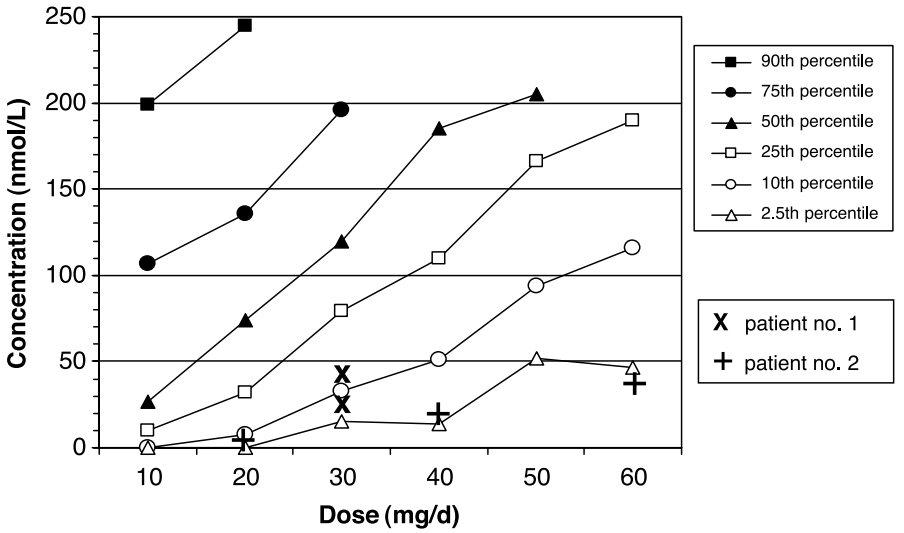

FIGURE 1. Distribution of serum concentrations of paroxetine at doses of 10 to 60 mg/d, based on a total of 1482 routine therapeutic drug-monitoring samples. The numbers of samples included were 45 for the dose 10 mg/d, 578 for the dose 20 mg/d, 159 for the dose 30 mg/d, 470 for the dose 40 mg/d, 41 for the dose 50 mg/d, and 154 for the dose 60 mg/d. Other doses were used in 35 cases. For clarity, the 50th, 75th, and 90th percentile values are omitted for the higher doses. The serum concentrations of the 2 CYP2D6 ultrarapid metabolizers are displayed with the symbols X (first patient, 2 samples) and + (second patient, 3 samples).

serum concentration in relation to the prescribed dose as it eases the process of distinguishing between ultrarapid metabolism and noncompliance. It should, however, be pointed out that genotyping does not identify all subjects who are phenotypically ultrarapid metabolizers. In previous studies, a relatively small proportion of those with the ultrarapid metabolizer phenotype is identified by genotyping for the duplicated or multiduplicated allele,[9,10] depending on the definition of the cutoff point between phenotypically extensive and phenotypically ultrarapid metabolizers. However, if the subject is identified as an intermediate or poor metabolizer by genotyping, noncompliance is obviously the most likely explanation. It would be of interest to conduct a prospective study genotyping all subjects with paroxetine concentrations in the lower range, for example, below the 5th or the 10th percentiles, to further elucidate this issue.

Cüneyt Güzey, MD*†
Olav Spigset, MD, PhD*†
*Department of Clinical Pharmacology, St Olav University Hospital, Trondheim, Norway and †Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway

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The Association Between Cytochrome P450-2D6 Genotype and Prescription of Antiparkinsonian Drugs in Hospitalized Psychiatric Patients Using Antipsychotics

A Retrospective Follow-up Study

To the Editors:

