Tardive dyskinesia and antipsychotics: a 5-year longitudinal study of frequency, correlates and course.
Eberhard, Jonas; Lindström, Eva; Levander, Sten

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Tardive dyskinesia and antipsychotics: a 5-year longitudinal study of frequency, correlates and course
Jonas Eberhard\textsuperscript{a}, Eva Lindström\textsuperscript{b} and Sten Levander\textsuperscript{a}

The present study comprised a naturalistic, multicentre, 5-year study of course and correlates of tardive dyskinesia (TD). One hundred and sixty-six patients treated with risperidone were included during 1995/96 and followed once a year for 5 years. Mean age at inclusion was 38 years, and mean illness duration was 12 years. Tardive dyskinesia was assessed by the Abnormal Involuntary Movement Scale, and each patient's cognitive function was tested with a comprehensive computerised test battery. At study entry, 14% had TD according to a criterion index. Fifty percent were aware of it, but few reported distress. Age and sex did not correlate with TD, but schizophrenia and bipolar diagnoses did. The presence and intensity of TD correlated with all Positive and Negative Syndrome Scale for Schizophrenia symptom dimensions except the affective factor, but not with type of medication or chlorpromazine-equivalent levels. Tardive dyskinesia patients were cognitively impaired in tests reflecting mental speed, but not in other cognitive modalities. Over the 453 patient years of exposure, five patients developed TD and 14 became free of it. Our findings support the view that TD: (i) is a dynamic phenomenon; (ii) is only partly drug-induced; (iii) has a mild course during treatment with modern neuroleptics; and (iv) appears to have some correlation with mental slowness. \textit{Int Clin Psychopharmacol} 21:35–42 © 2006 Lippincott Williams & Wilkins.

Introduction
The main indications for antipsychotic drug treatment are schizophrenia and other psychotic disorders. Most patients require maintenance therapy with antipsychotic drugs because only 10–15% of those treated will have a complete and lasting remission after the first episode (Kissling, 1989). Longer treatment duration and high doses are said to increase the risk of developing tardive dyskinesia (TD), a syndrome of abnormal movements that often appears late in the course of antipsychotic treatment. The earliest sign of TD often comprises mild movements of the tongue, chewing, licking or smacking movements. Later, the patient develops choreiform movements of the hands, fingers and arms (Gardos and Cole, 1995). Involvement of the respiratory muscles, trunk, head, back or pelvis is more rare.

The pathogenesis of TD is unknown. Spontaneous dyskinetic movements have been reported in never-medicated patients (Kraepelin, 1919; Fenn \textit{et al.}, 1996; McCreadie \textit{et al.}, 1997). One hypothesis postulates that the syndrome is caused by the induction of dopamine receptor supersensitivity by the antipsychotic drug (Klawans, 1973). The finding that classical antipsychotics can induce dyskinetic movements after months or years of treatment, and that these movements are partly masked by increased doses, supports this theory (Marsden and Jenner, 1980).

There is no specific treatment for TD (Gardos and Cole, 1995). However, different clinical trials with variable results have been performed (Mouret \textit{et al.}, 1991; Moss \textit{et al.}, 1993; Adler \textit{et al.}, 1999; Shamir \textit{et al.}, 2001; Richardson \textit{et al.}, 2003). Discontinuation of antipsychotics as soon as signs of TD emerge may help, but this approach is not always feasible because of exacerbation of psychotic symptoms. Using low doses of conventional antipsychotics does not protect against TD (Oosthuizen \textit{et al.}, 2003) but may lessen the risk (Casey, 1991), as well as switching to an atypical antipsychotic drug. For example, it is claimed that clozapine treatment is rarely associated with TD (Casey, 1987; Gerlach and Casey, 1988). Moreover, three controlled trials have documented the efficacy of clozapine in improving TD (Lieberman \textit{et al.}, 1991; Tammenga \textit{et al.}, 1994; Spivak \textit{et al.}, 1997). Quetiapine may have a similar effect (Emsley \textit{et al.}, 2004), as may sertrindole (Perquin, 2005).

