (male)	p=.049	.43	.12
Only tardive dyskinesia patients (N=80)			
Brain damage	p=.003	.33	.33
CGI therapeutic effect	p=.045	.39	.23
Age	p=.089	.43	.19
Parkinsonism total score (negatively related)	p=.079	.47	−.20
Sex (male)	p=.077	.50	.20

*Scores for tremors and akathisia are excluded from total score for parkinsonian symptoms.

that, when entered sequentially, made statistically significant ($p < .05$) contributions to the regression relationship. The variable most related to the incidence of tardive dyskinesia was age, which was highly significant ($p<.001$). Then followed length of time spent in a psychiatric hospital, score for CGI therapeutic effect (a high score indicates little improvement, i.e., there tended to be a greater incidence of tardive dyskinesia among patients with little therapeutic improvement), fluphenazine treatment, and, finally, the total score for parkinsonian symptoms, which was related inversely to tardive dyskinesia (i.e., patients with fewer parkinsonian symptoms tended to have a higher incidence of tardive dyskinesia). When the score for tremors or the scores for both tremors and akathisia are excluded from the total score for parkinsonian symptoms, the inverse relationship between tardive dyskinesia and parkinsonian symptoms becomes more pronounced (see table 3). A test of goodness of fit of the model showed the fit to be satisfactory ($\chi^2=1.6$, df=4, $p=.8$).

Variables Predicting Severity of Tardive Dyskinesia

This analysis related the severity of tardive dyskinesia, as measured by the total score, to the other variables by the usual multiple linear regression model. A first analysis was carried out on all 261 patients by a computer program using a stepwise inclusion procedure (15). Table 4 shows the six variables that, when entered sequentially, were significantly related to the total score for tardive dyskinesia. The same five variables found to be related to the incidence of tardive dyskinesia were also related to the severity of the disorder, although there is some change in their relative importance. Again, the inverse relationship between tardive dyskinesia and parkinsonian symptoms was more pronounced when the score for tremors and aka-

thisia were excluded from the parkinsonism total score. In addition, the sex of the patient enters the relation, with male patients tending to show more severe forms of the condition than female patients. The six variables included in the equation account for 18.5% of the total variation in the scores for tardive dyskinesia among the 261 patients.

Finally, we repeated this analysis including only those 80 patients who had tardive dyskinesia (table 4). This analysis revealed that among the patients with tardive dyskinesia, those with previous brain damage tended to have more severe forms of the disorder.

DISCUSSION

Recent surveys show a higher incidence of tardive dyskinesia than was first reported. In this study, tardive dyskinesia was found to be present in 31% of a population of 261 schizophrenic outpatients treated by neuroleptics; this percentage is similar to that reported by Fann and associates (7). Age was clearly the most important contributory factor; older patients were more susceptible to tardive dyskinesia. It has also been our clinical experience that the older the patient is when first started on neuroleptics, the sooner he or she is likely to develop the syndrome. This would indicate a need for caution when prescribing neuroleptics to the elderly patient. A 1977 study (16) suggested biochemical changes in the striatum with aging, and it might be hypothesized that these changes could favor the appearance of tardive dyskinesia.

Among patients of the same age, those for whom neuroleptic treatment was producing little therapeutic effect were more likely to present severe forms of tardive dyskinesia. When linked with the finding on age, this suggests that in some cases it may be beneficial to withdraw neuroleptics from older patients who are responding poorly to treatment.

Crane (2, 4) has reported that severe tardive dyskinesia is seldom observed in patients with severe parkinsonism, and vice-versa. Our findings support this, especially when tremors and akathisia are not included among the other parkinsonian symptoms. These two symptoms were excluded because our clinical experience has shown that a patient with tremors or akathisia may manifest tardive dyskinesia, whereas a patient with akinesia or rigidity seldom does. There tended to be a high incidence of tardive dyskinesia among patients being treated with fluphenazine (oral or enanthate). Although fluphenazine was the only piperazine drug given to these patients, one might expect this finding would also apply to the other piperazine-like drugs, which are responsible for a higher incidence of parkinsonian symptoms. It is possible that the hyperkinetic parkinsonian symptoms of tremor and akathisia are precursors of hyperkinetic symptoms of dyskinesia. Thus, these symptoms could be expected to coexist with dyskinetic symptoms in patients shifting from one syndrome to the other. In contrast, the hypokinetic parkinsonian symptoms of rigidity and akinesia could reduce or cover the expression of dyskinesia.

