TABLE 1. Changes in Psychopathological and Extrapyramidal Symptom Scores and Electrocardiographic Indices

	Baseline	After Dose Reduction	*P* (2-Tailed)
PANSS score			
Total	91.5 ± 18.7	83.6 ± 21.1*	0.0023†
Positive	22.3 ± 7.2	19.4 ± 6.9*	0.0327†
Negative	25.7 ± 4.5	24.3 ± 4.9	0.0574†
General	43.5 ± 9.5	39.9 ± 11.0*	0.0068†
DIEPSS score	8.1 ± 3.4	6.2 ± 2.8*	0.0425†
ECG indices			
Heart rate (beats per minute)	83.1 ± 14.0	72.0 ± 12.6*	0.0013‡
QTc (ms)	428.6 ± 17.0	400.6 ± 22.7*	0.0001‡
$CV_{R\text{-}R}$ (%)	2.06 ± 1.28	4.36 ± 1.83*	0.0005‡

*Values significantly differ from baseline.
†Paired nonparametric measure (Wilcoxon signed rank test).
‡Paired Student *t* test.

size examining the rate of sudden unexplained death in Japanese schizophrenics. Our data indicate a crucial need to explore if the high dose of multiple neuroleptic medications associate with an elevated risk for sudden unexplained death among Japanese schizophrenic population.

In summary, our preliminary data showed that, in Japanese schizophrenics who have been chronically ill and taking high doses of multiple neuroleptics, a careful dose reduction would not necessarily lead to psychotic deterioration. Rather, it may improve some of the psychopathological and/or the extrapyramidal symptom. In addition, the observed ECG improvements would also be a potential benefit of this procedure.

Nobutoshi Kawai, MD, PhD*
Yuriko Yamakawa, MD*
Takafumi Hori, MD, PhD†
Hirokazu Tachikawa, MD, PhD†
Takasi Asada, MD, PhD†
*Department of Clinical Psychiatry, Mitsukaido-Kosei Hospital, Mitsukaido-shi, Ibaraki and†Department of Psychiatry, Institute of Clinical Medicine, University of Tsukuba, Tsukuba-shi, Japan.
nobunenn@ka2.so-net.ne.jp

REFERENCES

1. Takei N, Inagaki A. JPSS-2 research group. Polypharmacy for psychiatric treatments in Japan. *Lancet*. 2002;360:647.
2. Yamauchi K, Baba K, Ikegami N, et al. A survey of drug utilization in psychiatric hospitals in Japan: comparison of 1973, 1979, and 1993. *Psychiatr Neurol Jpn*. 2000;102: 640–652.
3. Baldessarini RJ, Cohen BM, Teicher MH. Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychosis. *Arch Gen Psychiatry*. 1988;45:79–91.
4. Volavka J, Cooper TB, Czobor P, et al. High-dose treatment with haloperidol: the effect of dose reduction. *J Clin Psychopharmacol*. 2000;20:252–256.
5. Davis JM, Chen N. Dose response and dose equivalence of antipsychotics. *J Clin Psychopharmacol*. 2004;24:192–208.
6. Weiden PJ, Aquila R, Dalheim L, et al. Switching antipsychotic medications. *J Clin Psychiatry*. 1997;58(suppl 10):63–72.
7. Reilly JG, Ayis SA, Ferrier IN, et al. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet*. 2000; 355:1048–1052.
8. Goodnick PJ, Jerry J, Parra F. Psychotropic drugs and the ECG: focus on the QTc interval. *Expert Opin Pharmacother*. 2002;3: 479–498.
9. Agelink MW, Majewski T, Wurthmann C, et al. Effects of newer atypical antipsychotics on autonomic neurocardiac function: a comparison between amisulpiride, olanzapine, sertindole, and clozapine. *J Clin Psychopharmacol*. 2001;21:8–13.
10. Cohen H, Loewenthal U, Matar M, et al. Association of autonomic dysfunction and clozapine. Heart rate variability and risk for sudden death in patients with schizophrenia on long-term psychotropic medication. *Br J Psychiatry*. 2001;179:167–171.
11. Inagaki A, Inada T, Fujii Y, et al. Dose Equivalence of the Psychotropic Drugs. Tokyo, Japan: Seiwa Shoten Publishers; 1999 (in Japanese).
12. Inada T, Yagi G. Evaluation and Diagnosis of Drug-Induced Extrapyramidal Symptoms: Commentary on the DIEPSS and Guide to Its Usage. Tokyo, Japan: Seiwa Shoten Publishers; 1996.
13. Smith RC. Lower-dose therapy with traditional neuroleptics in chronically hospitalized schizophrenic patients. *Arch Gen Psychiatry*. 1994;51:427–429.
14. Morganroth J. A definitive or thorough phase 1 QT ECG trial as a requirement for drug safety assessment. *J Clin Electrocardiol*. 2004; 37:25–29.

