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Orofacial Dyskinesia, Cognitive Function and Medication

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The presence of tardive dyskinesia in a sample of 43 patients with schizophrenia and 37 psychopaths who had been hospitalised for many years and exposed to large amounts of medication was assessed while testing their cognitive function. Subjects who showed no evidence of abnormal movements performed significantly better on the test of delayed recall, but there were no differences in performance on any of the other tests of cognitive function used. Multiple regression analysis revealed that age and the total lifetime dose of neuroleptic medication received (in chlorpromazine equivalents) were the only variables to predict the Abnormal Involuntary Movement Scale score, although a large amount of variance in this variable was unaccounted for. The duration of treatment with neuroleptics did not predict AIMS score.

In the thirty years since the introduction of the phenothiazines there have been numerous reports of orofacial dyskinesias attributed to these drugs. There is little doubt that these disorders are now recognised more frequently. In 1955 Mettler & Crandell (1959) found a large number of neurological disorders in psychiatric patients, but no reference was made to any syndrome resembling tardive dyskinesia (TD). This is important because the study was performed before the introduction of the phenothiazines. Crane (1968) observed that 90% of cases of TD had been reported since 1964, and that the majority of sufferers were chronic schizophrenics—especially those who had received physical treatments such as ECT, leucotomy and insulin coma. His impression was that large doses of drugs were responsible, with increasing age also playing a part. Kane & Smith (1982) found the average prevalence of TD to be 20% in neuroleptic-treated patients, compared with 5% in untreated patients. These figures originated from 70 prevalence studies, which overall suggested that increasing age and female sex were the two factors most consistently associated with an increased risk of the disorder.

Despite this, many psychiatrists believe that TD is related to prolonged exposure to neuroleptics, an opinion propounded most forcibly by Klawans (1973), and supported for example by the findings of Smith *et al* (1978) who found a small but significant correlation between TD and total fluphenazine intake in patients over the age of 50. They suggested that dose schedule may be more important than total dose. More recently, Mukherjee *et al* (1982) have demonstrated a significant association between TD and the use of high potency or depot neuroleptics, and also increasing age.

Neurological impairment has long been considered aetiologically important in TD, although as Kane & Smith (1982) suggest there is not much evidence in support of this. Famuyiwa *et al* (1979) found that schizophrenic patients with TD performed less well on a paired associate learning test than those who did not have the disorder, although there were no differences between the two groups on other tests of cognitive function, nor in indices of cortical atrophy on computerised tomography (CT) scan. Similarly, Jeste *et al* (1980) in their CT scan study were unable to find evidence of cortical atrophy in schizophrenic patients with TD.

There are many problems in comparing the results of different studies. Definitions of TD differ in the extent to which a pure bucco-lingual-masticatory triad is specified, or in whether the tremors of parkinsonism or axial and limb movements should be included. Different selection criteria are used, so that experimental groups differ in age, duration of illness and treatment, and environmental factors which may influence the assessment of abnormal movements through anxiety and arousal. Most studies have been based on limited drug history data, relying either on medication at the time of the study or on detailed information collected over limited periods of time. Given the difficulties in determining precisely the total amount of medication received during the course of an individual's illness, a more detailed investigation of chronic neuroleptic administration in relation to TD is particularly important at a time when the use of such medication is being questioned. This study attempts to do this, and also to investigate the relationship between TD and cognitive impairment, by examining the following hypotheses:

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1. Patients who exhibit TD perform less well on tests of cognitive function than patients without the disorder.

2. Using multiple regression analysis the total cummulative dose of neuroleptics can be used to predict TD score.

Method

Patients were selected from two sources: four long-stay wards in the Royal Edinburgh Hospital, and four long-stay wards in the State Hospital, Carstairs. All contained stable populations of male long-stay patients. The case notes of all patients were examined to exclude those over the age of 65 and those with a history of alcohol abuse, head injury, leucotomy, serious physical illness, organic psychosis, or mental subnormality. The research diagnostic criteria of Spitzer *et al* (1972) were applied to the remaining subjects, and the duration of admission, number of ECTs, and years of education obtained from their case notes. Detailed drug information was obtained from prescription sheets, which were available (for all but four subjects, who were excluded) as far back as the original admission. These were checked against entries from the medical notes and nursing notes, ensuring that dates and amounts of medication prescribed were as accurate as possible. Occasional medication was not recorded. For each of the six most widely prescribed neuroleptics (chlorpromazine, trifluoperazine, thioridazine, fluphenazine decanoate, haloperidol and flupenthixol decanoate) the starting date, dose, date of change of dose and date of discontinuation were noted. This information was summarised by a computer program which calculated the total equivalent dose for all drugs, using chlorpromazine equivalents (Davis, 1974).

