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# Cognitive impairment, clinical course and treatment history in out-patients with bipolar affective disorder: relationship to tardive dyskinesia

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SYNOPSIS Clinical, neuropsychological and psychopharmacological characteristics were investigated for their ability to distinguish individuals with and without involuntary movements (tardive dyskinesia), among a population of 40 out-patients with bipolar affective disorder and a history of exposure to neuroleptics and lithium. Impaired performance on a test of cognitive flexibility bore the primary association with both the presence and the severity of involuntary movements. The additional relationships identified emphasized further that individual vulnerability to involuntary movements appeared to be associated not with greater duration or dosage of treatment, but with features of the bipolar illness, including number and type of affective episodes, for which that treatment was prescribed.

## INTRODUCTION

Research on tardive dyskinesia is much concerned with the identification of factors which might contribute to individual vulnerability to the emergence of involuntary movements during long-term neuroleptic treatment (Kane & Smith, 1982). This search has been pursued most actively in patients with schizophrenia, for which neuroleptics are ubiquitously prescribed, and studies over the past five years have revealed a generally consistent association between involuntary movements and cognitive impairment (Waddington, 1987). Among the most recent studies, such associations have been reported in a variety of schizophrenic populations and using a range of neuropsychological assessment procedures (Waddington & Youssef, 1986*a*, *b*; Wade *et al.* 1987; DeWolfe *et al.* 1988; Sorokin *et al.* 1988), and appear most robust in relation to involuntary movements with an orofacial topography (Waddington *et al.* 1987; DeWolfe *et al.* 1988). These associations are suggestive of some relationship between orofacial dyskinesia and organic brain dysfunction, and are complemented by evidence that schizophrenic patients with such movement disorder are more likely to show neurological signs (Wegner *et al.* 1985; Youssef & Waddington, 1988*a*).

Clearly, if this association between involuntary movements and cognitive deficit in schizophrenia provides a clue to more general determinants of vulnerability to tardive dyskinesia, it should be demonstrable in other diagnostic groups which are prescribed neuroleptics and in which this movement disorder has been described. Following a preliminary report that such a relationship may be evident at least in older patients with bipolar affective disorder (Wolf *et al.* 1983), we have recently reported bipolar patients with tardive orofacial dyskinesia to be more cognitively impaired than similar patients without involuntary movements (Waddington & Youssef, 1988). However, our study population was predominantly of chronically-ill bipolar in-patients with a mean age in the seventh decade. The present investigation was, therefore, undertaken to extend this approach, with more sophisticated statistical methods, to a

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larger and more representative population of younger out-patients with bipolar affective disorder.

## METHOD

### Patients and assessment

The subjects of this study were 62 out-patients attending a mood disorder clinic at St Patrick's Hospital, Dublin, and who consented to participation. They were each assessed using the Abnormal Involuntary Movement Scale (AIMS; National Institute of Mental Health, 1976) by the same rater, who was unaware of each patient's diagnosis, clinical and treatment histories; the presence or absence of tremor was also recorded. After the AIMS examination, patients were evaluated neuropsychologically using Trail Making Tests A and B from the Halstead-Reitan battery (Reitan, 1955).

### Clinical and treatment history

Only after completion of these assessments were each patients' case notes reviewed for demographic details and information on clinical and treatment history. The following variables were recorded: age, sex, age at first illness, duration of illness, number of affective episodes, presence or absence of a family history of affective disorder in a first degree relative, duration of exposure to neuroleptics, average daily dose of neuroleptics over that duration (converted to mg of chlorpromazine equivalents (Davis, 1976)), current neuroleptic dose (in mg of chlorpromazine equivalents, on the day of AIMS examination), duration of exposure to anticholinergics, duration of exposure to lithium, presence or absence of a history of exposure to antidepressants. To these were added the following: time (in seconds), to complete each of Trail Making Tests A and B, presence or absence of current tremor.