There may be an association between emergence of TD and a concomitant reduction in cognitive functions among schizophrenic patients (Waddington and Youssef, 1996). The mechanism of such an association is unknown. Nevertheless, this points to the importance of studying TD and cognition together to clarify whether there is a causal link. In such a case, it might be possible to prevent the emergence of TD by treatment of the cognitive dysfunction, or vice versa.
The present study aimed to investigate the nature of TD in a population of subjects who were undergoing long-term treatment for a psychotic disorder. Patients were treated either with risperidone only, risperidone plus another medication, or other antipsychotic drugs (conventional as well as atypical). Apart from the relationships between TD, type of medication and dose, we also evaluated whether TD correlated to demographic characteristics, and to cognitive factors.

Methods
The study was performed as a naturalistic, national, multicentre, point-prevalence trial. Patients treated with risperidone for at least 2 weeks were included, and then followed prospectively for a total of 5 years.

At the day of inclusion, symptoms were rated using the Positive and Negative Syndrome Scale for Schizophrenia (PANSS; Kay et al., 1987). Signs of TD were rated using the Abnormal Involuntary Movement Scale (AIMS; Guy, 1976). The intention was for these ratings then to be performed annually for the remainder of the study period. Ratings were performed in the morning, approximately 12 h after the last dose of antipsychotic treatment, between 08.00 and 10.00 am. Cognitive function was assessed with a comprehensive computerised automated psychological test battery (APT), further described below, as well as by Eberhard et al. (2003).

Patients
The study included 223 patients at start-up (132 men and 91 women). Mean age was 38.5 ± 11.6 years (median 37 years; range 18–79 years) and mean age at first admission 26.7 ± 10.3 years (median 24 years; range 6–54 years). All patients were diagnosed according to DSM-IV (American Psychiatric Association, 1994). AIMS data were obtained in most of the participating centres, yielding data for 166 of the patients that constitute the study population for this report.

Measurements
The PANSS rating scale has been translated into Swedish, and the inter-rater reliability and construct validity has been ascertained (von Knorring and Lindström, 1992). The rating scale includes 30 items, each of which is accompanied by a complete definition, as well as detailed anchoring criteria in a seven-point format ranging from 1 = absent to 7 = extreme. The total score of the PANSS may thus vary between 30 and 210 points. The original PANSS version is divided into three sub-scales of positive, negative and general symptoms.

AIMS is a 12-item instrument assessing abnormal involuntary movements associated with antipsychotic drugs, such as dystonia and dyskinesia, as well as ‘spontaneous’ motor disturbances related to the illness itself. Scoring the AIMS consists of rating the severity of movement in three main anatomic areas (facial/oral, extremities and trunk), based on a five-point scale (0 = none, 4 = severe) (Table 1).

Patients were assessed as having TD or not according to the Schooler and Kane (1982) severity criteria for definite TD, which requires a score of 2 or higher on at least two items of the AIMS or a score of 3 or higher on one item.

Neurocognitive tests
In a number of sites, the comprehensive computerised test battery, APT (Automatic Psychological Test), was used to test the patients (Eberhard et al., 2003). Only APT data pertaining to the study entry are presented in this report. The tests given were: finger tapping (five subtests), reaction time (four subtests), selective attention (two subtests), simultaneous capacity, vocabulary, grammatical reasoning, visuo-spatial skill (two subtests), verbal working memory, non-verbal working memory (which also reflects executive functions) and long-term verbal memory. Finally, the patients filled in their self-rated performance on seven visual analogue scales. Performance in the APT tests is generally expressed as the vector sum of indices of speed and of accuracy.

Ethics
The study was approved by the local research ethic committees, and informed consent was obtained from each patient.

Results
The diagnoses of the 166 patients are displayed in Table 2, together with clinical and demographic information. Most of the subjects were assessed more than once, from 2–6 times over the 5 years. However, only a few subjects were able to participate in six consecutive sessions.

