Family history of primary movement disorders as a predictor for neuroleptic-induced extrapyramidal symptoms

REBEKKA LENCER, GUNNAR EISMANN, MEIKE KASTEN, KEMAL KABAKCI, VERENA GEITHE, JENNY GRIMM and CHRISTINE KLEIN

Background A genetic susceptibility to extrapyramidal symptoms caused by treatment with neuroleptic medication has been suggested.

Aims To identify predictor variables for neuroleptic-induced extrapyramidal symptoms, particularly considering family history of primary movement disorders.

Method We investigated 100 in-patients receiving a stable neuroleptic medication with regard to occurrence of extrapyramidal symptoms, drug history and detailed family history of primary movement disorders.

Results Step-wise logistic regression analysis revealed that a positive family history was a significant predictor for lifetime prevalence of extrapyramidal symptoms, including reported and currently observed symptoms. The duration of exposure to neuroleptic medication and age were further predictors.

Conclusions Our findings underline the notion of genetic susceptibility for secondary extrapyramidal symptoms and suggest possible shared genetic factors in primary and secondary movement disorders as well as psychotic disorders.

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Neuroleptic-induced extrapyramidal symptoms often lead to non-compliance and consequently poorer treatment outcome (Gerlach, 2002). Extrapyramidal symptoms may also occur with modern, atypical neuroleptic medication (Tarsy et al., 2002). Risk factors include age, psychiatric diagnosis, psychopathology, and dosage and duration of neuroleptic exposure, but no clear-cut predictor has been identified as yet (Ayd, 1961; Swett, 1975; Nasrallah et al., 1988; Berardi et al., 2000; Srinivasan et al., 2001). More recently, genetic factors have been suggested to have a role in the susceptibility to extrapyramidal symptoms (Basile et al., 2002; Segman et al., 2002). Given that a genetic predisposition may increase the susceptibility to such symptoms, a positive family history of primary movement disorders may be associated with their development. An increasing number of polymorphisms in dystonia and parkinsonism genes have been shown to be associated with primary movement disorders (Klein & Ozelius, 2002; Gasser, 2003). We therefore investigated whether a family history of primary movement disorders might be a predictor of extrapyramidal symptoms in patients receiving typical and atypical neuroleptic medication.

METHOD

Patients and diagnosis Participants were consecutively recruited from people admitted as in-patients of the Department of Psychiatry and Psychotherapy at the University of Lübeck. Each participant gave written informed consent after having been carefully informed about the study. The study was approved by the local ethics committee. Participants had to meet the following inclusion criteria:

(a) stable neuroleptic medication for at least 1 week;
(b) no neurological disease;
(c) no significant history of head trauma;
(d) no other medication that could potentially induce movement disorder.

Operational psychiatric lifetime diagnoses according to DSM-IV (American Psychiatric Association, 1994) were established using the German version of the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) and the Structured Clinical Interview for Personality Disorders (SCID–II; Spitzer & Williams, 1987). Diagnoses were divided into four categories: organic psychiatric disorders, including all forms of alcohol and drug dependence; psychotic disorders; affective disorders; and other Axis I or Axis II disorders. Psychopathological symptom severity was rated on the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962). Each participant underwent a complete neurological examination with particular emphasis on specific signs of acute dystonic reaction, parkinsonism, akathisia and tardive dyskinesia. The following rating scales were used to assess the severity of extrapyramidal symptoms (van Harten et al., 1997): the Abnormal Involuntary Movement Scale (AIMS; National Institute of Mental Health, 1973); the Tsui Rating Scale for Cervical Dystonia (Tsui et al., 1986) and the Burke Rating Scale for Primary Torsion Dystonias (Burke et al., 1985); Part III of the Unified Parkinson’s Disease Rating Scale (UPDRS; Movement Disorder Society Task Force on Rating Scales for Parkinson’s Disease, 2003); the global score on the Hillside Scale (Fleischacker et al., 1991) and the Barnes Akathisia Scale (Barnes, 1989). History of extrapyramidal symptoms on previous neuroleptic treatment was explored in a structured interview developed by our group, covering the typical symptoms of acute dystonic reaction, parkinsonism, akathisia and tardive dyskinesia. To check the reliability of their answers, participants were asked about the consequences of the development of their movement disorder (for example, change in medication or administration of biperiden). In addition, clinical records covering former treatment phases were reviewed to complete the information. Family history of movement disorders was obtained by means of a structured interview developed in our department, specifically covering symptoms of Parkinson’s disease (stiffness of movement, gait problems, tremor, change in facial expression, lateralisation of symptoms), dystonia and psychiatric disorders in first-degree to third-degree relatives. This
structured interview had previously been shown to provide reliable data in a large epidemiological study (Klein et al, 1999). A diagnosis of a primary movement disorder was only made if the criteria for the disorder were clearly fulfilled by the symptom description given by the patient. Relatives were asked to also undergo the structured interview whenever possible.

