Effects of Antipsychotic Treatment on Tardive Dyskinesia: A 6-Month Evaluation of Patients From the European Schizophrenia Outpatient Health Outcomes (SOHO) Study

Diederik E. Tenback, M.D.; Peter N. van Harten, M.D., Ph.D.; Cees J. Slooff, M.D., Ph.D.; Mark A. Belger, B.Sc.; Jim van Os, M.D., Ph.D.; and the SOHO Study Group

Objective: To compare the incidence and persistence of tardive dyskinesia between patients diagnosed with schizophrenia (ICD-10 and/or DSM-IV) who were treated with second-generation antipsychotics and first-generation antipsychotics in routine clinical practice.

Method: The European Schizophrenia Outpatient Health Outcomes (SOHO) study is a 3-year, prospective, observational study. Each country had a start date for patient enrollment before October 2000. All enrollment was completed by June 30, 2001. A simple, global measure of tardive dyskinesia was rated by participating clinicians. For the current analysis, data at baseline, 3 months, and 6 months were analyzed using a generalized estimating equation model.

Results: Second-generation antipsychotics conferred a lower risk for tardive dyskinesia at 6 months than first-generation antipsychotics (0.9% vs. 3.8%, odds ratio [OR] = 0.29, 95% confidence interval [CI] = 0.18 to 0.46). In addition, patients with tardive dyskinesia at baseline who were receiving second-generation antipsychotics were less likely than patients receiving first-generation antipsychotics to have tardive dyskinesia symptoms at 6 months (43.6% vs. 60.8%, OR = 0.50, 95% CI = 0.30 to 0.85). A sensitivity analysis suggested no bias related to pharmaceutical industry financial support.

Conclusion: The results suggest that the relative advantage of second-generation antipsychotics in terms of lower rates of incidence and persistence of tardive dyskinesia, observed in technical randomized controlled trials, generalizes to routine clinical care.

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Received Oct. 28, 2004; accepted Feb. 23, 2005. *From the Psychiatric Centre Altrecht, Den Dolder, the Netherlands (Dr. Tenback); Symfora Group Psychiatric Centre, Amersfoort, the Netherlands (Dr. van Harten); the Department of Psychotic Disorders, Mental Health Centre Drenthe, Assen, the Netherlands (Dr. Slooff); European Commercialisation Statistics, Eli Lilly and Company Limited, Windlesham, Surrey, U.K. (Mr. Belger); and the Department of Psychiatry and Neuropsychology, South Limburg Mental Health Research and Teaching Network, European Graduate School of Neuroscience (EURON), Maastricht University, Maastricht, the Netherlands, and Division of Psychological Medicine, Institute of Psychiatry, London, U.K. (Dr. van Os).*

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Members of the SOHO Study Group are listed at the end of the article.

Corresponding author and reprints: Jim van Os, M.D., Ph.D., Department of Psychiatry and Neuropsychology, Maastricht University, P.O. Box 616 (DRT 10), 6200 MD Maastricht, the Netherlands (e-mail: j.vanos@sp.unimaas.nl).

Antipsychotic treatment is a major risk factor for tardive dyskinesia.[1,2] In the course of antipsychotic treatment for patients with a first episode of schizophrenia, about 18% develop tardive dyskinesia after 4 years.[3] A prevalence of tardive dyskinesia of up to 58% in outpatients with schizophrenia has been reported.[4]

The second-generation antipsychotics are described as "atypical" because of a hypothesized lesser propensity to cause extrapyramidal symptomatology (EPS), including tardive dyskinesia, compared with first-generation antipsychotics.[1,5] Several studies focusing on tardive dyskinesia reported a lower rate of treatment-emergent tardive dyskinesia in patients treated with second-generation antipsychotics in comparison with patients treated with first-generation antipsychotics.[6,7] Recent meta-analytic work summarizing effect sizes from studies that primarily included randomized controlled trials (RCTs) confirms that second-generation antipsychotics as a group confer a lower risk for tardive dyskinesia than do first-generation antipsychotics.[1] However, to what degree such findings from technical efficacy RCTs that include selected patient populations and have very high attrition rates can be generalized to routine clinical practice remains unknown.