### Statistical analysis

Data were expressed as means $\pm$ S.D. or as percentage prevalences, and analysed using the Student's $t$ test or the Fisher probability test (2-tailed), respectively. Binary response measures (i.e. presence or absence of involuntary movements) and continuous response measures (i.e. severity of involuntary movements) were additionally analysed by stepwise multiple logistic regression and stepwise multiple linear regression procedures, respectively. These stepwise multiple regression methods examined relationships between each AIMS measure and the 15 demographic, clinical and treatment variables. Each analysis first identifies the variable having the strongest association with the specified AIMS measure. Taking that variable into account, the variable having the next strongest association is then identified, this sequence continuing until a hierarchy of all variables making significant contributions ($P < 0{\cdot}05$) to the regression model has been generated. Overall adequacy of the final logistic model was confirmed using the goodness-of-fit tests of Hosmer & Lemeshow and of Brown, as previously described (Waddington *et al.* 1987).

## RESULTS

Of the 62 patients studied, 49 were subsequently found to satisfy DSM-III criteria (American Psychiatric Association, 1980) for bipolar affective disorder. Of these 49, five patients had not received neuroleptics or had received them for less than one month, and were deemed not to be at risk; complete information on all variables was not available for a further four patients. It is to the resulting group of 40 patients (mean age $41{\cdot}6 \pm 14{\cdot}0$, range 22–74 years) that all further discussion relates. They had each received long-term treatment with lithium and had, for varying durations in the past, been treated with neuroleptics; only 16 were currently receiving neuroleptic medication.

For 25 patients (20 currently normothymic, 3 depressed and 2 hypomanic) there were either no or only minimally abnormal involuntary movements, while in 15 (13 currently normothymic, 1 depressed and 1 hypomanic) there were involuntary movements of greater than minimal severity (prevalence: 37·5%). In 10 instances, involuntary movements were very mild (9 with an orofacial topography, one with a limb-trunkal topography), while in only 5 (12·5%) were they more prominent (3 with an orofacial topography, 2 with both orofacial and limb-trunkal involvement) and satisfied the more stringent research criteria of Schooler & Kane (1982).

The 15 patients with and the 25 without involuntary movements could not be distin-

Table 1. *Characteristics of bipolar patients with and without abnormal involuntary movements*

| | Involuntary movements | |
|---|---|---|
| | Absent | Present |
| Number (male/female) | 25(15M,10F) | 15(8M,7F) |
| Age (yr) | 39·0 ± 12·8 | 46·1 ± 15·3 |
| Age at first illness (yr) | 24·5 ± 8·3 | 32·2 ± 9·8* |
| Duration of illness (yr) | 14·5 ± 8·2 | 13·9 ± 8·8 |
| Number of affective episodes | 4·2 ± 2·5 | 5·7 ± 6·0 |
| Family history | 7/25 | 5/15 |
| Neuroleptic treatment | | |
| Duration of neuroleptics (yr) | 2·4 ± 3·6 | 1·6 ± 2·2 |
| Average neuroleptic dose (mg) | 485 ± 443 | 307 ± 270 |
| Current neuroleptic dose (mg) | 58 ± 81 | 20 ± 53 |
| Anticholinergic treatment | | |
| Duration of anticholinergics (yr) | 1·3 ± 2·7 | 0·4 ± 0·5 |
| Lithium treatment | | |
| Duration of lithium (yr) | 5·6 ± 4·8 | 4·5 ± 3·7 |
| Antidepressant treatment | | |
| History of antidepressant use | 11/25 | 12/15 |
| Trail Making Test A (sec) | 50·7 ± 25·0 | 74·1 ± 31·2* |
| Trail Making Test B (sec) | 107·1 ± 50·6 | 212·8 ± 163 3*** |
| Current tremor | 9/25 | 8/15 |