The Association Between Cytochrome P450 2D6 Genotype and Prescription Patterns of Antipsychotic and Antidepressant Drugs in Hospitalized Psychiatric Patients

A Retrospective Follow-up Study

To the Editors:

The response to antipsychotic and antidepressant drugs is variable: approximately 20% to 40% of the psychiatric patients do not respond satisfactorily to pharmacotherapy.[1,2] This variability in response can be attributed to causes like genetics and disease. One of the genetic factors is polymorphism of the gene locus for cytochrome P450 2D6 (CYP2D6). Approximately 5% to 10% of the white population can be classified as poor metabolizer (PM) by lacking CYP2D6 activity and 1% to 10% as ultrarapid metabolizer (UM) by gene duplication resulting in high enzyme activity.[3–6] As most antipsychotic and antidepressant drugs are at least partly metabolized by CYP2D6, this might implicate a high risk of unsatisfactory response to these drugs in up to 20% of psychiatric patients. Switching to other drugs and changes of dosage regimen are an overall expression of unsatisfactory response to treatment.[2,7,8] This retrospective follow-up

study investigates whether hospitalized psychiatric patients classified as PM or UM for CYP2D6 show more frequent unsatisfactory response (as measured by more frequent switching of drug and dosage regimen) to treatment with antipsychotic and antidepressant drugs compared with patients classified as extensive metabolizer (EM) for CYP2D6.

The study was conducted in 2 psychiatric hospitals with approximately 450 beds for long-stay patients with chronic psychiatric disorders. Hospitalized patients treated with antipsychotic or antidepressant drugs were identified by using prescription data from pharmacy records as available from the department of clinical pharmacy of the Wilhelmina Hospital Assen, The Netherlands. The study protocol was reviewed and approved by an independent medical ethical committee.

Patients were eligible if they were hospitalized, and at least 180 days' prescription data were available. At least 1 antipsychotic or antidepressant drug primarily metabolized by CYP2D6 had to be started at least 30 days after the start of the observation period and at least 90 days before the end of the observation period. These criteria were chosen because it was expected that unsatisfactory response occurs during the first 90 days of a drug episode. The observation period was defined as the period in which prescription data were available. A drug episode was defined as the duration between the start of an antipsychotic or antidepressant drug and the first switch or discontinuation of that drug, or the end of the observation period, whichever came first. Prescription data were collected from April 1988 until November 2002. Patients were genotyped after the end of the observation period. No further inclusion or exclusion criteria were applied apart from written informed consent before entry in the study. All patients were included between March 2002 and October 2002.

Primary end point of this study was the frequency of switching. A switch was defined as a switch to another drug within the same therapeutic group (ie, from 1 antidepressant to another antidepressant or from 1 antipsychotic to another antipsychotic) within 4 weeks after or during tapering the previous drug. Secondary end point was the frequency of switching of dosage regimen. A switch of dosage regimen was defined as a change of the prescribed daily dose of the same drug. In case the patient restarted the drug after previous discontinuation of the same drug, only the first episode was taken into account.

Primary determinant was the CYP2D6 genotype. The CYP2D6 genotype was determined by polymerase chain reaction–restriction fragment length polymorphism. CYP2D6*3(A), *4(B), *6(T), *7(E), and *8(G) were investigated using a long-distance and multiplex polymerase chain reaction as described by Stüven et al.[9] These variants allow identification of approximately 98.7% of the PMs in a white population.[4] The presence of gene duplication that may lead to ultrarapid metabolism was analyzed by an allele-specific polymerase chain reaction and was performed as described by Lovlie et al.[6] Patients were defined as PM if they were homozygous or heterozygous for noncoding alleles. Patients were defined as UM if gene duplication was detected and mutant alleles were absent. All other patients were classified as EM.