Statistical procedure

Pearson's chi-squared tests for independence were performed to investigate the relationship between categorical outcome variables (lifet ime occurrence of extrapyramidal symptoms, including reported and currently observed symptoms; reported extrapyramidal symptoms during previous treatment phases; currently observed extrapyramidal symptoms; extrapyramidal symptoms on typical neuroleptic medication; extrapyramidal symptoms on atypical neuroleptic medication; lifetime occurrence and currently observed acute dystonic reaction, parkinsonism, akathisia and tardive dyskinesia) and possible categorical predictor variables (gender; age; psychiatric diagnostic category; dosage range; duration of exposure to any neuroleptic medication; duration of exposure to typical neuroleptic medication; duration of exposure to atypical neuroleptic medication; positive family history of primary movement disorder).

To achieve the required expected cell frequency of more than 5 in \( \chi^2 \)-tests, we defined three different age groups: 18–40 years, 41–60 years and >60 years. For the same reason, duration of exposure to neuroleptic medication was categorised as <6 months, 6 months to 5 years, and >5 years. For easier comparison, drug dosages were defined as low, medium or high, based on current clinical practice. Chi-squared values are reported with two-tailed probabilities. Relationships between possible predictor and outcome variables with \( P < 0.5 \) revealed by \( \chi^2 \)-tests were entered in a step-wise logistic regression analysis to identify predicted probabilities for extrapyramidal symptoms (probability to enter at 0.05). By use of a logistic regression analysis, all predictor variables are considered within one testing procedure, including intercorrelations, which reduces the probability of type I errors. All statistical procedures were performed using the Statistical Package for the Social Sciences (version 11.0).

RESULTS

Demographic and clinical data are listed in Table 1. Most patients (62%) had been admitted for treatment of a psychotic disorder: schizophrenia or schizophreniform disorder (n = 30), schizoaffective disorder (n = 10) or delusional disorder (n = 2). Fourteen patients were receiving neuroleptic treatment for an organic psychiatric disorder: substance-induced psychotic episodes (n = 10), delirium (n = 3) or organic delusional disorder (n = 1). Eighteen patients were treated for an affective disorder: unipolar depressive disorder with psychotic symptoms (n = 10), bipolar disorder with psychotic symptoms (n = 8; five manic and three depressive episodes). Six patients had other psychiatric disorders: borderline personality disorder (n = 5) or dissociative disorder (n = 1). Analysis of variance including post hoc comparisons revealed that patients with an affective disorder were significantly older than patients from the other groups (F = 3.39, d.f. = 3, \( P = 0.01 \)), who did not differ significantly with respect to age. The distribution of men and women differed significantly between the diagnostic groups (\( \chi^2 = 17.74 \), d.f. = 1, \( P < 0.01 \)), whereas symptom severity measured by BPRS scores was similar in all groups. More patients had ever been treated with atypical neuroleptic medication (87%) than with typical neuroleptics (64%).

Lifetime prevalence of extrapyramidal symptoms

Lifetime prevalence of extrapyramidal symptoms, including both reported and currently observed symptoms, was 65% (Table 2). Acute dystonic reactions occurred most commonly (41%), followed by parkinsonism (37%), akathisia (19%) and tardive dyskinesia (4%). It should be noted that several patients suffered from more than one type of extrapyramidal disorder. Of those who had experienced such symptoms, more patients had been exposed to typical than to atypical medication. Details of mean age and distribution of gender are given in Table 2.