Analysis of the AIMS ratings
AIMS scores over the five years are presented in Fig. 1. The scores were not calculated on identical groups of
subjects because most of the subjects did not participate in all sessions over all years. A more rigid approach is to analyse data at study entry (i.e. for the 166 subjects of whom all were treated with risperidone at that time). We therefore performed a factor analysis of the Session 1 AIMS 1 to AIMS 7 ratings, which suggested that all items belonged to a common factor. Analyses with Cronbach’s alpha yielded a value of 0.84 for the full scale, suggesting homogeneity. All items except AIMS 7 had similar distribution of scores; AIMS 7 had smaller variance. Therefore, a SUM-TD value of Items 1–7 was calculated. None of the separate items had a markedly deviant correlation with this SUM value. In addition, a CRITERION value was checked using the Schooler and Kane (1982) rule (one score of 3 or at least two scores of 2 yields CRITERION = 1, else 0) (Table 3).

Table 2  DSM-IV diagnoses of the 166 patients and chi-square test of sex differences

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>Sex (M/F)</th>
<th>Age (years)</th>
<th>Onset age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>295 Schizophrenia</td>
<td>117</td>
<td>80/39</td>
<td>37.4</td>
<td>25.8</td>
</tr>
<tr>
<td>295/296 Schizoaffective/bipolar</td>
<td>20</td>
<td>5/15</td>
<td>43.3</td>
<td>27.2</td>
</tr>
<tr>
<td>297 Delusional syndrome</td>
<td>9</td>
<td>5/4</td>
<td>38.1</td>
<td>32.1</td>
</tr>
<tr>
<td>298 Psychotic disorder*</td>
<td>9</td>
<td>2/7</td>
<td>32.4</td>
<td>28.1</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
<td>7/4</td>
<td>37.2</td>
<td>27.1</td>
</tr>
<tr>
<td>Total</td>
<td>166</td>
<td>97/69</td>
<td>37.9</td>
<td>26.3</td>
</tr>
</tbody>
</table>

Chi squared (d.f = 4) = 17.2, P<0.01.
*NOS.

**Fig. 1**

Fluctuations of the average Abnormal Involuntary Movement Scale (AIMS) values over the course of the study.

AIMS 8 reflects the global severity of symptoms, AIMS 9 the disability and AIMS 10 reflects awareness and distress. Only subjects who scored at least 1 on SUM-TD were considered for AIMS 10 analyses (n = 60). According to a stepwise linear regression analysis, all AIMS 1–7 ratings, except AIMS 1 (facial expression), contributed significantly to the AIMS 8 (global severity) rating (r = 0.84). By contrast, a corresponding analysis showed that AIMS 9 (disability) was predicted only by AIMS 3 (jaw) and AIMS 5 (arms) (r = 0.68). Similarly, AIMS 10 (awareness and distress) was predicted only by AIMS 1 (facial expression) and AIMS 3 (jaw). Approximately 25% of the AIMS 10 (awareness and distress) variance was explained by these two variables. SUM-TD correlated significantly with AIMS 8 (r = 0.82), AIMS 9 (r = 0.57) and AIMS 10 (r = 0.45).

Twenty-three of the 166 subjects (14%) had TD at study entry according to the CRITERION index. Of those, eight were not aware of their TD, 10 reported awareness but no distress (AIMS 10 score 1) and five were aware and distressed (AIMS 10 score > 1).

**AIMS scores in relation to sex, age and illness characteristics**

Subjects with schizophrenia, schizoaffective disorder, or bipolar disorder, are expected to be exposed to higher doses of antipsychotic drugs and longer drug treatment times than the other diagnostic groups. Such subjects (n = 137) did not differ significantly from patients with other diagnoses (n = 29) with respect to sex, age, age at onset of illness, AIMS 8, AIMS 9 or AIMS 10 ratings. As expected, they had significantly higher SUM-TD scores (1.8 versus 0.41, t = 4.08, P < 0.001). However, the two groups did not differ significantly in TD CRITERION: 21/137 versus 2/29 (not significant).