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The aim of the current study, therefore, was to examine, in routine clinical practice, the rate of emergence and persistence of tardive dyskinesia and the effects of second-generation antipsychotics and first-generation antipsychotics on these rates. To this end, we used data from the European Schizophrenia Outpatient Health Outcomes (SOHO) study, a large observational study conducted in 10 European countries. Since the study was pharmaceutical industry sponsored, a sensitivity analysis was conducted to examine possible observer bias.

METHOD

Design and Patients

The SOHO study is an ongoing, 3-year, prospective, observational health outcome study of the treatment of schizophrenia in Europe. The study is being conducted currently in 10 European countries (Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain, and the United Kingdom). Each country had a start date for patient enrollment before October 2000. All enrollment was completed by June 30, 2001. Enrollment followed a nonrandomized process to provide 2 patient cohorts of approximately equal size: patients with schizophrenia defined according to ICD-10 and/or DSM-IV who initiated or changed to treatment with olanzapine or an antipsychotic other than olanzapine. Patients were enrolled after a treatment decision was made independent from participation in the study. Entry criteria were (1) initiating or changing antipsychotic medication for the treatment of schizophrenia and (2) presenting within the normal course of care in the outpatient setting.

Patients were included regardless of whether the new antipsychotic drug was substituted for a previous medication or was an addition to existing treatment. Data were collected using a data collection form with a selection of measures that considered simplicity and ease of use with no training requirement. Investigators assessed the tardive dyskinesia and EPS (acute dystonia/akathisia/parkinsonism) that they judged to be associated with antipsychotic drug treatment. Tardive dyskinesia and EPS were rated on a 4-point scale: 1 = not present, 2 = present but does not significantly interfere with patient's functioning or health-related quality of life, 3 = present and significantly interferes with patient's functioning or health-related quality of life, and 4 = present and interference with functioning outweighs therapeutic effect. For the purpose of the current analyses, the variable was treated as dichotomous (present [2, 3, and 4] vs. not present [1]). *Incidence* refers to tardive dyskinesia not present at baseline and scored present at the 3- or 6-month follow-up, and *persistence* refers to tardive dyskinesia scored present at baseline and at the 3- and 6-month visits.

Alcohol and/or substance dependence or abuse was rated dichotomously if the investigator judged patients to suffer from diagnosable alcohol and/or substance dependence or abuse. Full details of the SOHO study design have been published previously.[8]

Ethics Committee approval and informed consent were obtained as required by national regulations.

Data Analysis

To assess outcomes associated with second-generation or first-generation antipsychotics in actual practice, treatment cohorts were defined according to the class of antipsychotic initiated at the baseline assessment. Each individual had 3 observations: baseline, 3-month follow-up, and 6-month follow-up. The proportions of patients at the 6-month visit who remained on their initial antipsychotic without adding any additional antipsychotics, remained on their initial antipsychotic and had an additional antipsychotic added, and switched antipsychotics were summarized by cohort. Patients for whom a new antipsychotic was initiated without discontinuation of their existing antipsychotic were assigned to the cohort corresponding to the class of the newly initiated antipsychotic.

A generalized estimating equation model with a logit link and a repeated-measurements approach was used to model the data. The unstructured covariance matrix was used in the analysis. Prognostic covariates were agreed upon by the SOHO advisory board and included in the model. Covariates included baseline age, sex, length of illness, prior (and type of) antipsychotic, monotherapy or combination antipsychotic therapy, reasons for change of antipsychotic, alcohol abuse, and EPS. (A full list is available on request.) Pairwise comparisons of the first-generation antipsychotic cohort with the second-generation antipsychotic cohort at the 6-month visit using the cohort-by-visit interaction term were calculated. Odds ratios [ORs] and 95% confidence intervals [CIs] are reported for each of these comparisons. Approximately 80% of the sample was included in the model, due to missing values in the covariates.

