The CYP2D6 Poor Metabolizer Phenotype May Be Associated With Risperidone Adverse Drug Reactions and Discontinuation

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Objective: The cytochrome P450 2D6 (CYP2D6) enzyme metabolizes risperidone. CYP2D6 poor metabolizers have no CYP2D6 activity (7% of whites and 1%–2% of other races). This study tested whether the CYP2D6 poor metabolizer phenotype was associated with adverse drug reactions (ADRs) and discontinuation due to ADRs.

Method: Adult inpatients and outpatients were recruited from July 2000 to March 2003 including (1) 325 who were stabilized on risperidone therapy and classified as either expressing moderate-to-marked ADRs (22%, 73/325) or not (78%, 252/325) and (2) 212 who discontinued risperidone and were classified as discontinued due to ADRs (38%, 81/212) or for other reasons (62%, 131/212). Genetic tests were performed by allele-specific polymerase chain reaction and/or by the AmpliChip CYP450 microarray system for up to 34 separate CYP2D6 alleles. Two logistic regression models with dependent variables (moderate-to-marked ADRs while taking risperidone and risperidone discontinuation due to ADRs) were evaluated with respect to the CYP2D6 phenotype.

Results: The odds ratios (ORs) and 95% confidence intervals (CIs) for the CYP2D6 poor metabolizer phenotype in the univariate analyses and after correcting for clinical variables were (1) OR = 3.1 (CI = 1.4 to 7.0) and 3.4 (CI = 1.5 to 8.0) for moderate-to-marked ADRs on risperidone and (2) OR = 3.0 (CI = 0.85 to 10.6) and 6.0 (CI = 1.4 to 25.4) for discontinuation due to ADRs.

Conclusions: The CYP2D6 poor metabolizer phenotype appears to be associated with risperidone ADRs and discontinuation due to ADRs; however, this finding requires further study in larger patient populations. The CYP3A5 and p-glycoprotein exon 21 and 26 genotypes were not significantly associated with risperidone response.

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Roche Molecular Systems, Inc., markets the AmpliChip CYP450 microarray system, which detects CYP2D6 and CYP2C19 gene variations. Francisco J. Diaz, Ph.D. (Department of Statistics, Universidad Nacional, Medellin, Colombia), calculated interrater reliability analysis. Tom Cooper, M.A. (Nathan Kline Institute, Orangeburg, N.Y., and New York University School of Medicine, New York, N.Y.), supervised laboratory analysis for plasma risperidone concentrations.

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Promising new pharmacogenetic technologies, such as the CYP450 GeneChip and the newer AmpliChip CYP450 microarray system (utilizing oligonucleotide arrays on a computer chip), have been recognized by leading scientific journals such as *Science* as potentially viable methods for future genetic testing.[1] Even science writers in lay magazines such as *Time*[2] have predicted that by the year 2015, DNA chips or similar technologies will be used to tailor medications to each patient's genetic makeup ("personalized prescriptions"). Yet few research efforts have addressed how this technology might help psychiatrists improve patient care or prevent adverse drug reactions (ADRs; traditionally called *side effects* in psychiatric textbooks) in routine patient care settings. Meanwhile, ADRs remain a major complication for psychiatry in particular and medicine in general by limiting patient tolerance of what may otherwise be effective drugs.[3]

A prime candidate for clinical application of genetic technologies is the cytochrome P450 2D6 (CYP2D6)

gene. The CYP2D6 enzyme metabolizes a wide range of nonpsychiatric drugs, opioids,[4] antipsychotics, and antidepressants.[5] The CYP2D6 enzyme is inhibited by some antidepressants, particularly paroxetine, fluoxetine, and bupropion.[6] Over 40 different CYP2D6 alleles can affect the activity of the CYP2D6 enzyme and, in various combinations, give rise to different phenotypes. The most clinically significant is the poor metabolizer phenotype with 2 nonfunctional CYP2D6 alleles and no CYP2D6 activity (the enzyme is absent in the body). The proportion of poor metabolizers in European and U.S. whites is 7% and in other races is 1% to 2%. The CYP2D6 enzyme plays a major role in risperidone metabolism and converts risperidone via aliphatic hydroxylation to the active metabolite 9-hydroxyrisperidone. Risperidone and 9-hydroxyrisperidone can be further metabolized by N-dealkylation, presumably by the CYP3A enzyme.[7] Carbamazepine[8] and other CYP3A inducers[9] decrease risperidone levels, and CYP3A inhibitors can increase risperidone levels[9]; thus, CYP3A also plays an important role in risperidone metabolism.[7,8]