Only patients with schizophrenia/schizoaffective/bipolar disorder (n = 137) were analysed with respect to current age, age at onset of illness and duration of illness in relation to AIMS data. There were 83 men and 54 women. Mean age was 38 ± 11.6 (18–76) years, mean age
at onset of illness was 26 ± 7.3 (6–50) years and mean duration of illness was 12.3 ± 10.1 (0–53) years. Twenty-one had TD according to CRITERION. The differences in age, age at onset, and illness duration between TD and non-TD patients were remarkably small. Furthermore, sex was not a significant factor between the two groups (15/83 versus 6/54). A correlational analysis between AIMS 8, AIMS 9 and AIMS 10, and SUM versus the above factors (age, age at onset, illness duration, sex) yielded numerically small coefficients of which none approached significance.

Summing up, an analysis of TD and AIMS ratings versus medication will not be confounded with differences in sex, age and illness duration variables.

**Analyses of the AIMS ratings over time**

**Comparisons between adjacent years**

One hundred and thirty-six patients were rated at least twice and at most six times. All ratings could be combined to 417 pairwise comparisons between two adjacent ratings with 1 year in between. In 82% (n = 342) of the comparison years, there was no TD at entry or exit. In 6% (n = 25) of the comparison years, there was TD at entry and exit. Six and a half percent (n = 27) became free of TD over 1 year, and 5.5% (n = 23) developed TD over the same time.

A corresponding analysis for SUM-TD yielded means of 1.54 for year 1 and 1.69 for year 2 and the SD for the pooled observations was 3.10. The median correlation for SUM-TD between adjacent years was 0.75 (representing a minimum value of test/retest reliability and underlining the stability over time of the ratings). The increase of SUM-TD during the year was non-significant (correlated Student’s t-test).

**Comparisons between study start and end-point**

The results of the start to end-point analyses with respect to the TD criterion and TD SUM change are summarized in Table 4. The total length of the study was 453 patient years of exposure.

Of the 30 patients who either had TD at study entry, or developed it sometime during the course of the study, five had remaining TD at study end-point, two of whom developed TD in spite of stable, unchanged medication. Twelve of the 30 patients had TD at study entry, and had recovered at end-point.

The remaining 13 patients had transient TD at 1 or more yearly assessments, eight of whom developed and recovered from TD during stable and unchanged medication. Three developed, and then recovered from TD while medicated by low-dose conventional antipsychotics.

### Table 4 Increase/decrease in the number of patients with tardive dyskinesia over the course of the study

<table>
<thead>
<tr>
<th>Follow-up (years)</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Developing tardive dyskinesia (criterion)</td>
<td>1 2 –</td>
</tr>
<tr>
<td>With resolving tardive dyskinesia (criterion)</td>
<td>6 5 1</td>
</tr>
<tr>
<td>With tardive dyskinesia SUM increase &gt;2 scores</td>
<td>5 4 1</td>
</tr>
<tr>
<td>With tardive dyskinesia SUM increase 1–2 scores</td>
<td>5 7 –</td>
</tr>
<tr>
<td>With tardive dyskinesia SUM decrease &gt;2 scores</td>
<td>3 5 1</td>
</tr>
<tr>
<td>With tardive dyskinesia SUM decrease 1–2 scores</td>
<td>3 2 –</td>
</tr>
</tbody>
</table>

### Table 5 Number of antipsychotic drugs over 5 years

<table>
<thead>
<tr>
<th>Year</th>
<th>No drugs</th>
<th>One drug</th>
<th>Two drugs</th>
<th>Three drugs</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 0</td>
<td>0</td>
<td>132</td>
<td>30</td>
<td>4</td>
<td>166</td>
</tr>
<tr>
<td>Year 1</td>
<td>14</td>
<td>101</td>
<td>26</td>
<td>3</td>
<td>144</td>
</tr>
<tr>
<td>Year 2</td>
<td>7</td>
<td>94</td>
<td>17</td>
<td>4</td>
<td>122</td>
</tr>
<tr>
<td>Year 3</td>
<td>8</td>
<td>86</td>
<td>14</td>
<td>4</td>
<td>112</td>
</tr>
<tr>
<td>Year 4</td>
<td>11</td>
<td>74</td>
<td>7</td>
<td>4</td>
<td>96</td>
</tr>
<tr>
<td>Year 5</td>
<td>11</td>
<td>73</td>
<td>12</td>
<td>5</td>
<td>101</td>
</tr>
</tbody>
</table>

### Medication

The numbers of antipsychotic drugs prescribed over the five years are listed in Table 5. At study entry, all 166 patients were treated with risperidone (80% of them in monotherapy). Thirty-four patients were prescribed at least one other neuroleptic drug, and four of those a third drug. In the following years, 55%, 53%, 49%, 45% and 47%, respectively, were on risperidone monotherapy.