A sensitivity analysis was conducted by examining effect sizes of second-generation antipsychotics excluding individuals who were initiated on treatment with olanzapine.

RESULTS

A total of 10,972 patients were enrolled in the SOHO study, of whom 9912 were considered in the analysis of tardive dyskinesia at baseline. Approximately 9% (N = 912) were diagnosed with existing tardive dyskinesia. Of the 9912 patients with tardive dyskinesia data at baseline, 8632 patients were eligible for analysis at 6 months (a total of 8774 patients had data at 6 months, but data on tardive dyskinesia were missing for 142 of these patients). This sample of 8632 constituted the final risk set in which all analyses were conducted.

Table 1. Baseline Demographics by Cohort for Patients With Schizophrenia Receiving First-Generation or Second-Generation Antipsychotics

Variable	Second-Generation Antipsychotic		First-Generation Antipsychotic
	Any	Non-Olanzapine	
Patients, N	8739	3363	1173
Female, %	41.7	42.6	45.8
Age, mean ± SD, y	40.0 ± 13.2	39.9 ± 13.0	41.5 ± 12.3
Age at first contact, mean ± SD, y	28.9 ± 10.8	28.2 ± 10.2	29.1 ± 10.2
In first episode of schizophrenia, %	10.8	8.6	5.8
Antipsychotic upon presentation, %[a]	74.2	77.2	76.6
Extrapyramidal symptomatology, %	38.6	37.7	34.4
Tardive dyskinesia scale rating,[b] %			
1	90.6	90.5	90.8
2	7.5	7.8	7.7
3	1.6	1.3	1.4
4	0.3	0.4	0.1
Total with tardive dyskinesia present	9.4	9.5	9.2
Substance dependence, %	2.6	2.4	2.8
Alcohol abuse, %	2.9	3.3	3.1

[a]Percentage of patients who received antipsychotic treatment during the 6 months prior to study enrollment.
[b]The tardive dyskinesia scale was scored as follows: 1 = not present, 2 = present but does not significantly interfere with patient's functioning or health-related quality of life, 3 = present and significantly interferes with patient's functioning or health-related quality of life, 4 = present and interference with functioning outweighs therapeutic effect.

Baseline Patient Characteristics

Despite the absence of randomization in the study, there were only few differences between the treatment cohorts in any of the baseline demographic characteristics as shown in Table 1. The sample mean (SD) age was 40.1 (13.1) years, and 42.2% of the patients were female. With respect to baseline severity of schizophrenia, the overall mean (SD) score on the Clinical Global Impressions scale (CGI)[9] was 3.42 (1.01), between mildly and moderately ill. In the last 6 months prior to the study enrollment, roughly two thirds of patients received first-generation antipsychotics (61.7%), while 41.8% received second-generation antipsychotics and 15.9% had no antipsychotic treatment. Reasons for change in antipsychotic treatment (not mutually exclusive) were lack of effectiveness (63.6%), intolerability (34.6%), noncompliance (15.2%), and patient request (28.4%). A relatively large proportion of patients (37.9%) experienced EPS at baseline.

Six-Month Follow-Up

Attrition at 6 months was low: 88.5% of baseline patients (8774/9912) were interviewed at 6 months. Most patients (83%) remained on the antipsychotic treatment that was initiated at baseline. Of these, 65% received monotherapy (Table 2).

The rate of emerging tardive dyskinesia was higher in the first-generation antipsychotic than in the second-generation antipsychotic group: 3.8% versus 0.9% (OR = 0.29, 95% CI = 0.18 to 0.46). Similarly, persistence of tardive dyskinesia was more frequent in the first-generation antipsychotic than the second-generation antipsychotic cohort: 60.8% versus 43.6% (OR = 0.50, 95% CI = 0.30 to 0.85).