We classified the CYP2D6 metabolic pathway of each antidepressant and antipsychotic drug according to the available evidence. Drugs for which an in vivo relationship between CYP2D6 genotype and pharmacokinetic properties has been documented were taken into account in the present analysis (antidepressants: amitriptyline, clomipramine, desipramine, fluvoxamine, fluoxetine, imipramine, maprotiline, mianserine, nortriptyline, paroxetine, and venlafaxine; antipsychotics: haloperidol, perphenazine, risperidone, sertindol, thioridazine, and zuclopenthixol).

The incidences of switches of drug and changes of dosage regimen were assessed for EMs, PMs, and UMs. The incidence of drug switches for PMs and UMs relative to EMs was estimated as a hazard ratio together with a 95% confidence interval (95% CI) using Cox proportional hazard analysis. The incidence of changes in dosage regimen for PMs and UMs relative to EMs was estimated as an incidence density ratio together with a 95% CI using Poisson regression analysis. The hazard ratio and the incidence density ratio can be interpreted as a relative risk, and results were therefore expressed as an RR with a 95% CI.[10]

The potential study population consisted of 435 hospitalized psychiatric patients with chronic psychiatric disorders. A total of 220 patients complied with the inclusion criteria. Informed consent was given by 132 (60%) of the patients. For 1 sample, no result could be obtained because of poor DNA amplification. Therefore, the study population existed of 131, mainly white (>95%), patients with a mean age of 54 (SD 16.2) and 46.6% (n = 61) men. We found poor or ultrarapid metabolism in 14.5% of the included patients [10.7% PM (n = 14) and 3.8% UM (n = 5)]. This frequency is as expected in a white population (6%–20%).[3–6] The prevalence of PMs (10.7%) is high compared with the prevalence in other white populations but is not significantly different. Overall, there were 254 episodes of antidepressant and antipsychotic drugs during the observation period [mean observation period 4.39 (SD 2.46) years]. Antidepressant drugs accounted for 43.3%, and antipsychotic drugs accounted for 56.7% of all episodes. Antidepressant drugs were used by 64 EMs, 10 PMs, and 3 UMs, and antipsychotic drugs were used by 89 EMs, 12 PMs, and 5 UMs. Overall, of all drug episodes, 88 (35%) ended with a switch. There were 542 changes of dosage regimen.

Table 1 shows that for antidepressant drugs, CYP2D6 genotype PM was associated with more frequent switching [RR 3.50 (95% CI 1.52–8.10)] and

TABLE 1. CYP2D6 Genotype and Relative Risk of Switching of Drug and Dosage Regimen Changes

	Switch of Drug, RR (95% CI)	Dosage Regimen Changes, RR (95% CI)
Antidepressants	N = 110	N = 110
EM	1 (reference)	1 (reference)
PM	3.50 (1.52–8.10)	2.18 (1.36–3.49)
UM	0.46 (0.06–3.41)	0.11 (0.02–0.43)
Antipsychotics	N = 144	N = 144
EM	1 (reference)	1 (reference)
PM	1.38 (0.58–3.27)	2.18 (1.61–2.95)
UM	1.01 (0.25–4.20)	1.27 (0.76–2.14)

N indicates number of observed drug episodes.

with more dosage regimen changes [RR 2.18 (95% CI 1.36–3.49)]. For antidepressant drugs, CYP2D6 genotype UM was also associated with fewer dosage regimen changes [RR 0.18 (95% CI 0.08–0.45)], but not with switches. For antipsychotic drugs, an association was found between CYP2D6 genotype PM and changes in dosage regimen [RR 2.18 (95% CI 1.61–2.95)] but not for switching. For antipsychotic drugs, no association was found with CYP2D6 genotype UM.

There are some limitations to our findings. First, the reasons for switching were not recorded. Therefore, it is not possible to determine whether the increased RR of switching and changes of dosage regimen was the result of treatment failure, adverse effects, or other reasons. However, the main purpose of this study was to determine whether PMs and UMs had, overall, a more frequent unsatisfactory response compared with EMs, that is, to investigate whether psychiatrists have more problems in finding the optimum pharmacotherapy for PMs and UMs. The reason of unsatisfactory response as well as the diagnosis of the included patient is irrelevant for this hypothesis. Second, our results may be biased. Selection bias may have occurred because at least 1 antidepressant or antipsychotic drug had to be started at least 30 days after the start of the observation period. Therefore, the included patients may represent a population of unstable patients more likely to start with antidepressant and antipsychotic drugs. The high prevalence of PMs can possibly be explained by this selection bias. Third, we could only study 5 patients classified as UM and 14 patients classified as PM for CYP2D6. Despite this, we found significant results, but our findings need confirmation in a larger number of, especially UM, patients.