Cytochrome P450-2D6 (CYP2D6) genotype may be associated with several adverse effects of antipsychotic drugs. Approximately 5% to 10% of the white population can be classified as poor metabolizers (PM) by diminished CYP2D6 activity. These patients may be at higher risk of dose-dependent adverse effects because most antipsychotic drugs are at least partly metabolized by CYP2D6.[1] One of the most frequently occurring dose-dependent adverse effects in users of antipsychotic drugs are some of the extrapyramidal syndromes (EPS) (ie, parkinsonism, akathisia, and dystonia). In several studies, an association between CYP2D6 genotype and EPS has been established, although results are conflicting.[1] When a patient experiences EPS, the treating psychiatrist can decide

to switch to another antipsychotic drug. However, in a previous study published in this journal, we did not find an association between CYP2D6 genotype PM and more frequent switching of antipsychotic drugs compared with extensive metabolizers (EM) for CYP2D6. As a possible explanation, we suggested that psychiatrists prefer to treat EPS (parkinsonism, akathisia, and dystonia, but not tardive dyskinesia) with antiparkinsonian drugs rather than to switch to another drug.[2] The objective of this study is to test this hypothesis by investigating whether in a group of antipsychotic users, PMs for CYP2D6 are more frequently treated with antiparkinsonian drugs compared with EMs for CYP2D6.

METHODS

The study was conducted in 2 psychiatric hospitals with approximately 450 beds for long-stay patients with chronic psychiatric disorders. The study protocol was reviewed and approved by an independent medical ethical committee (TPWO, Arnhem, The Netherlands).

A retrospective follow-up design was used to assess the association between CYP2D6 genotype and EPS as an adverse effect of antipsychotic drugs. The potential study population consisted of 138 long-stay patients of whom the CYP2D6 genotype was determined in a previous study.[2]

Patients were eligible for the present study if at least 1 antipsychotic drug that is metabolized by CYP2D6 was started at least 30 days after the start of the observation period and at least 90 days before the end of the observation period. This resulted in the inclusion of 129 patients. Prescription data were collected from April 1988 until February 2005. Primary end point of this study was the start of an anticholinergic antiparkinsonian drug (either biperidene or trihexyphenidyl) at least 7 days after the start of a drug episode of an antipsychotic drug at least partly metabolized by CYP2D6. Biperidene and trihexyphenidyl are indicated for the treatment of EPS caused by antipsychotic drugs. The interval of 7 days was chosen to prevent inclusion of prescriptions of antiparkinsonian drugs for prophylactic use. Antipsychotic drug episodes during which antiparkinsonian drugs were started within 7 days after the start of the antipsychotic drug were excluded from analysis. In case of treatment with 2 or more antipsychotic drugs at the same time, only the drug episode with a starting date closest to the start of biperidene or trihexyphenidyl was taken into account.

We classified the CYP2D6 metabolic pathway of each prescribed antipsychotic drug according to the available published evidence up to April 2005. Antipsychotic drugs for which an in vivo relationship between CYP2D6 genotype and pharmacokinetic properties has been documented were classified as primary CYP2D6 drugs (haloperidol, perphenazine, risperidone, sertindol, thioridazine, and zuclopenthixol). Antipsychotic drugs for which either in vivo evidence exists that these are partly metabolized by CYP2D6 or in vitro evidence of metabolism by CYP2D6 was available were classified as partly CYP2D6 drugs (chlorpromazine, clozapine, pimozide, olanzapine, and quetiapine). Episodes of other antipsychotic drugs were not included.

Primary determinant was the CYP2D6 genotype. The CYP2D6 genotype was determined by polymerase chain reaction (PCR)–restriction fragment length polymorphism CYP2D6*3(A), CYP2D6*4(B), CYP2D6*6(T), CYP2D6*7(E), and CYP2D6*8(G) were investigated using a long-distance and multiplex PCR as described by Stuven et al.[3] The presence of gene duplication that may lead to ultrarapid metabolism was analyzed by an allele-specific PCR and was performed as described by Lovlie et al.[4] Patients were defined as PM if they were homozygous or heterozygous for noncoding alleles. Patients were defined as ultrarapid metabolizers (UM) if gene duplication was detected and mutant alleles were absent. All other patients were classified as EM.