Sensitivity Analyses

Excluding patients treated with olanzapine at the 6-month visit yielded a somewhat attenuated but essentially similar pattern of results. The incidence of tardive dyskinesia for first-generation antipsychotics versus second-generation antipsychotics was 3.8% versus 1.4% (OR = 0.43, 95% CI = 0.25 to 0.72). Persistence of tardive dyskinesia for first-generation antipsychotics versus second-generation antipsychotics was 60.8% versus 46.7% (OR = 0.60, 95% CI = 0.33 to 1.11).

DISCUSSION

Findings

Treatment with second-generation antipsychotics was associated with a lower incidence and a lower persistence of tardive dyskinesia compared to treatment with first-generation antipsychotics. A sensitivity analysis excluding the product of the sponsor (olanzapine) yielded slightly reduced and statistically somewhat more imprecise effect sizes, but overall the pattern of the findings was similar. The results concur with those from RCTs[1] and generalize to routine clinical practice. Furthermore, in patients with existing tardive dyskinesia, treatment with second-generation antipsychotics is more effective than treatment with first-generation antipsychotics with respect to clinical improvement. No RCT data or conclusive evidence is available for second-generation antipsychotics on reduction of existing tardive dyskinesia.[10] However, a number of smaller studies and case reports are suggestive for an effect of second-generation antipsychotics on reduction of existing tardive dyskinesia.[11] The current report, however, has a number of advantages over prior work, including presence of a control group, longer duration of treatment, and sufficient statistical power.

Methodological Issues

The results should be interpreted in the context of several methodological limitations. The measure for tardive dyskinesia used is likely to cause underreporting. Weiden et al.[12] compared clinicians' with clinical researchers' recognition of the major extrapyramidal syndromes using standardized ratings; the major finding was a high rate of clinical underrecognition of all major extrapyramidal syndromes, especially tardive dyskinesia. In the current study, the patients presented themselves fully dressed in

Table 2. Treatment Patterns at 6 Months After Baseline[a]

Variable	Second-Generation Antipsychotic					First-Generation Antipsychotic		2+ Antipsychotics[b]
	Olanzapine	Risperidone	Quetiapine	Amisulpride	Clozapine	Per Os	Depot	
N at baseline	5376	1918	790	328	327	688	485	268
N at 6 months	4716	1711	690	282	301	625	449	233
Patients with 6-month data	87.7	89.2	87.3	86.0	92.0	90.8	92.6	86.9
On monotherapy after baseline visit	86.2	87.1	82.4	84.8	89.0	72.5	77.1	…
Outcome at 6 months								
Still taking drug initiated at baseline	89.1	84.4	75.2	77.6	87.4	75.5	80.8	…
On monotherapy	71.8	68.0	53.3	58.9	74.4	50.6	56.3	…
Any concomitant medication use	47.9	62.8	56.5	44.6	58.8	60.7	53.1	62.2
Anticholinergic use	8.7	23.6	12.5	12.1	10.0	26.0	29.0	25.3
Antidepressant use	19.5	20.7	22.5	21.8	20.9	17.9	12.5	19.3
Anxiolytic/hypnotic use	28.9	37.2	35.5	21.8	34.6	36.9	27.2	32.2
Mood stabilizer use	9.7	9.8	12.5	8.2	17.9	12.3	7.6	14.2

[a]Values are percentages unless otherwise noted.
[b]More than 1 antipsychotic started at baseline.

regular outpatient settings where a more formal physical examination may not be standard. Moreover, treatment was defined by cohorts according to the class of antipsychotic initiated at the baseline assessment. The results presented here should be attributed to these cohorts as opposed to the subsequent effects that may have resulted from changes in medication regimens after baseline for individual patients.

Although sponsored observational trials are potentially subject to bias, the results suggest that the comparison between first-generation antipsychotics and second-generation antipsychotics, which in the context of this trial arguably may not be biased, is in favor of the second-generation antipsychotics in terms of 6-month risk of tardive dyskinesia. The position of second-generation antipsychotics as a treatment for existing tardive dyskinesia requires further investigation; however, in the absence of other safe and effective therapies, the data suggest that second-generation antipsychotics may be useful.

Drug names: clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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