The risperidone manufacturer's studies[10] suggest that 9-hydroxyrisperidone and risperidone have similar pharmacologic properties, and plasma concentrations of the total active moiety (sum of risperidone and 9-hydroxyrisperidone) were similar in 2 CYP2D6 poor metabolizer subjects and in 9 extensive metabolizer subjects, leading to the manufacturer's proposal that CYP2D6 expression polymorphism is therapeutically unimportant in risperidone therapy.[10] However, in a pilot follow-up study,[9] 2 of 12 patients with severe risperidone ADRs were CYP2D6 poor metabolizers. Further, in a risperidone case-control study,[9] the prevalence of at least moderate ADRs was 100% (3/3) in the CYP2D6 poor metabolizer group and only 35% (6/17) in the extensive metabolizer group ($p = .074$). Case reports[11,12] and small studies[13–15] further suggest that CYP2D6 genotype may influence risperidone ADRs.

This study was designed to test if the CYP2D6 poor metabolizer phenotype is associated with risperidone ADRs and discontinuation of risperidone due to ADRs in the clinical environment. Would the CYP2D6 phenotype prove useful in predicting which patients discontinue risperidone therapy in a real clinical setting? If genetic testing is to be introduced as a standard clinical tool, it is important to determine if it can provide meaningful information for clinicians in the uncontrolled, "noisy" clinical environment where psychiatrists use different doses, prescribe comedications, and often make experience-based decisions that vary from patient to patient. If a single test seems likely to be of value in this environment, it is the CYP2D6 genotype. However, there must be clinical evidence that variation in CYP2D6 expression influences treatment outcomes in the clinical environment where one anticipates employing it.[16–18]

METHOD

Patient Recruitment

From July 2000 to March 2003, 554 patients who were receiving risperidone prescribed by their physicians or who had been discontinued from risperidone therapy were recruited at the adult inpatient and outpatient psychiatric facilities in Central Kentucky. After the study was completely described to the subjects, written informed consent was obtained. The inpatient facilities included both Eastern State Hospital (ESH) in Lexington, which admits approximately 1600 patients per year and serves as the primary psychiatric hospital for acute admissions in one third of Kentucky, and Central State Hospital in Louisville, which admits approximately 900 patients per year and covers a different catchment area. Outpatients were recruited from the Blue Grass Community Mental Health Centers, providing outpatient services for ESH's catchment area, and from the University of Kentucky Outpatient Clinic. No patients from our pilot study were recruited.[9]

Patient Characteristics

Three hundred twenty-five patients were stabilized on risperidone therapy. Ten subjects excluded from this study group had tremor-inducing neurologic disorders that made risperidone's contribution to ADRs difficult to assess. The 325 patients were all taking a stable risperidone dose for at least 5 days (to reach steady state) and most for at least 1 week (97%, 315/325 of the sample). None of these patients were discontinued from risperidone immediately after their evaluation.

Two hundred twelve patients were recruited who had been discontinued from risperidone therapy. Seven additional subjects were excluded from this group because 6 had concomitant medical problems at the time of risperidone discontinuation, and 1 had a severe history of noncompliance with a possibility that she never took the prescribed risperidone. Detailed demographic and clinical characteristics of the 2 patient groups are provided in Table 1.

Patient Assessments

As in prior work,[16,17] the English version of the Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)[19] was used by the research team. This scale includes all types of ADRs and provides a final summarized rating (Table 2). All patients were classified as having or not having at least moderate (moderate or marked) risperidone ADRs. Moderate ADRs were classified as ADRs that interfere moderately with patient performance.[19] All clinical ratings and assessments were done blind to the genetic tests.

Chart reviews and patient interviews ascertained the reason for the most recent risperidone discontinuation.