Mental state assessments were performed using Wiles' (1976) glossary for the Brief Psychiatric Rating Scale (BPRS) of Overall & Gorham (1962), and the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976) was used to measure movement disorders on two occasions a month apart. This is a five-point rating scale measuring abnormal involuntary movements in seven areas, including the muscles of facial expression, tongue, jaw, lips, upper and lower extremities, neck, shoulders and hips; subjects were thus rated for such movements in body areas other than the orofacial region. All measurements were made 60 seconds after the subject had started a motivation test, and continued over a 60 second period. The test consisted of a boring and repetitive task in which subjects were given a page on which the letter X was printed more than 1000 times; they were then asked to circle as many as they wished, the score being the number circled before stopping. The purpose of this test was to assess the extent to which volitional impairment—an important clinical component of chronic schizophrenia—affected performance on the tests of cognitive function. The AIMS ratings were therefore made under standard conditions, with subjects unaware that they were being observed. Following this, the Paired Associate Learning test described by Inglis (1959), Williams' test of delayed recall (Graham-White, 1969), and Raven's (1960) progressive matrices were given to all subjects. Data were analysed using the Statistical Package for the Social Sciences.

TABLE I
Prevalence of TD by diagnosis

	Schizophrenics	*Psychopaths*
Non-TD	7	22
TD	36	15

Corrected $\chi^2 = 14.23$; $P < 0.001$

Results

Test/re-test reliability for the AIMS was satisfactory (Pearson's $r = 0.87$, $P < 0.001$). The presence or absence of movement disorder was established on the basis of the AIMS score over the two test periods; subjects with a total score of two or less were classified as having no abnormal movements. Eight subjects were excluded because they could only be tested on one occasion, leaving 25 subjects with no TD and 43 with TD. Although TD was more common in patients with schizophrenia a small number of psychopaths exhibited the disorder (Table I). A univariate model was used to identify relationships between TD and demographic data, treatment and test variables. With the exception of the total equivalent dose and amount of ECT received, which were both highly skewed, the distribution of all the dependent variables did not differ significantly from that of a normal distribution using the Kolmogorov-Smirnov 'goodness of fit' test. When the medication variable was transformed by taking its square root, it conformed more closely to a normal distribution.

Table II compares the demographic characteristics of the two groups. The TD group were significantly older, had been in hospital much longer, and had received more medication and ECT than the non-TD group, who had fewer psychiatric symptoms and performed significantly better on the motivation test than the TD group. On all three tests of cognitive function the TD group performed less well than the other group, although the differences were only significant for the delayed recall and its age-adjusted memory quotient. The greater age of the TD group appears to account for their performing less well on the progressive matrices; when the age-adjusted IQs are compared the differences disappear (Table III).

Discussion

These results are in accordance with other studies which suggest that TD is associated with increased age, longer hospitalisation, and exposure to large amounts of neuroleptics and ECT. As this is one of few studies to have attempted a direct measurement of the total intake of drugs, it is important to consider some of the weaknesses of this measure.

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TABLE II
Subject characteristics

	Non-TD (n=25)		*TD (n=43)*		*F ratio*	*Significance*
	Mean	*s.d.*	*Mean*	*s.d.*		
AIMS score	0.39	0.60	8.55	4.94	96.79	<0.001
Age (years)	37.0	7.2	50.5	10.2	33.80	<0.001
Years of admission	10.2	4.6	21.2	10.6	23.74	<0.001
Years of education	9.5	2.9	10.6	2.1	3.07	NS
STE[1]	775	1477	3127	2397	19.41	<0.001
Total no. of electro-shocks received[2]						
Mean	0.90		9.2			
Mean rank	32.4		44.0			

1. Square root of the total equivalent dose of neuroleptics received.
2. Mann-Whitney $U = 500$; $P = 0.0125$ (two tailed).