*** $P < 0·005$; * $P < 0·05$.

guished in terms of their age or sex distribution (Table 1). On univariate comparison, those with involuntary movements were significantly older at first illness, but could not be distinguished by duration of illness, number of affective episodes over that duration, or family history of affective disorder. In terms of neuroleptic exposure, they could not be distinguished by univariate comparison of duration of treatment but tended to have received lower average daily doses over that duration and to be receiving lower current doses of neuroleptics ($P < 0·1$) on the day of AIMS examination; the overall mean current daily doses indicated for each group in Table 1 are low as the number of patients currently in receipt of such treatment was modest (among the 15 patients with involuntary movements, 3 were currently receiving a mean of 100 mg/day each, while 12 were not currently receiving such treatment; among the 25 patients without involuntary movements, 13 were currently receiving a mean of 112 mg/day each, while 12 were not currently receiving such treatment). Duration of exposure to anticholinergics also failed to distinguish patients with and without involuntary movements; only 1 of 15 patients with involuntary movements and 3 of 25 patients without involuntary movements were currently in receipt of anticholinergics. Univariate comparison of duration of treatment with lithium failed to distinguish those with and without involuntary movements; patients with involuntary movements were somewhat more likely ($P < 0·1$) to have a history of exposure to antidepressants. However, poor performance on neuropsychological testing, particularly in Trail Making Test B, readily distinguished patients with involuntary movements. They were just as likely to show current tremor as were patients without such movement disorder.

Stepwise logistic regression analysis confirmed poor neuropsychological test performance in Trail Making Test B to be the variable most strongly associated with the presence of involuntary movements (Table 2). The stepwise algorithm generating the 'best' final logistic regression model then proceeds differently from a series of univariate comparisons (Fleiss *et al.* 1986). It takes into account at each of a series of subsequent steps any highly intercorrelated measures, to derive a hierarchy of variables significantly associated with the presence of such movement disorder; at each step, variables that have been selected are reconsidered, so that those which are redundant because of such intercorrelations can be rejected. In this way, lower current neuroleptic dose had the next

Table 2. *Hierarchy of variables significantly related to the presence or absence of involuntary movements as determined by stepwise logistic regression analysis*

| Variable | $\beta$ | SE$\beta$ | $\beta$/SE$\beta$ | $\chi^2$ | $P$ |
|---|---|---|---|---|---|
| Trail Making Test B | 0·14 | $0·72 \times 10^{-1}$ | 1·89 | 9·93 | < 0·002 |
| Current neuroleptic dose | −0·27 | 0·17 | −1·60 | 6·59 | < 0·01 |
| Average daily neuroleptic dose | $-0·15 \times 10^{-1}$ | $0·89 \times 10^{-2}$ | −1·74 | 3·98 | < 0·05 |
| History of antidepressant use | 7·40 | 3·86 | 1·92 | 3·67 | < 0·05 |
| Duration of illness | −1·12 | 0·61 | −1·84 | 11·99 | < 0·002 |
| Duration of lithium | $-0·38 \times 10^{-1}$ | $0·27 \times 10^{-1}$ | −1·43 | 4·27 | < 0·05 |

Goodness-of-fit tests: Hosmer, $\chi^2 = 11·98$, $P = 0·10$; Brown, $\chi^2 = 1·22$, $P = 0·54$

Table 3. *Hierarchy of variables significantly related to the severity of involuntary movements as determined by stepwise linear regression analysis*

| Variable | $\beta$ | SE$\beta$ | $\beta$/SE$\beta$ | $P$ | $R^2$ |
|---|---|---|---|---|---|
| Trail Making Test B | $0{\cdot}98 \times 10^{-2}$ | $0{\cdot}22 \times 10^{-2}$ | 4·27 | < 0·001 | 0·34 |
| Number of affective episodes | 0·36 | $0{\cdot}76 \times 10^{-1}$ | 4·82 | < 0·001 | 0·51 |
| Current neuroleptic dose | $-0{\cdot}84 \times 10^{-2}$ | $0{\cdot}36 \times 10^{-2}$ | −2·34 | < 0·05 | 0·57 |
| Duration of illness | $-0{\cdot}77 \times 10^{-1}$ | $0{\cdot}36 \times 10^{-1}$ | −2·15 | < 0·05 | 0·62 |
| Constant | 1·94 | — | — | — | — |

strongest association with the presence of involuntary movements. At subsequent steps, lower average daily dose of neuroleptics, history of exposure to antidepressants, shorter duration of illness and shorter duration of exposure to lithium were identified to complete the hierarchy; no other variables made further significant contributions to the logistic regression model, and the goodness-of-fit of the final model was satisfactory.