Frequent switching from drug or dosage can be seen as an overall expression of unsatisfactory response to treatment including both treatment failure and unacceptable adverse effects. Differences in response can be adjusted for by switching dosage regimen or switching 1 drug to another.[2,7,8] Our results suggest that problems arise while finding the optimum pharmacotherapy regarding antidepressant drugs in PMs for CYP2D6. The lack of association between CYP2D6 genotype PM and switching for antipsychotic drugs may be explained by several reasons. One explanation could be that the acceptation of adverse effects during treatment with antipsychotic drugs is higher compared with treatment with antidepressants, and during treatment with antipsychotic drugs, it is possible to treat adverse effects with antiparkinsonian medication. Schillevoort et al[11] showed a higher prescription rate for antiparkinsonian drugs in PMs compared with EMs. Although the increased risk for switching 1 antipsychotic to another was not found, the risk of switching dosage was significantly increased. The treating psychiatrist possibly recognizes the problems in finding the optimum pharmacotherapy but tries to change the dosage instead of switching the drug. Furthermore, during treatment with antidepressants, it takes several weeks before the onset of response. During these first weeks, the adverse effects are present, and therefore the psychiatrist and the patient possibly switch to another drug more easily compared with treatment with antipsychotics where the onset of response is more rapid. The significant result for CYP2D6 genotype UM and switching dosage of antidepressant drugs may be explained by the lack of response during the first weeks as well. During these first weeks, the adverse effects are absent, and the psychiatrist possibly changes the dosage more easily instead of switching to another drug.

Genotyping psychiatric patients for CYP2D6 before starting pharmacotherapy may prevent unsatisfactory response. If CYP2D6 genotype information is available, before starting pharmacotherapy, an individualized advice for the choice of drug and dosage is possible. This information could improve the response to antidepressant and antipsychotic drugs as measured by less switching of drug and dosage. Furthermore, Chou et al[12] suggested that cost of treating PMs was greater than the cost of treating EMs. Genotyping before starting pharmacotherapy possibly can prevent these increased costs. In our cohort, hospitalized psychiatric patients who started with an antidepressant drug primarily metabolized by CYP2D6 were most likely to profit from genotyping CYP2D6. Prospective trials are necessary to establish the clinical value of genotyping CYP2D6

before starting pharmacotherapy in specific patients and psychiatric patients in general.

In conclusion, CYP2D6 genotype is associated with increased switching and dosage regimen changes in users of antidepressant drugs and with more frequent changes of dosage regimen in users of antipsychotics. These results suggest that genotyping of CYP2D6 may identify patients who are prone to unsatisfactory response to pharmacotherapy in hospitalized psychiatric patients.

Hans Mulder, PharmD*†
Frederik W. Wilmink, MD, PhD‡
Tim L. Beumer, PhD§
Wim J. Tamminga, PhD§
Jaap N. Jedema, PharmD†
Antoine C.G. Egberts, PhD*
*Department of Pharmacoepidemiology & Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht University; †Department of Clinical Pharmacy, Wilhelmina Hospital Assen; ‡Psychiatric Hospital GGZ Drenthe, Assen and §Pharma BioResearch Group BV, Zuidlaren, The Netherlands
h.mulder@wza.nl

ACKNOWLEDGMENT

This study was supported financially by the Psychiatric Hospital GGZ Drenthe, Assen, The Netherlands.