Currently observed extrapyramidal symptoms

At the time of examination, most patients were taking an atypical neuroleptic medication (Table 3). Extrapyramidal symptoms were diagnosed in 34% of patients. The most commonly observed symptom was parkinsonism (19%), followed by acute dystonic reaction (15%), akathisia (5%) and tardive dyskinesia (3%). Again, some patients were diagnosed with more than one type of extrapyramidal symptom. Table 3 gives further clinical characteristics and details concerning dosages of neuroleptic medication.

Reported symptoms and family history of primary movement disorders

Fifty-three patients (29 men and 24 women, mean age 36.3 years, s.d. = 13.2) reported that they had experienced extrapyramidal symptoms during previous treatment phases. Information about the family history of primary movement disorders was available for 98 participants and could be assessed for a total of 1316 relatives, 438 of whom were first-degree relatives. Thirty-two of these 98 patients (20 men and 12 women) reported a positive family history, resulting in a total of 47 affected relatives, or a prevalence of a primary movement disorder of 3.5% among all relatives. Specifically, the prevalences were 1.1% (n = 14) for Parkinson’s disease, 1.6% (n = 21) for tremor and 0.9% (n = 2) for dystonia. Among relatives of patients with lifetime extrapyramidal symptoms (n = 848), the prevalences were 1.4% (n = 12) for Parkinson’s disease, 2.4% (n = 20) for tremor and 1.1% (n = 9) for dystonia, whereas among the relatives of patients without lifetime extrapyramidal symptoms (n = 468), the prevalences were 0.4% (n = 2) for Parkinson’s disease, 0.2% (n = 1) for tremor and 0.6% (n = 3) for dystonia. A subgroup analysis was performed using data from 27 (2.1%) first-degree relatives of 21 patients who were seen personally by one of the investigators. In all of them, the presence or absence of a primary movement disorder was confirmed as established by the family history interview (25 relatives without a primary movement disorder, 1 with dystonia and 1 with tremor). In order to avoid multiple inclusion of patients with more than one affected relative in further statistical analyses, we considered only the closest relative of those patients. This resulted in 12 patients with a relative with Parkinson’s disease (5 first-degree relatives and 7 second-degree relatives), 11 patients with a relative with tremor (6 first-degree relatives and 5 second-degree relatives) and 9 patients with a relative with dystonia.
prevalence of acute dystonic reaction was related to the subtype of primary movement disorders occurring in relatives ($\chi^2=8.27$, d.f.=3, $P=0.04$). Lifetime acute dystonic reaction occurred in 7 of 9 (78%) patients with a family history of dystonia, but only in 7 of 12 (58%) patients with a family history of Parkinson’s disease, 4 of 11 (36%) patients with a family history of tremor and 22 of 44 (50%) patients with a negative family history.

**Age**

We further observed a strong relation between age and lifetime prevalence of EPS ($\chi^2=15.13$, d.f.=2, $P<0.01$), reported EPS ($\chi^2=15.70$, d.f.=2, $P<0.01$) and lifetime prevalence of acute dystonic reaction ($\chi^2=9.82$, d.f.=2, $P<0.01$). The prevalence of the three related outcome variables was higher in the youngest age group than in either of the other age groups (Table 4).

**Duration of exposure to neuroleptic medication**

The duration of exposure to any neuroleptic medication was related to the lifetime prevalence of EPS ($\chi^2=17.86$, d.f.=2, $P<0.01$), the prevalence of reported EPS ($\chi^2=3.96$, d.f.=2, $P<0.01$) as well as the lifetime occurrence of parkinsonism ($\chi^2=6.67$, d.f.=2, $P=0.04$) and akathisia ($\chi^2=8.41$, d.f.=2, $P=0.02$). More specifically, the duration of exposure to typical neuroleptics was associated with the lifetime prevalence of EPS ($\chi^2=18.71$, d.f.=3, $P<0.01$), the prevalence of reported EPS ($\chi^2=27.78$, d.f.=3, $P<0.01$), occurrence