Table 1. Description of Patients Taking Risperidone and Discontinued From Risperidone

	Taking Risperidone (N = 325)					Discontinued From Risperidone (N = 212)				
Variable	Mean	SD	Median	25th Percentile	75th Percentile	Mean	SD	Median	25th Percentile	75th Percentile
Age started on risperidone, y	43.5	13.5				38.6	11.3			
Age at recruitment, y	43.5	13.5				40.5	11.4			
Age started on psychiatric medications, y	28.2	12.5				23.8	9.1			
No. of hospitalizations			2	1	6			3	1	7
Body mass index, kg/m^2	30.8	9.5				30.5	7.2			
Education, y	11.3	3.3				11.5	2.6			
	%	N				%	N			
Male	53	173				55	117			
Race										
White	79	256				85	181			
Black	20	64				12	26			
Other	1	5				3	5			
Inpatients	77	249				77	163			
Marital status										
Single	47	152				45	96			
Divorced	27	87				27	58			
Married	15	49				20	42			
Other	11	37				8	16			
Most frequent DSM-IV diagnosis										
Schizophrenia	28	90				30	64			
Schizoaffective disorder	20	64				20	40			
Bipolar disorder	15	50				20	43			
Major depressive disorder	12	39				12	26			
Daily smoking										
Current	64	207				71	150			
Ever	74	241				81	171			
Abuse/dependence										
Alcohol										
Last year	35	112				38	80			
Ever	62	200				68	145			
Drug										
Last year	28	91				30	64			
Ever	49	159				55	117			
Organic central nervous system lesion	31	102				35	75			
Genotype										
CYP2D6[a]										
Poor metabolizers[b]	8	27				5	11			
Intermediate metabolizers[c]	9	30				15	32			
Extensive metabolizers[d]	79	256				77	164			
Ultrarapid metabolizers[e]	4	12				3	5			
CYP3A5										
Poor metabolizers	76	247				78	165			
P-glycoprotein										
Exon 26 T/T	19	62				25	54			
Other[f]	81	263				75	158			
Exon 21 T/T	11	36				17	36			
Other[g]	89	289				83	176			
GSTM1										
Absent[h]	50	162				48	102			
GSTT1										
Absent[h]	21	68				21	45			

[a]The tested alleles were *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *14, *15, *17, *18, *19, *20, *25, *26, *29, *30, *31, *35, *36, *37, *40, *41, *43, *52, and a number of duplicated alleles.
[b]Poor metabolizers were identified when 2 of any combination of the null alleles *3,*4,*5,*6,*52, and *4xn were present. Prevalences of 5% to 8% are consistent with prevalences expected in this population.
[c]Intermediate metabolizers included anyone with a null allele (*3,*4,*5,*6,*52,*4xn) coupled with a low activity allele (*9,*10,*29,*41) or 2 low activity alleles (*9,*10, *29, *41).
[d]Extensive metabolizers included anyone not defined as a poor, ultrarapid, or intermediate metabolizer by default.
[e]Ultrarapid metabolizers were identified as patients with a *1xn or *2xn coupled with another functional allele (*1,*2,*35,*41,*17,*10).
[f]Exon 26 on risperidone: T/C 51% (167/325) and C/C 30% (96/325); exon 26 off risperidone: T/C 50% (106/212) and C/C 25% (52/212).
[g]Exon 21 on risperidone: G/T 43% (140/325), G/G 44% (145/325), A/T 1% (3/325), and G/A < 1% (1/325). Exon 21 off risperidone: G/T 42% (89/212), G/G 38% (80/212), A/T 2% (5/212), and G/A 1% (1/212).
[h]Remaining subjects have the enzyme.