REFERENCES

1. Hirschfeld RMA, Montgomery SA, Aguglia E, et al. Partial response and nonresponse to antidepressant therapy: current approaches and treatment options. *J Clin Psychiatry*. 2002; 63:826–837.
2. Fava M. Management of nonresponse and intolerance: switching strategies. *J Clin Psychiatry*. 2000;61(suppl 2):10–12.
3. Meyer UA. Pharmacogenetics and adverse drug reactions. *Lancet*. 2000;356:1667–1671.
4. Tamminga WJ, Wemer J, Oosterhuis B, et al. CYP2D6 and CYP2C19 activity in a large population of Dutch healthy volunteers: indications for oral contraceptive-related gender differences. *Eur J Clin Pharmacol*. 1999;55: 177–184.
5. Tamminga WJ, Wemer J, Oosterhuis B, et al. The prevalence of CYP2D6 and CYP2C19 genotypes in a population of healthy Dutch volunteers. *Eur J Clin Pharmacol*. 2001;57: 717–722.
6. Lovlie R, Daly AK, Molven A, et al. Ultrarapid metabolizers of debrisoquine: characterization and PCR-based detection of alleles with duplication of the CYP2D6 gene. *FEBS Lett*. 1996;392:30–34.
7. Weiden PJ, Aquila R, Dalheim L, et al. Switching antipsychotic medications. *J Clin Psychiatry*. 1997;58(suppl 10):63–72.
8. Bull SA, Hunkeler EM, Lee JY, et al. Discontinuing or switching selective serotonin-reuptake inhibitors. *Ann Pharmacother*. 2002;36:578–584.
9. Stüven T, Griese EU, Kroemer HK, et al. Rapid detection of CYP2D6 null alleles by long distance- and multiplex-polymerase chain reactions. *Pharmacogenetics*. 1996;6:417–421.
10. Clayton D, Hills M. *Statistical Models in Epidemiology*. New York: Oxford University Press; 1995.
11. Schillevoort I, Boer de A, Weide van der J, et al. Antipsychotic-induced extrapyramidal syndromes and cytochrome P450–2D6 genotype. *Pharmacogenetics*. 2002;12:235–240.
12. Chou WH, Yan FX, Leon de J, et al. Extension of a pilot study: impact from the cytochrome P450 2D6 polymorphism on outcome and costs associated with severe mental illness. *J Clin Psychopharmacol*. 2000;20: 246–251.

Tadalafil in a Patient With Treatment-Resistant Depression and Antidepressant Polypharmacy

To the Editors:

Erectile dysfunction (ED) is a frequent condition especially in patients with depression.[1] In this context, ED might be caused by the underlying disorder or a side effect of the medication. Here, we present a former depressed patient with persistent ED, who was treated with different medications and other somatic options and finally successful with the new phospho-diesterase-5-inhibitor, tadalafil.

CASE

A 45-year-old white male with a long history of recurrent major depressive disorder was admitted to our hospital because of a severe treatment-resistant major depressive episode with psychotic features. The initial 17-item Hamilton Rating Scale for Depression score was 28, and the score on the Clinical Global Impression Scale was 7. His actual pretreatment consisted of tranylcypromine 40 mg, lithium carbonate 800 mg, diazepam 10 mg, and pipamperone 100 mg daily. After standard safety procedures and addition of antipsychotic medication with olanzapine 10 mg daily, our patient received 10 right unilateral electroconvulsive therapy sessions. A slight improvement of mood was seen, but the patient developed an intolerable impairment of cognitive functions (disorientation, forgetfulness, and anterograde amnesia). During frequent cardiovascular monitoring, the dosage of tranylcypromine was increased to 70 mg daily. Additionally, 5 sessions of repetitive transcranial magnetic stimulation were applied. None of these treatments led to a major improvement in psychopathology. Therefore, an augmentation with levothyroxine in supraphysiological doses up to 300 μg/d was begun. Afterward, a significant improvement in mood and motivation was perceived, the patient regained weight, and his obsessive suicidal ideations ceased (Hamilton Rating Scale for Depression score, 13). Nevertheless, the patient still had persistent ED. After once receiving 25 mg of sildenafil on our ward—causing the desired effect after sexual stimulation—the patient was kept under cardiovascular surveillance (because of potential pharmacodynamic interactions such as hypotonia), but no adverse effects emerged despite a comedication consisting of some drugs with orthostatic dysfunction properties. Therefore, the patient could further be treated with sildenafil (still on 25 mg for use), which enabling him to use it according to his requirements, and was well tolerated after usage during weekend vacations. Furthermore, an additional antidepressant effect became measurable. At discharge, the Hamilton Rating Scale for Depression score was 7, and the Clinical Global Impression Scale score was 3. After recovery from a depressive lapse under psychosocial stress which did not make a change in treatment necessary, the patient asked for a medication that would have allowed him to have sexual intercourse in a ''less time-restricted way,'' as he said. Therefore, 10 mg of tadalafil in the morning was prescribed. The patient had sexual intercourse with full erections at 5 PM and 11 PM, which was also confirmed by his wife. Afterward, the patient received the medication for 14 days which enabled him to have sexual intercourse on a regular basis. No side effects were noted and neither a