Evidence That Early Extrapyramidal Symptoms Predict Later Tardive Dyskinesia: A Prospective Analysis of 10,000 Patients in the European Schizophrenia Outpatient Health Outcomes (SOHO) Study

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Objective: This study examined whether extrapyramidal symptoms predict incidence of tardive dyskinesia 1 year later.

Method: Simple, global measures were used to rate extrapyramidal symptoms and tardive dyskinesia in a prospective, observational health outcomes study. Baseline and 3-, 6-, and 12-month data on 9,298 patients were analyzed by using a Cox proportional-hazard model. Onset of tardive dyskinesia was examined in two groups: 1) no tardive dyskinesia at baseline (broad risk set) and 2) no tardive dyskinesia at baseline and 3 months (narrow risk set).

Results: Baseline extrapyramidal symptoms predicted later onset of tardive dyskinesia (broad risk set: hazard ratio=2.0, narrow risk set: hazard ratio=1.6). In analyses adjusted for age, gender, and medication exposure, this effect size was not reduced. About half of patients who developed tardive dyskinesia had earlier extrapyramidal symptoms.

Conclusions: Although the association of tardive dyskinesia and extrapyramidal symptoms is significant, extrapyramidal symptoms do not robustly identify individuals at high risk for tardive dyskinesia. However, drug regimens and disease processes that increase extrapyramidal symptoms are likely to result in increased risk of tardive dyskinesia.

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Research suggests that antipsychotic-induced extrapyramidal symptoms, such as parkinsonism, dystonia, and akathisia, increase the risk for tardive dyskinesia in elderly patients (1–3). However, only scant (4) and sometimes conflicting (5) evidence exists that younger patients exposed to antipsychotics are similarly at risk. Indirect evidence exists, however, as meta-analyses noted a lower risk of extrapyramidal symptoms (6) and lower risk of tardive dyskinesia (7) in patients treated with second-generation antipsychotics. We used prospective data from a large cohort of patients treated in routine clinical settings to 1) calculate incidence rates of tardive dyskinesia and 2) examine early extrapyramidal symptoms as a predictor of tardive dyskinesia incidence.

Method

The Schizophrenia Outpatient Health Outcomes (SOHO) study is a 3-year prospective, observational health outcome study of the treatment of schizophrenia in Europe. Treatment regimens were decided by the treating psychiatrists; half the patients were selected because their treatment was to be changed to olanzapine, and half were selected because their treatment was to be changed to other antipsychotic drugs (8). Data were collected with a selection of measures that were simple and easy to use with no required training. Investigators assessed the tardive dyskinesia and extrapyramidal symptoms (defined as dystonia, akathisia, or parkinsonism) that they observed during treatment with antipsychotic medication. Tardive dyskinesia and extrapyramidal symptoms were separately 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 outweighs therapeutic effect. Full details of the study design have been published previously (8). Ethics committee approval and informed consent were obtained as required by national regulations.

Each individual had four observations: baseline and 3-, 6-, and 12-month follow-up. For the purposes of these analyses, extrapyramidal symptoms and tardive dyskinesia were treated as dichotomous outcomes; present was defined as a score of 2, 3, or 4, and not present was defined as a score of 1. In order to take into account the waxing and waning course of tardive dyskinesia, a sensitivity analysis approach was used with two different risk sets: one including all individuals with no tardive dyskinesia at baseline (broad risk set) and one including participants with no tardive dyskinesia at baseline and no tardive dyskinesia at 3 months (narrow risk set).

In order to calculate the incidence rates of tardive dyskinesia, three time bands were constructed: baseline to 3 months, 3 to 6 months, and 6 to 12 months. Each person was allocated person-time according to the interval from baseline to the visit in which the patient was diagnosed with tardive dyskinesia or, if no such diagnosis was made, to the last visit.

Incidence rates for each time band were calculated by dividing the number of incident cases by the person-years. The total incidence of tardive dyskinesia was calculated by dividing the total number of incident cases of tardive dyskinesia by the total person-years.

To assess extrapyramidal symptoms as a risk factor for tardive dyskinesia, Cox proportional-hazard regression analysis was used. Prognostic covariates were those agreed on by the study's advisory board, and additional confounders were included as guided by previous literature (2, 9). Thus, apart from the predictor variable (extrapyramidal symptoms at baseline), the covariates

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included treatment with second- or first-generation antipsychotics (pre- and postbaseline); scores on the Clinical Global Impression positive, negative, cognitive, and depressive items at baseline; sex and age at baseline and their interaction term; age at first contact; and first episode status (the full list of covariates is available on request). Approximately 80% of the sample was included in the model with all covariates, and the remainder were excluded because of missing values for the covariates.