TABLE III
Test results

Test	*Non-TD*		*TD*		*F ratio*	*Significance*
	Mean	*s.d.*	*Mean*	*s.d.*		
Brief Psychiatric Rating Scale	2.3	3.7	6.6	5.5	12.00	<0.001
Motivation test total score	434	377	234	300	1.04	NS
Paired Associate Learning test	19.8	15.8	26.1	16.9	2.33	NS
Delayed recall	4.6	4.4	11.0	9.2	10.50	<0.01
Memory quotient	113	19.3	97	18.7	11.12	<0.01
Progressive matrices	33.9	10.4	22.0	11.2	18.83	<0.01
IQ	96	13.1	93	11.7	1.05	NS

TABLE IV
Stepwise multiple regression with AIMS score as the dependent variable

Variable	*R^2 change*	*F ratio*	*Significance*
Age	0.22	17.55	<0.001
STE	0.10	9.05	<0.01
Total no. of electro-schocks received	0.02	2.19	NS
BPRS score	0.01	1.00	NS
Time on drugs	0.01	0.58	NS
Duration of hospital stay	0.00	0.31	NS
Motivation test total score	0.00	0.06	NS

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TABLE V
Stepwise hierarchical multiple regression with AIMS score as the dependent variable

	Variable	*R^2 change*	*F ratio*	*Significance*
Step 1	Age	0.21	20.25	<0.001
Step 2	STE	0.10	10.99	<0.001

Although the prescriptions were checked for accuracy against two other sources of information, there was no way of checking that subjects had actually taken the prescribed medication. The only exceptions to this were the depot neuroleptics; however, the cummulative totals of fluphenazine and flupenthixol together accounted for only 16% of the total equivalent dose, so it must be assumed that the measure of oral medication was open to distortion because of the possibility that subjects might have failed to take it from time to time. It has to be assumed that non-receipt of prescribed medication was randomly distributed throughout the sample.

The fact that the TD group were older could account for them having received more medication, the link between TD and medication being secondary to the more important relationship between age and TD. At this stage multivariate techniques were used, with the AIMS score of all 68 subjects as the dependent variable in two multiple regression analyses. Initially, the variables used to predict the AIMS score were age, motivation test total score, total equivalent dose (square root), total time (years) on medication, duration of admission, BPRS score, and amount of ECT received. For each regression, solution plots of the residual values showed no evidence of non-linearity of the relationship.

The results of the first regression are given in Table IV; the best predictors of the AIMS score were age and total equivalent dose. To investigate the relationship further it was hypothesised that age was the most important variable, the value of the total equivalent dose as a predictor of the AIMS score being dependent on its own relationship with age. These variables were entered together in a stepwise hierarchical regression with age on the first step, and the square root of the total equivalent dose (STE) on the second. The result (Table V) reveals that both age and STE predict the AIMS score, age alone accounting for 21% of the variance, and STE accounting for a further 10%. This suggests that age and total medication are associated with tardive dyskinesia, but the interpretation of this regression should be tempered with caution. About one-third of the total variance in the AIMS score is explained by these two variables, indicating that other factors unaccounted for in this study may make a considerable contribution. No attempt was made to measure the amount of anti-parkinsonian medication received by the subjects. TD may result not only from prolonged dopaminergic blockade, but also from the additional prolonged use of anticholinergic drugs. A further difficulty relates to the fact that subjects were assessed for TD while on medication, raising the possibility that the AIMS score is not representative of the severity of TD.

The poor performance of the TD group on the tests of delayed recall is further evidence of an association between TD and cognitive impairment. The results suggest that with increasing age and medication there is a greater likelihood of developing TD. However, the fact that the age-adjusted memory quotients were significantly worse in the TD group implies that the different amounts of medication received by the two groups, rather than age, may explain the differences in delayed recall. Anticholinergic drugs may produce confusion and memory impairment, especially in elderly subjects. Most patients in this study received such drugs to control extrapyramidal side-effects, although their use was not measured, and most neuroleptics possess anticholinergic properties to a varying extent. It is possible to speculate that the combined anticholinergic properties of neuroleptics and anti-parkinsonian medication to which the subjects were exposed might explain the relationship between total equivalent dose and delayed recall performance, although it must be stressed that this is speculative, given the absence of measures of anticholinergic activity in this study.