### Table 1 Demographic and clinical characteristics of the sample

<table>
<thead>
<tr>
<th>Psychiatric disorder</th>
<th>$n$</th>
<th>Age, years Mean (s.d.)</th>
<th>Gender (male/female) n/n</th>
<th>BPRS score Mean (s.d.)</th>
<th>Duration of exposure</th>
<th>&lt; 6 months n</th>
<th>6 months to 5 years n</th>
<th>&lt; 5 years n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic disorder</td>
<td>14</td>
<td>37.6 (14.9)</td>
<td>12/2</td>
<td>34.2 (12.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>62</td>
<td>38.5 (13.8)</td>
<td>32/30</td>
<td>38.5 (10.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affective disorder</td>
<td>18</td>
<td>49.6 (15.8)</td>
<td>3/15</td>
<td>39.7 (11.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Axis I or II</td>
<td>6</td>
<td>31.5 (8.6)</td>
<td>1/5</td>
<td>45.3 (9.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>100</td>
<td>39.9 (14.7)</td>
<td>48/52</td>
<td>38.5 (11.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Exposure to neuroleptic medication**

<table>
<thead>
<tr>
<th>Any neuroleptic</th>
<th>100</th>
<th>38</th>
<th>128</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical neuroleptic</td>
<td>64</td>
<td>34</td>
<td>30</td>
<td>18</td>
</tr>
<tr>
<td>Atypical neuroleptic</td>
<td>87</td>
<td>42</td>
<td>45</td>
<td>9</td>
</tr>
</tbody>
</table>

**BPRS, Brief Psychiatric Rating Scale.**

### Table 2 Clinical characteristics and lifetime prevalences of extrapyramidal symptoms

<table>
<thead>
<tr>
<th>Lifetime prevalence of</th>
<th>$n$</th>
<th>Age, years Mean (s.d.)</th>
<th>Gender (male/female) n/n</th>
<th>Duration of exposure</th>
<th>&lt; 6 months n</th>
<th>6 months to 5 years n</th>
<th>&lt; 5 years n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any EPS</td>
<td>65</td>
<td>37.6 (14.7)</td>
<td>34/31</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute dystonic reaction</td>
<td>41</td>
<td>35.6 (13.8)</td>
<td>20/21</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>37</td>
<td>38.0 (13.5)</td>
<td>20/17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akathisia</td>
<td>19</td>
<td>35.8 (13.8)</td>
<td>11/8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tardive dyskinesia</td>
<td>4</td>
<td>36.8 (11.0)</td>
<td>3/1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Symptoms experienced under exposure to**

| Any neuroleptic             | 65  | 38.7 (15.2)            | 25/22                    | 15                  | 10            | 20                    |
|----------------------------|-----|------------------------|--------------------------|---------------------|---------------|----------------------|------------|
| Typical neuroleptic        | 47  | 37.3 (15.9)            | 17/17                    | 13                  | 16            | 5                     |
| Atypical neuroleptic       | 34  | 37.3 (15.9)            | 17/17                    | 13                  | 16            | 5                     |

**EPS, extrapyramidal symptoms.**
of EPS on typical neuroleptics ($\chi^2=7.83$, 

$d.f.=2$, $P=0.02$), lifetime prevalence of 

acute dystonia ($\chi^2=10.68$, 

$d.f.=3$, $P=0.01$), parkinsonism ($\chi^2=12.75$, 

$d.f.=3$, $P<0.01$) and akathisia ($\chi^2=8.59$, 

$d.f.=2$, $P=0.04$). The duration of the exposure to 

atypical neuroleptics was related to the 

prevalence of reported EPS ($\chi^2=14.91$, 

$d.f.=3$, $P=0.01$). As summarised in Table 4, we 

found the prevalence of all statistically 

related outcome variables to increase with 

longer duration of neuroleptic medication.

For all other relationships between 

possible predictor variables (gender, psychiatric diagnostic category or dosage range) and outcome variables considered in $\chi^2$ tests, $P>0.05$. Thus, only the following possible predictor variables were entered in a logistic regression analysis: family history of primary movement disorders; age; duration of exposure to any neuroleptic medication; duration of exposure to typical neuroleptics; and duration of exposure to atypical neuroleptic medication. Occurrence of tardive dyskinesias was excluded from outcome variables because of the small number of cases identified.