In a similar manner, stepwise linear regression analysis identified poor neuropsychological test performance in Trail Making Test B as the variable having the strongest association with increasing severity of involuntary movements (Table 3). Thereafter, number of affective episodes, lower current neuroleptic dose and shorter duration illness were identified to complete the hierarchy; no other variables made further significant contributions to the linear regression model, and the final model was satisfactory ($100 \times R^2 = 62\%$).

## DISCUSSION

This study has investigated clinical, neuropsychological and psychopharmacological characteristics which might potentially distinguish individuals with tardive dyskinesia from those without, among a population of out-patients with bipolar affective disorder and a history of exposure to neuroleptics as well as lithium. Clearly, our findings cannot be generalized to bipolar populations who have received lithium with little exposure to neuroleptics. Cognitive impairment bore the primary association with the presence of what were predominantly orofacial (buccal-lingual-masticatory) involuntary movements, using both univariate and stepwise logistic regression analyses. This association was most robust on neuropsychological evaluation with Trail Making Test B, a number-letter sequence task involving visual scanning, conceptual flexibility and visuomotor co-ordination, and which is highly sensitive to general organic brain dysfunction (Reitan, 1955, 1958). It was less evident with Trail Making Test A, a number–number sequence task which requires the performance of similar motor sequences but does not place demand on cognitive flexibility. Also, the great majority of our patients with tardive dyskinesia showed orofacial but not limb-trunkal movements, and the presence or absence of peripheral tremor did not distinguish patients with and without tardive dyskinesia. This would appear to exclude any substantial contribution of motor impairment to poor performance on Trail Making Test B. The present finding confirms, using alternative neuropsychological testing, the results of our recent study on a population of bipolars who were predominantly older in-patients and were, therefore, evaluated using a simple test of the integrity of their orientation, awareness and immediate memory (Waddington & Youssef, 1988). It parallels the results of a number of similar studies on populations of schizophrenic patients (Waddington, 1987; Wade *et al.* 1987; Waddington *et al.* 1987; DeWolfe *et al.* 1988; Sorokin *et al.* 1988).

In the present study, univariate analysis indicated bipolar out-patients with involuntary movements to be significantly older at the onset of their illness than patients without such movement disorder, as well as more cognitively impaired as judged by Trail Making Test B; we have noted a similar association in a population of schizophrenic out-patients (Waddington & Youssef, 1986*c*). This relationship was not evident on stepwise logistic analysis, as it was lost at the stage of controlling for intercorrelations with the primary variable. Rather, such analysis had the power to reveal additional variables associated with the presence of in-

voluntary movements. The negative relationships with current neuroleptic dose and with average daily dose over total duration of exposure to neuroleptics are similar to those which we have reported in schizophrenia using the same analytical approach (Waddington *et al.* 1987). The former relationship may reflect that lower current doses of neuroleptics are less likely to mask involuntary movements. However, we have argued in the context of schizophrenia that the superficially paradoxical relationship, between the presence of a presumed tardive side effect and prior receipt of lower average daily doses of the presumed offending agent, reflects some critical difference(s) in the illness of patients with and without vulnerability to involuntary movements which resulted in different treatment patterns (Waddington *et al.* 1987). It is striking that so similar a relationship was encountered here in bipolar affective disorder.