Table 2. Trial of Patients Taking Risperidone and Discontinued From Risperidone

	Taking Risperidone (N = 325)					Discontinued From Risperidone (N = 212)				
Variable	Mean	SD	Median	25th Percentile	75th Percentile	Mean	SD	Median	25th Percentile	75th Percentile
No. of risperidone trials			1	1	2			1	1	2
Dose (current or at discontinuation)	4.0	2.3				3.7	2.6			
Maximum risperidone dose	5.0	2.9				4.6	2.9			
Current risperidone trial, wk			1.8	1	7.5					
All risperidone trials, mo			2.3	0.5	14			1	0.3	6.6
Risperidone satisfaction (1–7)[a]			5	4	6			3	1	5
No. of comedications			3	1	4			2	1	3
	%	N				%	N			
Naive to antipsychotics	15	47				14	29			
First risperidone trial	64	209				70	148			
Taking no other medications	9	30				10	21			
Taking valproic acid	31	99				25	53			
Taking lithium	8	26				7	15			
Taking anticholinergics	19	62				19	41			
Taking amantadine	1	3				0.5	1			
Taking β-blockers	1	3				1	3			
Taking CYP3A substrates	45	147				36	77			
Taking CYP2D6 substrates	25	82				28	60			
Variables that may influence risperidone ADRs										
Risperidone dose										
High[b]	15	48				11	23			
Low[c]	23	73				35	75			
Typical antipsychotics	11	34				13	28			
Atypical antipsychotics	14	46				15	31			
Any antiparkinsonian drugs[d]	21	67				20	43			
CYP inhibitors[e]	32	105				28	59			
CYP inducers[f]	7	23				10	22			
ADRs according to UKU										
None	35	113								
Mild	43	139								
Moderate	20	66								
Marked	2	7								
Reason for discontinuation										
ADRs						38	81			
Lack of response						20	42			
Noncompliance						20	43			
Doctor's choice						12	26			
Patient's request						7	14			
Other						3	6			

[a]Patient satisfaction with risperidone using a Likert scale: 1 (terrible) to 7 (delighted).
[b]Higher than 1.5 mg/day in demented patients, higher than 4 mg/day in naive patients or in patients older than 64 years of age, and higher than 6 mg/day in rest of patients.[20]
[c]Lower than 0.75 mg/day in demented patients, lower than 2 mg/day in naive patients or in patients older than 64 years of age, and lower than 3 mg/day in rest of patients.[20]
[d]Taking anticholinergic medication amantadine or β-blockers for extrapyramidal side effects.
[e]Intermediate definition for CYP inhibitors: taking fluoxetine, paroxetine, bupropion, fluvoxamine, sertraline, nefazadone, erythromycin, or celecoxib.[6,21] See Table 3 for more details.
[f]Taking carbamazepine, phenytoin, thioridazine, mesoridazine, phenobarbital, butalbital, primidone, or felbamate.[9,21,22] See Table 3 for more details.
Abbreviations: ADR = adverse drug reaction, UKU = Udvalg for Kliniske Undersogelser Side Effect Rating Scale.

The main cause of discontinuation (Table 2) was identified in each patient blind to any genotype information.

Risperidone Dosing

This is a naturalistic study; each patient's treating physician prescribed risperidone. Table 2 describes risperidone trials in 2 samples. As recommended, risperidone doses vary remarkably according to patient type; published guidelines were used to define a high risperidone dose as higher than 1.5 mg/day in demented patients, 4 mg/day in naive patients or in patients older than 64 years of age, and 6 mg/day in the remaining patients.[20] On the basis of these guidelines,[20] a low dose was considered to be less than 0.75 mg/day in demented patients, 2 mg/day in naive patients or in patients older than 64 years of age, and 3 mg/day in the remaining patients.

Comedication

The majority of patients were taking other medications. Several medications can cause clinically significant CYP2D6 and/or CYP3A inhibition. We first considered fluoxetine, paroxetine, bupropion, fluvoxamine, sertraline,

Table 3. Comedication With CYP Inhibitors and Inducers According to CYP2D6 Phenotype[a,b,c]