The relative risk of treatment with biperidene or trihexyphenidyl was estimated with a logistic mixed-effects model and expressed as an odds ratio (OR) with a 95% confidence interval (CI) using EM as the reference group. The mixed-effects model was used because there was more than 1 drug episode per patient, and therefore, the data were not independent. Mixed-effects models make adjustments for multiple measurements in the same subject. Data were analyzed for all included episodes of antipsychotic drug treatment (primary CYP2D6 drugs and partly CYP2D6 drugs) and separately for antipsychotics primarily metabolized by CYP2D6. Finally, data were investigated for the potential confounders age, sex, and prescribed daily dose. A P value of 0.05 or less was regarded as significant. Data were analyzed using S-plus 6.2 CorrelatedData Library (insightful), www.insightful.com.[5,6]

RESULTS

In our study population (N = 129), we found poor or ultrarapid metabolism in 12.4% of the included patients (10.1% PM, n = 13, and 2.3% UM, n = 3). The included patients were mainly white (>95%), with a mean age of 54 years (SD, 16.3), and 46.5% (n = 60) were men. In total, there were 267 drug episodes of antipsychotic drugs at least partly metabolized by CYP2D6 during the observation period. After exclusion of drug episodes with prophylactic use, 164 drug episodes were available for analysis. Antiparkinsonian drugs were started in 32 (20%) drug episodes of antipsychotic drugs (primary CYP2D6 drugs, 69%, n = 22; partly CYP2D6 drugs, 31%, n = 10). Furthermore, antiparkinsonian drugs were started in 41% (9/22), 16% (22/139), and 33% (1/3) of the observed drug episodes in PMs, EMs, and UMs, respectively.

Table 1 shows that for antipsychotic drugs, CYP2D6 genotype PM was associated with a more frequent prescription of antiparkinsonian drugs (OR, 3.68; 95% CI, 1.40–9.65) in patients treated with antipsychotics primary or partly metabolized by CYP2D6. Analysis restricted to antipsychotics primarily metabolized by CYP2D6 showed a nonsignificant association with more frequent prescription of antiparkinsonian drugs (OR, 2.38; 95% CI, 0.69–8.28). The number of drug episodes in patients with CYP2D6 genotype UM was inadequate to allow analysis. Adjustments for age, sex, and prescribed daily dose did not significantly change the results obtained.

DISCUSSION

In this retrospective follow-up study, we found that in daily clinical

TABLE 1. Relative Risk for Treatment with Antiparkinsonian Drugs in Users of Antipsychotics

Antipsychotics	Drug Episodes with Start of Antiparkinsonian Drug Treatment (%)	OR (95% CI) of Treatment with Antiparkinsonian Drugs
EM	16 (22/139)	1 (reference)
PM	41 (9/22)	3.68 (1.57–8.65)

practice, PMs for CYP2D6 treated with antipsychotics use antiparkinsonian drugs more frequently compared with EMs for CYP2D6. In psychiatric patients, antiparkinsonian drugs are almost exclusively used for the treatment of EPS (parkinsonism, akathisia, and dystonia, but not tardive dyskinesia) and can therefore be considered a valid marker of EPS.

There are limitations to our findings. First, we could only study 3 patients classified as UM and 13 patients classified as PM for CYP2D6. Despite these low numbers, significant results were obtained for PMs, but these need confirmation in a larger number of patients. The number of UMs and the corresponding records of antiparkinsonian drugs were too low to allow formulation of any conclusions. Second, the reason for prescribing antiparkinsonian drugs was not recorded. Antiparkinsonian drugs can be prescribed for prophylactic use after prescription of antipsychotic drugs with a high potential of EPS. We prevented the inclusion of prophylactic use of antiparkinsonian drugs in the analysis by exclusion of drug episodes of antiparkinsonian drugs within 7 days after starting an antipsychotic drug. Third, we could only find a significant association between CYP2D6 genotype and prescription of antiparkinsonian drugs in patients using antipsychotics primarily or partly metabolized by CYP2D6. The analysis that was restricted to antipsychotics primarily metabolized by CYP2D6 only showed the same elevated risk, but did not have sufficient power to find a significant association. Future studies should include more patients (~250–300) to allow adequate analysis of data that are restricted to antipsychotics primarily metabolized by CYP2D6.