**Predictors revealed by logistic regression analysis**

We found that lifetime occurrence of EPS (yes or no) could be correctly predicted in 74% of all cases by knowing the duration of treatment with typical neuroleptics, and family history of primary movement disorders. Lifetime occurrence of acute dystonic reaction (yes or no) could be predicted in 65% of cases taking into account the exposure to typical neuroleptic medication and age. Both lifetime occurrence of parkinsonism (yes or no) and of akathisia (yes or no) were predicted correctly in 72% and 82%, respectively, by the duration of typical neuroleptic medication. Reported EPS (yes or no), regardless of the subtype, were correctly predicted in 82% of cases by the duration of exposure to typical neuroleptic medication, age and family history of primary movement disorders. Currently observed EPS (yes or no) were predicted in 68% of all cases by the family history of primary movement disorders. Extrapyramidal symptoms on typical neuroleptic medication (yes or no) could be predicted in 73% when considering the duration of exposure. As can be seen from the regression coefficients B in Table 5, the probability for the occurrence of symptoms always increased with the duration of exposure to neuroleptic medication, younger age and positive family history.

**DISCUSSION**

The main purpose of our study was to identify predictor variables for neuroleptic-induced extrapyramidal symptoms, for the first time considering family history of primary movement disorders.

**Prevalence rates for extrapyramidal symptoms and primary movement disorders**

Based on a sample that represents a typical cohort of in-patients with acute psychotic symptoms, we observed a lifetime prevalence of extrapyramidal symptoms of 65% and a point prevalence of 34%, comparable to rates reported in large epidemiological studies (Ayd, 1961; Swett, 1975; Owens & Johnstone, 1982). Compared with these studies, the mean age of our patients was low, and the rate of patients ever having been treated with atypical neuroleptics was high (87%). The percentage of patients who had been exposed to neuroleptics for less than 6 months was high (38%). The overall prevalence of about 3% for primary movement disorders in all relatives seems plausible. Higher prevalence rates of Parkinson’s disease, tremor and dystonia among relatives of patients with lifetime extrapyramidal symptoms than among relatives of patients without such symptoms are comparable with results reported by others, although our study was not designed as a population-based case-control study (Marder et al., 1996; Louis et al., 2003). The relatives’ diagnoses could be confirmed in a small subgroup.

**Predictors of extrapyramidal symptoms**

In our sample, logistic regression analysis revealed that a positive family history had significant predictive value for the occurrence of extrapyramidal symptoms. The
Table 4  Distributions of outcome and possible predictor variables

<table>
<thead>
<tr>
<th>Possible predictor</th>
<th>Outcome variable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lifetime EPS</td>
</tr>
<tr>
<td></td>
<td>(yes/no)</td>
</tr>
<tr>
<td>Family history1,2</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>27/5</td>
</tr>
<tr>
<td>Negative</td>
<td>36/30</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>18–40 years</td>
<td>46/11</td>
</tr>
<tr>
<td>41–60 years</td>
<td>12/18</td>
</tr>
<tr>
<td>&gt; 60 years</td>
<td>7/6</td>
</tr>
<tr>
<td>Lifetime exposure to any neuroleptic2</td>
<td></td>
</tr>
<tr>
<td>&lt; 6 months</td>
<td>15/23</td>
</tr>
<tr>
<td>6 months to 5 years</td>
<td>30/8</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>20/4</td>
</tr>
<tr>
<td>Lifetime exposure to typical neuroleptic3</td>
<td></td>
</tr>
<tr>
<td>&lt; 6 months</td>
<td>17/10</td>
</tr>
<tr>
<td>6 months to 5 years</td>
<td>18/1</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>15/3</td>
</tr>
<tr>
<td>No exposure</td>
<td>15/21</td>
</tr>
</tbody>
</table>

ADR, acute dystonic reaction; EPS, extrapyramidal symptoms.

1. Date available for 98 participants.
2. Numbers in each outcome variable column were compared within one testing procedure.