	Taking Risperidone (N = 325)		Discontinued From Risperidone (N = 212)			
			Non–Poor Metabolizers		Poor Metabolizers	
Variable	Non–Poor Metabolizers N = 298	Poor Metabolizers N = 27	No ADRs N = 127	ADRs N = 74	No ADRs N = 4	ADRs N = 7
Inhibitors, %						
At least 1 from narrow definition	19	22	13	30	0	14
At least 1 from intermediate definition	32	41	21	42	0	14
At least 1 from wide definition	38	41	26	50	0	28
Sertraline	11	15	6	10	0	0
Paroxetine	9	0	9	12	0	0
Bupropion	6	11	0	10	0	0
Fluoxetine	6	0	5	8	0	14
Citalopram	5	4	3	10	0	14
Fluvoxamine	1	0	1	1	0	0
Nefazodone	1	0	0	1	0	0
Celecoxib	1	4	1	0	0	0
Escitalopram	< 1	0	2	0	0	0
Erythromycin	0	0	1	0	0	0
Inducers, %						
At least 1	7	15	13	4	50	14
Carbamazepine	3	7	7	3	0	0
Phenytoin	3	4	2	1	25	0
Phenobarbital	1	0	0	0	0	0
Primidone	< 1	0	0	0	0	0
Thioridazine	0	4	1	0	25	0
Butalbital	0	0	1	0	0	0
Felbamate	0	0	1	0	0	0
Mesoridazine	0	0	1	0	0	14

[a]Narrow definition includes fluoxetine, paroxetine, or bupropion.
[b]Intermediate definition includes fluoxetine, paroxetine, bupropion, fluvoxamine, sertraline, nefazodone, erythromycin, or celecoxib.
[c]Wide definition includes fluoxetine, paroxetine, bupropion, fluvoxamine, sertraline, nefazodone, erythromycin, celecoxib, citalopram, or escitalopram.
Abbreviation: ADR = adverse drug reaction.

nefazodone, erythromycin, and celecoxib.[6,21] This intermediate definition of CYP inhibitors was used in the main analysis and in Table 2. A narrow definition that included only the very potent CYP2D6 inhibitors fluoxetine, paroxetine, and bupropion was also considered. Finally a wide definition included the intermediate definition plus citalopram and escitalopram.

The CYP inducers increasing CYP3A activity that were coprescribed in the sample were carbamazepine, phenytoin, phenobarbital, butalbital, primidone, felbamate, thioridazine, and mesoridazine.[9,21,22] Table 3 provides more specific information about the frequency of different CYP inhibitors and inducers according to CYP2D6 phenotype (more detail is included in the discontinuation group since CYP inhibitors and inducers had a significant effect). There are no known CYP2D6 inducers.

Plasma Risperidone Concentrations

Trough risperidone levels were measured using an early morning sample collected before the morning risperidone dose was given. Plasma risperidone and 9-OH risperidone concentrations were quantified at the Nathan Kline Institute (Orangeburg, N.Y.) using a published[23] liquid chromatography method with minor modifications. The limits of quantitation and detection were 2 ng/mL and 1 ng/mL, respectively, for both analytes. The plasma concentration ratio of risperidone/9-hydroxyrisperidone is an index of CYP2D6 activity and is usually ≤ 1 (or risperidone < 9-hydroxyrisperidone).[9,24] An inverted ratio > 1 (or risperidone > 9-hydroxyrisperidone) indicates a genetically deficient subject or treatment with a powerful CYP2D6 inhibitor.[9] Of the 325 subjects taking risperidone, 2% (7/325) did not provide enough blood, 2% (7/325) had undetectable levels, and 9% (30/325) had interfering substances. This left 281 patients (87%, 281/325) for whom it was possible to calculate the risperidone/9-hydroxyrisperidone ratio.

Genotyping

DNA was extracted from whole blood according to a previously described method.[25,26] Up to 34 CYP2D6 alleles and a number of duplicated CYP2D6 alleles were tested by allele-specific polymerase chain reaction (PCR) in our laboratory[25,26] and/or by the newer AmpliChip CYP450 microarray system at Roche Molecular Systems (Alameda, Calif.).[26] All samples were tested by both systems.