Although the degree of short-term memory impairment in these subjects was not great, it is important to bear this in mind when considering the need for long-term medication in a population who already have a multiplicity of handicaps. Caution should be exercised when contemplating the use of large doses of neuroleptics, especially with anti-parkinsonian medication in elderly subjects. The routine prescribing of combinations of such drugs should be questioned.

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Conclusions

This study has show that tardive dyskinesia may be associated with poor short-term memory performance. No relationship emerged between TD and the duration of exposure to medication, although both age and total amount of medication were found to predict the presence of TD. However, this study assessed dyskinesia when the subjects were still on medication. As it is quite possible that neuroleptics mask the manifestation of TD, this, together with the absence of any data concerning anti-parkinsonian medication, may have been responsible for the large amount of variance in the AIMS score not explained by age and STE. This problem can only be overcome by examining subjects before and after their medication has been discontinued, and obtaining more detailed information on the prescription of anti-parkinsonian medication.

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References

CRANE, G. E. (1968) Tardive dyskinesia in patients treated with major neuroleptics: a review of the literature. *American Journal of Psychiatry (Supplement)*, **124**, 40–48.

DAVIS, J. M. (1974) Dose equivalence of the anti-psychotic drugs. *Journal of Psychiatric Research*, **11**, 65–69.

FAMUYIWA, O. O., ECCLESTON, D., & DONALDSON, A. A. (1979) Tardive dyskinesia and dementia. *British Journal of Psychiatry*, **135**, 500–504.

GUY, W. (1976) *Assessment Manual for Psychopharmacology*, 534–537. US Department of Health, Education and Welfare.

INGLIS, J. (1959) A paried associate learning test for use with elderly psychiatric patients. *Journal of Mental Science*, **105**, 440–443.

JESTE, D., WAGNER, R. L., WEINBERGER, D., RIETH, K. & WYATT, R. J. (1980) Evaluation of CT scans in tardive dyskinesia. *American Journal of Psychiatry*, **137**, 247–248.

KANE, J. M. & SMITH, J. M. (1982) Tardive dyskinesia—prevalence and risk factors, 1959 to 1979. *Archives of General Psychiatry*, **39**, 473–481.

KLAWANS, H. L. (1973) The pharmacology of tardive dyskinesia. *American Journal of Psychiatry*, **130**, 82–86.

METTLER, F. A. & CRANDELL, A. (1959) Neurological disorders in psychiatric institutions. *Journal of Nervous and Mental Diseases*, **128**, 148–159.

MUKHERJEE, S., ROSEN, A. M., CARDENAS, C., VARIA, V. & ORLARTE, S. (1982) Tardive dyskinesia in psychiatric outpatients: a study of prevalence and association with demographic clinical and drug history variables. *Archives of General Psychiatry*, **39**, 466–469.

OVERALL, J. E. & GORHAM, D. R. (1962). The Brief Psychiatric Rating Scale. *Psychological Reports*, **10**, 799–812.

RAVEN, J. C. (1960) *Guide to the Progressive Standard Matrices*. London: H. K. Lewis.

SPITZER, R. & ENDICOTT, J. (1978) *Research Diagnostic Criteria* (3rd ed.). New York: New York State Psychiatric Institute.

SMITH, R. C., STRIZICH, M. & KLASS, D. (1978) Drug history and tardive dyskinesia. *American Journal of Psychiatry*, **135**, 1402–1403.

WILES, D. H. (1976) Brief Psychiatric Rating Scale—glossaries and rating instructions. *Psychological Medicine*, **6**, 407–415.

GRAHAM-WHITE, J. (1969) Williams' scale for the measurement of memory: test reliability and validity in a psychiatric population. *British Journal of Social and Clinical Psychology*, **8**, 141–151.

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