Table 5  Step-wise logistic regression analysis revealing significant predictor variables for occurrences of extrapyramidal symptoms (d.f. = 1 in all tests)

<table>
<thead>
<tr>
<th>EPS</th>
<th>Predictor</th>
<th>B</th>
<th>s.e.</th>
<th>( \text{Wald} )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime occurrence of EPS</td>
<td>Duration of typical neuroleptic</td>
<td>0.78</td>
<td>0.25</td>
<td>10.65</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>-0.85</td>
<td>0.35</td>
<td>5.95</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Positive family history</td>
<td>1.30</td>
<td>0.60</td>
<td>4.67</td>
<td>0.03</td>
</tr>
<tr>
<td>Lifetime occurrence of acute dystonia</td>
<td>Duration of typical neuroleptic</td>
<td>0.54</td>
<td>0.20</td>
<td>7.16</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>-0.88</td>
<td>0.36</td>
<td>6.17</td>
<td>0.01</td>
</tr>
<tr>
<td>Lifetime occurrence of parkinsonism</td>
<td>Duration of typical neuroleptic</td>
<td>0.53</td>
<td>0.20</td>
<td>7.16</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lifetime occurrence of akathisia</td>
<td>Duration of typical neuroleptic</td>
<td>0.63</td>
<td>0.24</td>
<td>6.81</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Reported EPS</td>
<td>Duration of any neuroleptic</td>
<td>1.98</td>
<td>0.41</td>
<td>23.28</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>-1.30</td>
<td>0.45</td>
<td>8.54</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Positive family history</td>
<td>1.45</td>
<td>0.62</td>
<td>5.57</td>
<td>0.02</td>
</tr>
<tr>
<td>Currently observed EPS</td>
<td>Positive family history</td>
<td>1.27</td>
<td>0.46</td>
<td>7.69</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EPS under typical neuroleptics</td>
<td>Duration of typical neuroleptic</td>
<td>0.90</td>
<td>0.40</td>
<td>4.97</td>
<td>0.03</td>
</tr>
</tbody>
</table>

B, regression coefficient; EPS, extrapyramidal symptoms; s.e., standard error.
probability of observed symptoms at the
time of examination, for which it was the
only predictor, as well as of lifetime preva-
ence of symptoms and reported symptoms,
was increased in patients who had a relative
with a primary movement disorder. The
strongest predictive value was found for
the duration of treatment with typical neu-oleptics (lifecycle occurrence of EPS, acute
dystonic reaction, parkinsonism, akathisia,
and EPS on typical neuroleptics) as well as
with any neuroleptic medication (reported
EPS). The probability of extrapyramidal
symptoms increased with longer duration
of exposure. Furthermore, younger age
was also a significant predictor for the
occurrence of symptoms, especially for
acute dystonic reaction.

Positive family history of primary movement
disorders
The finding that a positive family history
of primary movement disorders had a
significant impact on the occurrence of
extrapyramidal symptoms has two main
implications. First, our results suggest that
primary and secondary movement disor-
ders may share common genetic factors.
Second, the association with primary
movement disorders observed in patients
suffering from psychotic symptoms and
developing extrapyramidal symptoms
may represent a dysfunction within a
common pathway of the dopaminergic
system. This system is involved not only
in primary and secondary movement dis-
orders but also in psychotic disorders.
Earlier hypotheses suggest that such symp-
toms might represent exacerbated involun-
tary movements that are directly related
to cerebral dysfunctions underlying psy-
chotic diseases – i.e. a dysfunction within the
dopaminergic system (Ayd, 1961; 
Owen & Johnstone, 1982). Indeed, both
Kraepelin (1971) and Bleuler (1950) de-
scribed ‘spasmodic phenomena in the
musculature’ and ‘extraordinary move-
ments of the tongue and lips’ in patients
with psychosis long before the introduc-
tion of neuroleptic drugs. Other studies
have confirmed this observation by the
finding that prevalence and distribution
of extrapyramidal symptoms were the
same in treated and never-treated patients
and depended only on the age at onset
of the psychotic illness (Owen & John-
stone, 1982; Srinivasan et al., 2001).
Further studies should address the ques-
tion whether the occurrence of such
symptoms represents an endophenotype
for schizophrenia, as has been shown
for other neurological dysfunctions in
neuroleptic-naïve patients with psychosis
(Gottesman & Gould, 2003). Genetic
association studies of candidate genes, such
as dopamine receptor genes, will be the nat-
ural extension of our study to elucidate
the hypothesised common underlying
mechanism at the molecular level.