There are 3 other CYP2D6 phenotypes besides poor metabolizers. The ultrarapid metabolism phenotype usually has 3 or more copies of the active CYP2D6 gene[27] and may need higher doses of CYP2D6 substrates such as tricyclic antidepressants.[28] Subjects with normal CYP2D6

activity are classified as having an extensive metabolizer phenotype, with 1 or 2 functional copies of the CYP2D6 gene. An intermediate metabolizer phenotype has 1 nonfunctional CYP2D6 allele and 1 low activity CYP2D6 allele. Patient CYP2D6 genotypes were converted to a predicted CYP2D6 phenotype classification of poor, intermediate, extensive, or ultrarapid metabolizers as previously described by our laboratory (see footnotes of Table 1 for details).[26]

Additional genetic tests were conducted at our laboratory using allele-specific PCR. The glutathione-S-transferases (GST), GSTM1 and GSTT1 enzymes, which help eliminate reactive electrophiles,[29] were used as control metabolic enzymes that should not influence risperidone metabolism. The genotypes established whether these enzymes were expressed or deficient due to their deletion. The GSTT1 gene is even located on the same chromosome as the CYP2D6 gene (chromosome 22).

Polymorphism within CYP3A5 and the drug transporter P-glycoprotein (PgP), thought to be capable of influencing risperidone pharmacokinetics, were evaluated in an exploratory fashion. The CYP3A enzyme subfamily (CYP3A7, CYP3A4, and CYP3A5) accounts for up to 30% of the total cytochrome P450 in the liver. The CYP3A4 enzyme is the dominant isoform in this subfamily, but no polymorphic variations have yet been described that eliminate CYP3A4 expression. The CYP3A5 enzyme shares high homology with CYP3A4 and appears to metabolize many of the same substrates. The CYP3A5 enzyme is deficient in a large percentage of the population (approximately 80% of whites and 20% of blacks). While the clinical relevance of the CYP3A5 poor metabolizer phenotype remains unclear,[30] 2 alleles of the CYP3A5 gene (CYP3A5*3 and CYP3A5*6) result in inactive CYP3A5 expression. Prior published methods[30] were modified in our laboratory to identify the CYP3A5*3 and the CYP3A5*6 alleles. Subjects with a CYP3A5*3/*3, *3/*6, or *6/*6 genotype were considered deficient in CYP3A5 expression (CYP3A5 poor metabolizer).

The PgP is an ATP-dependent efflux pump located in the small intestine, brain, kidney, and other organs in the body where it may influence drug levels and tissue exposure to drugs.[31] Boulton et al.[32] showed that risperidone is a relatively good PgP substrate, and in a mouse strain with a genetic disruption of this gene (knockout), higher brain penetration of several antidepressants was found.[33] A human variant of the PgP gene (C3435T in exon 26) has attracted interest because of its association with increased levels of a PgP substrate digoxin.[34] Patients are classified as having 2 (T/T), 1 (C/T), or no (C/C) mutant alleles of the PgP exon 26 variation.[31] Patients with a T/T genotype had increased digoxin levels after oral administration[34] and increased risk for nortriptyline-induced postural hypotension.[35] Using established testing methods[36] and based on published literature,[34,35] it was hypothesized that subjects with T/T genotype would have lower PgP activity, and so they were compared with all remaining subjects. This specific PgP variant appears to be silent but may be tightly associated with other functional variants in the PgP gene including G2677 (A,T) in exon 21.[31] The exon 21 variant presents 2 possible mutations, T and A. It is believed that the 2677T variant may be translated into a PgP transporter with lower activity.[31] There are 6 possible individual genotypes for the PgP exon 21 variation (G/G, G/T, T/T, A/A, G/A, and T/A).[31] On the basis of published literature,[31] the 2677 T/T genotype was predicted to have lower PgP activity when compared with subjects carrying the other PgP genotypes.