### AIMS ratings versus medication

Associations between AIMS ratings and medication (type of drug/chlorpromazine level) were analysed by one-way analysis of variance (ANOVA) (type of drug) and Pearson correlations. All analyses were non-significant (i.e. there were no differences in AIMS SUM-TD among any of the drugs, and there were no significant correlations between AIMS SUM-TD and chlorpromazine level) (total and subdivided into chlorpromazine contribution from risperidone or from other drugs).

### Tardive dyskinesia and neurocognitive measures

Almost complete neurocognitive data sets were obtained for 82 subjects at study entry. Of those, 60 had no signs of TD, 10 had TD sum scores of 1–3, and 12 had TD. To simplify the analyses for this specific context, all primary test-specific neurocognitive speed indices were combined into three correlated meta-indices reflecting the main factor-analytically derived dimensions of the data. One metaindex (Motor 1) reflected speed in simple tasks (e.g. finger tapping and reaction times up to approximately 5 s) and the third metaindex (Motor 3) speed in complex tasks (typical response times of approximately 10 s). These meta-indices were expressed as Z-scores. Non-speed indices...
were calculated for relevant tests yielding indices of correct versus incorrect responses in most of the tests, and indices of overall performance in the primary abilities (verbal, reasoning and visuo-spatial domains), as well as in the three memory tasks. These indices were expressed as t-scores relative the norms of the test battery.

The three groups formed by SUM-TD scores (no signs, n = 60; sum score 1–3, n = 10; and TD, n = 12) were compared, by one-way ANOVAs and linear regression, for each of the neurocognitive indices. The more TD symptoms the patients had, the greater the significant increasing slowness for all of the three above described motor indices: Motor 1 (F = 7.24, P < 0.001); Motor 2 (F = 6.95, P < 0.01) and Motor 3 (F = 5.92, P < 0.05). Visuo-spatial skill displayed a similar pattern for one of the two subtests (F = 5.09, P < 0.05). Separating performance into accuracy and speed indices showed that the association with TD was significant only for the speed component. The same finding (although statistically stronger) was obtained for the grammatical reasoning test (F = 13.4, P < 0.001); in addition, this effect was found to reflect reduced motor and decision speed. Only one index of precision (number of correct versus incorrect responses) was significantly different among the three groups. In the selective attention subtest, which requires efficient visual search strategies, patients with higher SUM-TD scores made relatively more errors (F = 6.17, P < 0.05). Overall, similar findings (although statistically weaker) were obtained by analysing the clinically judged severity (TD8) and degree of handicap (TD9) in relation to the neurocognitive indices (product-moment correlations).

Discussion

Contrary to the common perception that TD is an irreversible side-effect of antipsychotic treatment, this study suggests that TD is actually a rather dynamic condition that is often not related to the type or dose of medication. On average, TD either emerged or resolved spontaneously in 12% of patients in any given year, which was also approximately the same level as the point prevalence of TD in this study (14%). Fifty percent of the patients were aware of their TD but few (22%) reported being distressed by it. Age, sex and diagnosis did not correlate with TD with one exception: patients with schizophrenia or bipolar disorder had more TD than patients with other diagnoses. The PANSS symptom level was stable over time and all symptom dimensions except the affective factor correlated significantly, but weakly, with the presence and intensity of TD. Thus, negative symptoms were not particularly strongly associated with TD. The presence and intensity of TD did not correlate with type of medication or chlorpromazine levels, either on a group or individual level. The finding that TD was independent of sex, age or diagnosis is unexpected in relation to findings in earlier studies.