Duration of neuroleptic medication
We observed a strong effect of duration
of exposure to neuroleptic medication,
especially of typical neuroleptics, on the
occurrence of extrapyramidal symptoms,
including the subtypes acute dystonic reac-
tion, parkinsonism and akathisia. Although
many authors have proposed such an
effect, retrospective studies rarely con-
ﬁrmed this notion (Marsalek, 2000). From
our results, however, it can be assumed
that the longer the exposure to neuroleptic
drugs, the higher the prevalence of these
symptoms. This finding may support the
hypothesis of an accumulating toxic effect
of neuroleptic drugs that is suggested to
be higher in the typical drugs than in the
atypical, with the exception of clozapine
(Gil-ad et al., 2001). An effect of dosage
on occurrence of extrapyramidal symptoms
at the time of examination could not be
conﬁrmed.

None of the predictor variables entered
in the logistic regression analysis was found
to predict the occurrence of extrapyramidal
symptoms in patients taking atypical neu-oleptics. The significant relation observed
in the χ² test between reported symptoms
and the duration of medication with atypi-
cal neuroleptics may be interpreted as a
trend. However, the long-term effect of
atypical neuroleptics on extrapyramidal
symptoms may yet not have been verified,
since only a small proportion of patients
had been exposed to these drugs for more
than 5 years (10%), and this aspect
remains a matter of debate (Tarsy et al.,
2002).

Other possible predictors: age,
gender and psychiatric diagnosis
We were able to validate young age as a
predictor for the occurrence of extrapyra-
midal symptoms, especially of acute dys-
tonia (Ayd, 1961; Swett, 1975). This finding
gives further support to the genetic in-
fluence on occurrence of these symptoms.
In contrast, there is no evidence from our data
for either diagnostic specificity or gender as
a predictor for the occurrence of symptoms.

Methodological limitations
Our study design must be regarded as some-
what explorative, since for most of the rela-
tives the diagnosis of a primary movement
disorder could only be established through
the family history interview. This procedure
might have reduced the validity and reliabil-
ity of the data, although special efforts were
made to rate a family history as positive
only if the criteria were unambiguously ful-
ﬁlled. In a clinical setting, this is also the
most practical way to gather information
and decide whether a patient is at risk of de-
veloping extrapyramidal symptoms because
of a positive family history.

We are aware that the way in which
we categorised neuroleptic dosages may
appear arbitrary. By deﬁnition, atypical
neuroleptic dosages cannot be converted
to chlorpromazine equivalents. We there-
fore decided to use a categorisation based
on clinical experience. The distribution of
doze ranges in our sample appears rea-
sonable (22% on low, 52% on medium
and 26% on high medication dosages).
Exact dosages could only be assessed for
the time of examination.

Genetic considerations
Our data imply two hypotheses. First, our
ﬁndings underline the notion of genetic sus-
cceptibility for secondary extrapyramidal
symptoms, and second, they suggest possi-
ble shared genetic factors in primary and
secondary movement as well as in psychotic
disorders.

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REFERENCES
American Psychiatric Association (1994) Diagnostic
and Statistical Manual of Mental Disorders (4th edn)
(GSM–IV). Washington, DC: APA.
extrapyramidal reactions. JAMA, 175, 1054–1060.
Pharmacogenomics in schizophrenia: the quest for
individualized therapy. Human Molecular Genetics, 11, 2517–2530.


**CLINICAL IMPLICATIONS**

- Neuroleptic medication with a known low risk of extrapyramidal symptoms (i.e. an atypical neuroleptic) is preferable for patients with a family history of primary movement disorders, especially dystonia.
- Atypical neuroleptics are also preferable in patients under 40 years old, particularly to reduce the occurrence of painful acute dystonic reaction.
- Patients who have been exposed to long-term typical neuroleptic medication should be switched to an atypical agent even though extrapyramidal symptoms might not have been observed as yet.

**LIMITATIONS**

- Our study design must be regarded as somewhat explorative owing to the family history approach.
- Our data-set might have been too small to confirm any dosage effect.
- The small sample size might also have been the reason why we did not observe the gender effect described elsewhere of a higher prevalence of acute dystonia in men and of parkinsonism, akathisia and tardive dyskinesia in women.

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