Statistics

The Statistical Package for the Social Sciences (SPSS)[37] was used for the calculations. The hypothesis was as follows: the CYP2D6 enzyme is of sufficient importance to risperidone metabolism such that a CYP2D6 poor metabolizer phenotype will have a significant association with risperidone ADRs and risperidone discontinuation due to ADRs in a routine psychiatric setting. Two statistical multivariate models were developed, using logistic regression, where the dependent variables were (1) the presence (73/325, 22%) or absence (252/325, 78%) of moderate-to-marked risperidone ADRs and (2) the discontinuation of risperidone due to ADRs (81/212, 38%) or for other reasons (131/212, 62%). The critical independent confounding variables included those that may (1) increase the risk of ADRs (high risperidone dose,[37] the coprescription of CYP inhibitors according to intermediate definition, and the use of typical or atypical antipsychotics) and (2) decrease the risk of ADRs (low risperidone dose[37] and the coprescription of antiparkinsonian drugs and CYP inducers). Table 2 describes definitions and frequencies of each of these confounders. Two-way cross-tabulations were performed for the univariate analyses (Tables 4 and 5) for which the odds ratios (ORs) were computed for each variable. Additionally, other possible independent variables from the list of patient demographics and clinical variables (Table 1) were also explored. The 95% confidence intervals (CIs) for the ORs were calculated (Tables 4 and 5). The significant clinical variables, or those with a p value close to significance, were selected for the logistic regression clinical models.[38] It was planned that once each of these 2 clinical models was developed, the CYP2D6 poor metabolizer phenotype (poor metabolizer versus other CYP2D6 phenotypes) would be tested for a univariate OR in a cross-tabulation. If this univariate OR was significant or close to significance, the CYP2D6 poor metabolizer phenotype would be introduced in the respective clinical model. The Hosmer-Lemeshow goodness-of-fit test[38] was used to assess the fitness of the logistic regression models; all fit well (Tables 4 and 5). Power and Precision software[39] was used

Table 4. Variables Associated With Presence of at Least Moderate Adverse Drug Reactions in Univariate Analyses and Logistic Regression (LR)

	Univariate Analyses			LR[b] Clinical Model (blind to genotype)			LR[c] Model With Genotype		
Variable	OR	CI	p	OR	CI	p	OR	CI	p
Clinical									
High dose[a]	1.3	0.7 to 2.7	.41						
Typical antipsychotic	2.4	1.1 to 5.0	.02	2.5	1.1 to 5.3	.02	2.4	1.1 to 5.2	.03
Atypical antipsychotic	0.58	0.25 to 1.4	.20	NS					
CYP inhibitors[a]	0.88	0.50 to 1.5	.65						
Low dose[a]	0.78	0.41 to 1.5	.45						
Antiparkinsonian drugs[a]	1.4	0.73 to 2.5	.33						
CYP inducer[a]	1.2	0.47 to 3.3	.66						
Outpatient status	0.58	0.29 to 1.1	.11	0.51	0.25 to 1.0	.05	0.46	0.22 to 0.94	.03
Organic central nervous system lesion	1.6	0.94 to 2.8	.08	1.7	0.96 to 2.9	.07	1.7	0.99 to 3.0	.06
Genotype									
CYP2D6 poor metabolizer	3.1	1.4 to 7.0	.004				3.4	1.5 to 8.0	.004
CYP3A5 poor metabolizer	1.1	0.57 to 1.9	.87						
P-glycoprotein exon 26[a]	1.0	0.52 to 2.0	.98						
P-glycoprotein exon 21	0.40	0.14 to 1.2	.08				NS		
GSTM1[a]	1.2	0.70 to 2.0	.53						
GSTT1[a]	0.84	0.45 to 1.6	.57						

[a]Variable was far from being significant.
[b]Hosmer-Lemeshow goodness of fit: $\chi^2 = 0.14$, df = 4, p = .99).
[c]Hosmer-Lemeshow goodness of fit: $\chi^2 = 0.33$, df = 4, p = .99).
Abbreviations: CI = 95% confidence interval, NS = nonsignificant, OR = odds ratio.

to estimate the approximate sample size needed for replication studies of nonsignificant differences.

Interrater Reliability

The ratings were conducted by an experienced researcher and clinician psychiatrist (J.dL.) and/or 2 experienced research nurses who had at least 5 years of state hospital experience with these types of patients and were in charge of recruitment. Many of the UKU ratings were obtained by the rating psychiatrist who assessed 76% (248/325) of the patients. For practical reasons, the remaining 24% (77/325) were obtained by 1 of the 2 experienced research nurses (the rating psychiatrist was unavailable at the time of the ratings). The 2 research nurses assessed patients with the rating psychiatrist for over 1 year and assessed more than 100 patients before conducting independent ratings. The research nurses and rating psychiatrists discussed difficult patient cases that they independently assessed when the blood was collected. When possible, the psychiatrist saw the patient later with the research nurse.