The association between the presence of involuntary movements and a history of exposure to antidepressants might indicate one of at least two relevant processes. Antidepressants might in themselves 'cause' tardive dyskinesia, or act synergistically with neuroleptics in this regard; there is a long-standing but inconsistent literature on this issue, which has recently been reviewed (Yassa *et al.* 1987). However, we suggest that more common exposure to antidepressants may reflect the prominence of some particular clinical feature of bipolar illness in this relatively young group, presumably depression, which was held to require such treatment. It is notable that Yassa & Schwartz (1984) have reported tardive dyskinesia to be associated with a relative predominance of depressive symptoms at early hospitalizations, and that no such relationship was evident in relation to affective episodes characterizing the overall clinical histories of older, chronically-ill bipolar patients (Waddington & Youssef, 1988). There is a controversial literature (reviewed by Wehr & Goodwin, 1987) that antidepressants can provoke manic episodes and worsen the course of bipolar illness. The present association between the presence of involuntary movements and a shorter duration of bipolar illness might be consistent with the view (Gardos & Casey, 1984; Yassa *et al.* 1984; Kane *et al.* 1986; Glazer *et al.* 1988) that certain forms of affective disorder may be particularly at risk for the early development of involuntary movements if prescribed neuroleptics.

The final relationship identified was between the presence of involuntary movements and shorter duration of exposure to lithium, and this emerged after controlling for the effects of duration of illness. It is consistent with previous reports in a young bipolar out-patient population (Mukherjee *et al.* 1986), a mixed population (Kane *et al.* 1986), and our own recent finding in older, chronically-ill bipolars (Waddington & Youssef, 1988). As with other associations, the cross-sectional nature of our data can confound its interpretation in longitudinal terms. Thus, lithium may be prophylactic against the development (or expression) of neuroleptic-associated involuntary movements, hence the less it is used the more likely it may be that dyskinesia is manifested; the complex arguments on this issue have recently been reviewed in the two studies cited above. However, we must ask *why* some bipolar patients might receive less prolonged lithium treatment than others. This may reflect their illness being different in some way from that of patients receiving more prolonged lithium therapy. Lithium might be started at a later stage of their illness if earlier affective episodes were primarily of depression (as discussed above; see also Post *et al.* 1986).

In seeking factors associated with the *severity* of involuntary movements, the issue may be conceptually different from that of vulnerability to the *presence* of such movement disorder. None-the-less, poor cognitive function on Trail Making Test B was also the primary variable associated with increasing severity of dyskinesia. Of the three other variables associated with severity, two had been similarly found to be associated with the presence of involuntary movements, i.e. negative relationships with current neuroleptic dose and with duration of illness, attesting to the robustness of their relationships to such movement disorder. The remaining association, between severity of involuntary movements and a greater number of affective episodes as well as a shorter duration of illness, suggests that factors predisposing to a higher frequency of affective relapse in such younger out-patients may also predispose to the development of involuntary movements of greater severity. There is evidence that in bipolar

disorder the likelihood of affective relapse and of involuntary movements each increase if neurological signs are present (Hoff *et al.* 1988; Youssef & Waddington, 1988*a*).

In summary, the present cross-sectional study extends to bipolar affective disorder many of the arguments we have derived from the results of similar studies on schizophrenic populations (Waddington, 1987; Waddington *et al.* 1987). Thus, we find no evidence that bipolar patients with involuntary movements have received longer treatment with, or higher doses of, neuroleptics than have similar patients without such movement disorder. Rather, they are characterized primarily by cognitive impairment, at least in terms of performance on Trail Making Test B, and by differences in other features of their bipolar illness for which neuroleptics as well as other psychopharmacological treatments were prescribed. As in schizophrenia, some neurological process may be an important vulnerability factor for the emergence of involuntary movements in bipolar affective disorder during long-term neuroleptic treatment. It appears to be intimately related to the disease process, not only across the conventional boundaries between the major functional psychoses but also (Youssef & Waddington, 1988*b*) in patients with evident neurodevelopmental deficits.

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