Older age as a risk factor for the development of TD was previously demonstrated by Schooler (1988), Jeste et al. (1995) and Sachdev (2000). Women, particularly those over the age of 40 years, are also believed to be at an increased risk for TD (Woerner et al., 1991). In addition, patients with affective psychosis (Rosenbaum, 1977; Rush, 1982; Casey, 1984; Spiket et al., 1985; Bowers and Swigar, 1988), as well as diagnostic groups other than affective disorders, are also at a greater risk for TD compared to schizophrenics. Furthermore, individuals prescribed neuroleptics for non-psychiatric conditions are at greater risk of developing TD (Miller and Jankovic, 1989). Other important risk factors, claimed to be related to TD, are duration of treatment and daily dose (Barany et al., 1983; Chiu and Lee, 1989; Correll et al., 2004).

In the present study, which covered 453 patient years from start to end-point, five patients developed TD and 14 became free of TD. This may be explained by treatment regimes. Approximately 50% were treated with risperidone monotherapy. Several studies have shown that not only that the risk of developing TD is lower during treatment with risperidone and other novel antipsychotics (Casey, 1999; Jeste and Lacro, 1999; Kane, 1999; Glazer, 2000a,b; Lund and Perry, 2000; Stanniland and Taylor, 2000; Worrall et al., 2000; Wirshing, 2001; Caroff and Mann, 2002; Llorca et al., 2002; Schwartz et al., 2002; Tandon, 2002) but also that risperidone itself may have an antidyskinetic effect (Carvalho et al., 2003). The finding of a lower than expected prevalence of TD, as well as the relatively mild course of patients with established TD, may be explained by the majority of patients being exposed to second-generation antipsychotics rather than conventional drugs (Lublin et al., 2005) and, if conventional drugs were used, they were prescribed in low doses.

We could not find any difference between subjects who had different drug regimes, including those who switched to conventional drugs only. This might be explained by patient selection effects (clinicians may be expected to switch treatment from one drug treatment to another on the basis of poor clinical effect or pronounced side-effects), as well as lack of statistical power for comparisons involving small subgroups of patients; only fairly large clinical effects would have been detected reliably.

In an earlier study by Glazet et al. (1993), 32% of patients were at risk for irreversible TD after 5 years of treatment with conventional neuroleptics. The figures increased to 52% after 15 years and to 68% after 25 years of treatment. In the present study, the prevalence of TD showed a slight decrease during 5 years of treatment. A majority of
our patients were treated by atypicals. However, other studies have also reported cases of TD during treatment with novel antipsychotics (Llorca et al., 2002; Gafoor and Brophy, 2003). In a study by Ipecki and Birsoz (2001), TD caused by risperidone resolved after switching to olanzapine. Such anecdotal findings might be expected if TD is a dynamic and illness-related phenomenon to some extent, as suggested by our data, rather than simply an irreversible side-effect of neuroleptics.

In the present study, 50% of patients were aware of their TD but only one in five reported distress. Dyskinetic movements may be more disturbing for significant others than for the patient. Nevertheless, TD may constitute a social problem that should be addressed.

Our findings are to some extent inconsistent with the mainstream literature, and therefore it is essential to consider the limitations of our study. Ours was a multicentre study into which only risperidone-treated patients were recruited, and this might represent a selection bias. At the time of the study, risperidone was a new compound, which carried hope of a better effect with fewer side-effects than previously available antipsychotic drugs. Therefore, it is reasonable to expect that patients who had a less than optimal clinical effect of conventional treatment might have been considered for risperidone treatment. However, the symptoms and side-effect ratings at inclusion did not differ much from that expected for an unselected group of outpatients suffering from a psychotic illness. Only a few patients participated in all six sessions, which can be expected in the present context, but, for a large majority of patients, there were observations covering at least 3 years. Nonetheless, this weakens our findings.