Tardive dyskinesia was more prevalent among patients who had spent longer periods of time in psychiatric hospitals (independent of their age). Since this variable appeared to be more important than the length of neuroleptic treatment, it may reflect the effect of regular high-dose neuroleptic administration in hospitals. Similarly, the finding that patients responding poorly to neuroleptics had a higher incidence of tardive dyskinesia might be related to past exposure to high neuroleptic doses. This would indicate that use of neuroleptics at higher than normal dosage should be limited to the most severe cases. However, the dose of neuroleptic currently received by the patient was not found to enter significantly into the regression relationship. This is not unexpected, since high doses of neuroleptics are known to mask tardive dyskinesia.

Previous brain damage tended to be present in the more severe cases of tardive dyskinesia but was not found to be implicated in the appearance of the disorder. The overall incidence of tardive dyskinesia among brain-damaged patients was not higher than among patients with no brain damage. Since the most severe forms of dyskinesia are incapacitating, a history of brain damage would appear to be a relative contraindication to neuroleptic treatment. In the same way, male patients also appeared to be more susceptible to severe forms of the disorder. Because men are often less responsive to neuroleptics than women, a possible explanation of their increased susceptibility to severe tardive dyskinesia is the use of higher neuroleptic dosage. Other factors, such as ECT, insulin treatment, antiparkinsonian medication at the time of examination (which in the clinic is always adjusted so as not to aggravate the tardive dyskinesia), and history of tricyclic antidepressant treatment were not found to be related to tardive dyskinesia in this population of schizophrenic outpatients.

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ADDENDUM

Most patients in this study treated with fluphenazine were receiving fluphenazine enanthate I.M. and were rated for tardive dyskinesia when they came to the clinic for their biweekly injections. Consequently, they were evaluated at a time when their fluphenazine blood levels were at their lowest, and dyskinetic movements that are normally masked at higher fluphenazine levels may thus have been exposed. This may have been responsible for the higher incidence of tardive dyskinesia we found among patients treated with fluphenzine.

Hypnotic Treatment of Smoking: The Single-Treatment Method Revisited

BY BERNARD BERKOWITZ, M.D., ANITA ROSS-TOWNSEND, PH.D., AND ROBERT KOHBERGER, PH.D.

The authors replicated Spiegel's single-treatment method by treating 40 self-referred patients in a one-hour hypnosis session for smoking. Their results, a 6-month total abstinence rate of about 25%, were comparable with Spiegel's experience. They recommend future studies that include nontreatment control groups to validate the effects of the hypnotic treatment method of smoking.

JOHNSTON AND DONOGHUE (1), in a 1971 review of the literature on hypnosis in the treatment of smoking, noted the difficulties involved in replicating results: "The hypnosis-smoking literature . . . is primarily anecdotal and rarely in the form of a controlled investigation. . . . Most articles claim many successes and, although they admit to some failures, it is never entirely clear who fails, and when, and why failures occur" (1). They concluded that "Most authors claim success, but their procedures cannot be reproduced." A review of reports since that time shows this still to be true, with the exception of the work of Spiegel (2, 3). His reports of a single-treatment method not only describe in detail the method used but also analyze the results of a 6-month follow-up with 615 patients. Our paper is an effort to address the deficiencies noted by Johnston and Donoghue by replicating Spiegel's method.

Received Sept. 6, 1977; accepted Nov. 14, 1977.

Dr. Berkowitz is Associate Professor of Psychiatry, Dr. Ross-Townsend is Associate Professor of Psychiatry, and Dr. Kohberger is Instructor, Division of Computer Science, Albany Medical College, Albany, N.Y. 12208.

TREATMENT

Spiegel has stated that his earlier, open-ended approach to treatment encouraged the patient to delay confrontation with the decision to terminate smoking (3). He thought that if the procedure were going to work, it would do so right away, so he moved to the single-treatment approach. Briefly, Spiegel's single-treatment method consists of taking a brief clinical and smoking history, the application of his Hypnotic Induction Profile, and the induction of trance and confrontation with three basic points: 1) for your body smoking is a poison; 2) you need your body to live; and 3) you owe your body this respect and protection. Three points are taught to the patient so that he can use them as a self-hypnotic exercise 10 times daily. Positively oriented suggestions are given by the therapist, who emphasizes the individual's own responsibility for his success. The method is described in detail elsewhere (2, 3).

0002-953X/79/01/0083/03/$00.40