The findings of previous studies investigating the association between CYP2D6 genotype and EPS are inconsistent. Several studies found a statistically significant association,[1,7,8] but other studies could not replicate these results.[1,9,10] Schillevoort et al[8] found an association between antiparkinsonian drugs and CYP2D6 genotype only in patients using antipsychotics primarily metabolized by CYP2D6. However, this result was established in a population screened for CYP2D6 upon admission, and therefore, the treating psychiatrist could consider this information. In that study, it was possible that the treating psychiatrist chose to treat EPS with antiparkinsonian drugs in PMs in the case of antipsychotics primarily metabolized by CYP2D6, but to switch to another antipsychotic in the case of antipsychotics not primarily metabolized by CYP2D6 because the cause of EPS is les likely, thereby underestimating the real risk in PMs. In our population, the CYP2D6 genotype was unknown to the treating psychiatrist.

The increased prescription rates of antiparkinsonian drugs in PMs for CYP2D6 can be seen as a determinant for unsatisfactory response in these patients. In an earlier study, we investigated whether PMs for CYP2D6 switched more often to other antidepressant drugs or antipsychotic drugs compared with EMs for CYP2D6. We found an association between CYP2D6 genotype PM and more frequent switching of antidepressants, but we could not find this association for switching of antipsychotic drugs.[2] These results suggested that the treating psychiatrist probably chose to treat EPS with antiparkinsonian drugs, instead of switching to another drug in patients using antipsychotic drugs.

Taken together, the CYP2D6 genotype PM is associated with an increased risk of EPS as measured by a more frequent prescription of antiparkinsonian drugs compared with EMs for CYP2D6.

Genotyping psychiatric patients for CYP2D6 before starting pharmacotherapy may identify patients at higher risk for dose-dependent adverse events. If CYP2D6 genotype information is available before starting pharmacotherapy, an individualized advice for the choice of drug and dosage is possible, thereby reducing the risk of EPS and the treatment of antiparkinsonian drugs thereof.

Hans Mulder, PharmD*†
Frederik W. Wilmink, MD, PhD‡
Svetlana V. Belitser*
Antoine C.G. Egberts, PhD*
*Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht; †Department of Clinical Pharmacy, Wilhelmina Hospital, Assen and ‡Psychiatric Hospital GGZ Drenthe, Assen, The Netherlands
hans.mulder@wza.nl

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Treatment of Neuroleptic-induced Tardive Dyskinesia with Levetiracetam

A Case Series

To the Editors:

Neuroleptic-induced tardive dyskinesia (TD) is a persistent, sometimes irreversible, side effect of neuroleptic therapy characterized by abnormal movements, including lingual and orofacial dyskinesia, grimacing, tics, choreic movements, athetosis, and dystonia.[1] Although atypical neuroleptics (eg, clozapine, risperidone, olanzapine) are less likely to produce neuroleptic-induced TD than typical agents,[2,3] neuroleptic-induced TD has been reported in approximately 1% of patients treated with atypical agents.[4,5] The pathophysiology of TD remains poorly understood; however, numerous theories have been proposed, including dopamine receptor supersensitivity[6] and dysfunction of γ-aminobutyric acid–mediated neurotransmission.[7]

Levetiracetam is an antiepileptic drug (AED) with novel mechanisms of action that have not been fully elucidated.[8] Levetiracetam was considered a candidate to reduce abnormal movements in TD.[9] In addition, levetiracetam has been extensively used as an adjunctive therapy because of its favorable safety profile and pharmacokinetic properties, including minimal hepatic metabolism associated with a low risk of drug interactions.[8]

In this series of patients, levetiracetam was added to each subject's usual therapeutic regimen in an open-label, naturalistic design. A total of 17 patients were enrolled in the order of their presentation at the DeKalb Community Service Board (Atlanta, Ga) within a 6-month period. Patients were provided with a complete description of the trial, and informed consent was obtained. Seven patients were treated on an inpatient basis, and 10 were treated on an outpatient basis. Eight men and 9 women, ranging in age from 24 to 70 years (mean, 50 years), were included in this analysis. Of these 17 patients, 13 were diagnosed with schizophrenia, 3 with schizoaffective disorder, and 1 with bipolar disorder.