The fact that many raters contributed data may have compromised reliability. However, poor reliability should manifest as low test–retest correlations over the years. Instead, we found that reliability was high for all important parameters. Tardive dyskinesia ratings were part of a large set of variables, and no specific focus was attached to them. There does not appear to have been any bias towards reporting improvement in clinically important variables such as PANSS and AIMS; rather, a remarkable stability existed in spite of many changes in drug treatment. The point prevalence of TD was in the expected range. The present study represents one of very few longitudinal studies of TD following patients over as much as 5 years, and the number of patients is fairly large compared with most studies of that kind. Tardive dyskinesia was found to be a reversible condition, and not directly related to drug therapy as is generally believed. The results indicate that TD may have a mild, long-term course even when the psychotic illness requires the continued use of neuroleptics. In agreement with one earlier study (Gardos et al., 1994), our findings indicate that chronic psychotic patients with mild to moderate TD, who are on stable treatment with neuroleptics, are not likely to experience a worsening of their TD symptoms and may have a spontaneous resolution of their TD symptom over time. Despite this conclusion, we believe that regular monitoring with validated rating scales for TD during long-term treatment with neuroleptics is commendable.

Higher AIMS ratings were associated with motor slowing and increased decision times, but not with the other cognitive domains (i.e. suggesting impairment of neuro-cognitive functions in association with TD). The reduction appeared to be more pronounced, relatively, for short response times, whereas more complex cognitive functions were spared in patients with TD. Earlier studies have focused on the relationship between TD and cognitive dysfunction (Struve and Willner, 1983; Wolf et al., 1983; Myslobodsky et al., 1985; Wegner et al., 1985; Waddington et al., 1987; Wade et al., 1987; DeWolfe et al., 1988; Tegeler et al., 1988; Karson et al., 1990; Waddington et al., 1990; Barbeau et al., 1993; Karson et al., 1993; Pourcher et al., 1993; Waddington et al., 1993; Waddington, 1995; Sachdev et al., 1996; Waddington and Youssef, 1996). The findings are not very consistent but most of the results support our findings indicating that there appears to be an association between TD and cognitive dysfunction. However, different methods with respect to how to measure cognitive dysfunction, together with the problem of selection bias of patients, make any comparisons difficult. For example, we were unable to replicate the differential association between orofacial TD symptoms and cognitive impairment. More studies using instruments that focus on the assessment of motor speed and decision times will be needed to further elucidate the relationship between TD and cognitive dysfunction. It should be noted that there was a significant linear relationship between the sum of TD scores and cognitive impairment (i.e. a dose–response relationship). Broadening the perspective, the striatal dopaminergic motor dysfunction ranges from full TD, via subclinical TD manifestations (a single checked item of lowest intensity of the AIMS instrument), to an absence of TD manifestations. The cognitive impairment can be assumed to be linearly related to the full range of TD manifestations. One remaining interesting issue is whether the positive effect on cognitive functions reported for the newer neuroleptics compared with traditional ones may be mediated by their less pronounced tendency to induce TD manifestations.

Acknowledgements

This study was initiated by Jansen-Cilag Sweden, as a naturalistic, prospective 5-year follow-up of a point prevalence study of patients medicated with risperidone, in 1995/96. Eva Lindström was a principal investigator...
involved, together with Jansen, in the conception and design of this project. Since the end of 2001, in addition to his affiliation at the Department of Psychiatry at Lund University, Jonas Eberhard has been employed as a medical advisor for H. Lundbeck A/S in Copenhagen. During the 6 years of data collection for this study, he held a position as attending psychiatrist at the Lund University Hospital psychiatric rehabilitation/habilitation unit for outpatients with chronic schizophrenia and other psychotic disorders. All the authors have participated as speakers and received honoraria from Jansen-Cilag. Apart from the authors, a number of Swedish psychiatrists at 11 sites were involved in collecting data. The list of contributing trial site investigators with a varying number of patients included: B. Andree, G. Arnell, M. Bela, B.-O. Bengtsson, I. Bergström, E. Bergquist, G. Björling, Å. Bliding, G. Cizinsky, Jakob Eberhard, A. Edsbagge, E. Efrin, G. Ek, L. Eklöf, H. Eriksson, L. Eriksson, L. Flyckt, L. Helldin, B. Johansson, M. Johansson, H. Jonsson, C. Carlsson, M. Källberg, T. Liljevikst, B. Lögdberg, C. Nilsson, A. Oredsson, R. Persson, P. Persson, S. Persson, B. Rembäck, C. Rolleri, M. Rosell, I. Sjödin, L. Smith, M. Sundvall, P. Thorslund, S. Torenfält and T. Wållsten.

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