Associations between extrapyramidal symptoms and tardive dyskinesia were expressed as hazard ratios, together with their 95% confidence intervals (CIs). Sensitivity and specificity values for baseline extrapyramidal symptoms were also calculated as a "test" for follow-up tardive dyskinesia. All analyses used the Stata program (10).

Results

A total of 9,298 patients had data for baseline extrapyramidal symptoms and for tardive dyskinesia at baseline and 3-month follow-up; 8,036 patients had data on tardive dyskinesia at all four measurement occasions. In the group of 9,298 patients, the prevalence rates of tardive dyskinesia and extrapyramidal symptoms at baseline were 9.2% and 37.8%, respectively. The mean age was 40.1 years (SD=13.1), and 57.6% of the patients were men, 9.8% were experiencing their first episode, and 37.6% had been exposed to a second-generation antipsychotic in the 6 months before enrollment; this proportion rose to 85.8% after baseline.

The total incidence for tardive dyskinesia was 3.0% (95% CI=2.6%–3.4%) in the broad risk set and 1.6% (95% CI=1.4%–1.9%) in the narrow risk set. In the unadjusted analyses, baseline extrapyramidal symptoms predicted tardive dyskinesia (broad risk set: hazard ratio=2.0, 95% CI=1.6–2.6; narrow risk set: hazard ratio=1.6, 95% CI=1.1–2.3). In the adjusted analyses, this effect size was not reduced (broad risk set: hazard ratio=2.3, 95% CI=1.6–3.2; narrow risk set: hazard ratio=2.1, 95% CI=1.3–3.3).

The sensitivity of baseline extrapyramidal symptoms as a test for follow-up tardive dyskinesia, i.e., the percent of patients who developed tardive dyskinesia who had been observed to have extrapyramidal symptoms at baseline, was around 50% (broad risk set: 53%; narrow risk set: 46%). The specificity for both broad and narrow tardive dyskinesia, i.e., the percent of subjects who did not develop tardive dyskinesia who had not been observed to have extrapyramidal symptoms, was 67%.

Discussion

Extrapyramidal symptoms predicted onset of tardive dyskinesia, suggesting important clinical implications. The validity of the finding, however, hinges on the validity of the clinical ratings of extrapyramidal symptoms and tardive dyskinesia. The measures used are simple; the assessment of extrapyramidal symptoms does not differentiate among akathisia, dystonia, and parkinsonism, nor does it give strict criteria for how to diagnose these syndromes. It could be argued that clinicians' assessments of extrapyramidal symptoms at baseline represent misclassification of tardive dyskinesia, because clinicians cannot distinguish between extrapyramidal symptoms and tardive dyskinesia. Although this cannot be excluded, and a degree of misclassification may have occurred, it could have explained the results only if clinicians had been misclassifying extrapyramidal symptoms and tardive dyskinesia inconsistently. This is unlikely to have been the case, as clinicians do not change randomly in their concepts of what constitutes the clinical presence of extrapyramidal symptoms and tardive dyskinesia. Furthermore, the most common form of extrapyramidal symptoms is parkinsonism, and it is unlikely that clinicians fail to differentiate between the hypokinetic syndrome parkinsonism and the hyperkinetic syndrome tardive dyskinesia. Akathisia, however, albeit less prevalent than parkinsonism, can more easily be mistaken for tardive dyskinesia.

Previous conflicting results in patients with first-episode schizophrenia could be due to limited statistical power (5), and our results concur with most previous work suggesting that extrapyramidal symptoms are a risk factor for tardive dyskinesia (1–4). Given the fact that the sensitivity and specificity of baseline extrapyramidal symptoms as a test for later tardive dyskinesia were too low to justify a high-risk prevention strategy (i.e., targeting individuals with existing extrapyramidal symptoms to prevent tardive dyskinesia), the clinical implication of the findings is, instead, that strategies aimed at reducing risk factors for extrapyramidal symptoms in the whole population of patients using antipsychotics are most likely to effectively reduce the morbidity force of tardive abnormal movements. Examples of such strategies are limitations on antipsychotic dose and selection of drugs and drug combinations with fewer extrapyramidal symptom effects.

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