No changes were made in the patients' antipsychotic treatment regimens during the course of the trial. Drugs used during the trial included haloperidol (n = 8), risperidone (n = 4), clozapine (n = 1), olanzapine (n = 3), fluphenazine (n = 3), aripiprazole (n = 2), and quetiapine (n = 2). Other concomitant drugs included AEDs (valproic acid, n = 2; carbamazepine, n = 2; gabapentin, n = 1), other drugs to treat neuroleptic-induced side effects (amantadine, n = 1; benztropine, n = 4), and antidepressants or mood stabilizers (bupropion, n = 2; buspirone, n = 1; escitalopram, n = 2; mirtazapine, n = 1; and lithium, n = 1).

Levetiracetam was added to each patient's baseline treatment regimen, starting at a dose of 250 mg BID. The dose of levetiracetam was titrated to response based upon the Abnormal Involuntary Movement Scale 1–10 (AIMS) and its tolerability, with a more rapid titration schedule for inpatients than for outpatients.

AIMS was used to assess clinical response to treatment with levetiracetam. Using a ranking of 0 (none) to 5 (severe), the scale evaluates facial, oral, extremity, and trunk movements. Global judgments of the severity, incapacitation, and patient awareness of abnormal movements are also included. The patient's dental status was also assessed. The AIMS scores of treatment with levetiracetam were measured at baseline and at least once thereafter at various times on days 1 to 196, the duration of the trial. The author, trained and experienced with the use of AIMS, was the sole rater.

The baseline AIMS score was also used to diagnose TD based on the Schooler-Kane criteria, which require a sum of 4: a score of greater than 3 on any one of the AIMS items 1 to 7 plus a score of greater than 1 on another categorical item.[10] Adverse effects were monitored and recorded during the trial.

The average dose of levetiracetam was 2089 mg/d (range, 1000–4000 mg/d). All patients experienced some improvement in symptoms of neuroleptic-induced TD with treatment with levetiracetam. The AIMS scores improved, on average, by 80% (range, 37%–100%). The average reduction in AIMS score, from 18.3 to 4.0, was statistically significant using the last observation carried forward Wilcoxon matched pairs signed rank test[11] (P = 0.00001526) (Fig. 1). The mean time to maximum improvement was 22.8 days (range, 3–105 days).

Overall, levetiracetam was generally well tolerated. Three inpatients reported ''mild'' sedation, but no dose adjustment was necessary. Dose was reduced from 4000 to 3000 mg/d for 1 outpatient who reported ''feeling depressed.'' No patient discontinued participation secondary to side effects. Five outpatients were lost to follow-up.

TD is a serious side effect of neuroleptic therapy that can impair a patient's quality of life and interfere with compliance with continued treatment—a dangerous consequence for patients who require chronic therapy. Although the use of atypical neuroleptic drugs instead of typical agents may lower the incidence of TD,[2,4,12] TD can still develop.[2,4,12] At present, TD induced by neuroleptic agents remains a serious concern,[13] and well-accepted effective treatments for this condition are lacking.

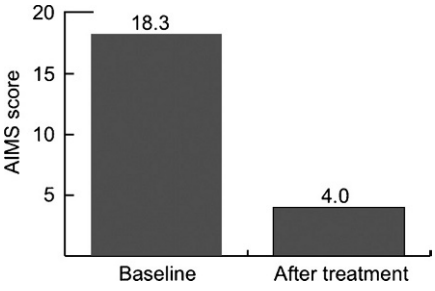

FIGURE 1. Change in average AIMS score from baseline to maximal improvement (P = 0.00001529).