Interrater reliabilities of the 3 raters were tested in 45 interviews. All 3 interviewers were present in the room and independently scored the patients. Interrater reliability was measured by intraclass correlation coefficients (ICC) using a 1-way random-effect analysis of variance.[40] The ICC is the ratio of between-subject variance to total variance. The closer ICC is to 1, the smaller the contribution of the raters to the total variance of the scores and, therefore, the larger their agreement.[41] The ICC for the dichotomous classification "presence or absence of at least moderate side effects" was very high: ICC = 0.95; CI = 0.92 to 0.97; F = 60.5, df = 44.90, p < .001. Similarly, when the whole range of the UKU global score (0 to 3) was used, the ICC continued to be very high: ICC = 0.92; CI = 0.87 to 0.95; F = 34.3, df = 44.90, p < .001.

RESULTS

Description of Adverse Drug Reactions

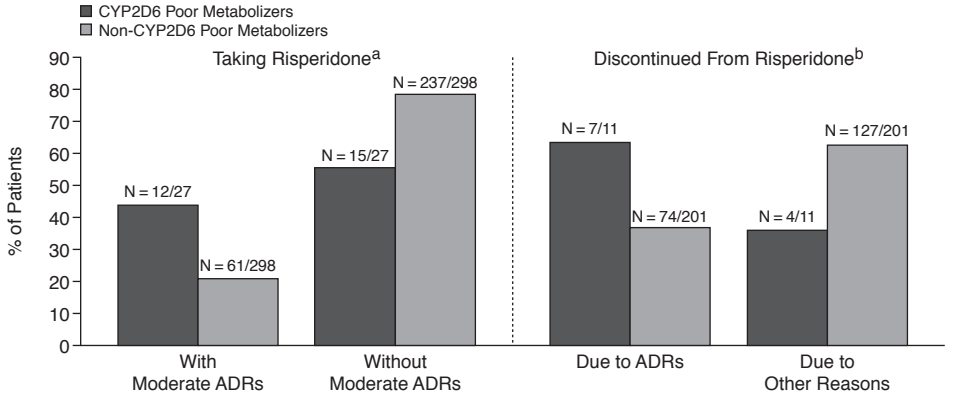
There were 73 patients with moderate-to-severe ADRs on risperidone therapy. According to the researcher assessment, most patients (92%, 67/73) had extrapyramidal side effects (including resting tremor [73%, 53/73]; stiffness [69%, 50/73]; hypersalivation [22%, 16/73]; and akathisia [7%, 5/73]). Other frequent ADRs were sedation (19%, 14/73) and sexual/urinary problems (4%, 3/73).

In 81 patients discontinued due to ADRs, according to the chart review (and information provided by the patient), the most frequent ADRs were any extrapyramidal side effects (57%, 46/81) (including akathisia [25%, 20/81]; stiffness [21%, 17/81]; resting tremor [20%, 16/81]; acute dystonic reactions [15%, 12/81]; and hypersalivation [14%, 11/81]), sedation (25%, 20/81), sexual/urinary problems (20%, 16/81), and upper gastrointestinal problems (9%, 7/81).

Variables Associated With Moderate-to-Marked Adverse Drug Reactions During Risperidone Therapy

Most of the clinical confounders that were predicted to affect patient ADRs were found not to be significant (Table 4). Only coprescription of typical antipsychotics was significantly associated with moderate-to-marked

Figure 1. Comparison of CYP2D6 Poor Metabolizers and Non–Poor Metabolizers in Patients Taking or Discontinued From Risperidone



[a]Odds ratio = 3.1 (CI = 1.4 to 7.0, p = .004).
[a]Odds ratio = 3.0 (CI = 0.85 to 10.6, p = .07).
Abbreviation: ADR = adverse drug reaction.

ADRs. Two other additional clinical variables were close to significance: outpatient status and an "organic" central nervous system (CNS) lesion. Thus, the logistic regression using clinical variables included typical antipsychotics, outpatient status, and presence of organic CNS lesions (the latter with borderline significance). The univariate analysis suggested that the CYP2D6 poor metabolizer phenotype increased the odds of having moderate ADRs by 3.1 (Figure 1). The multivariate OR, 3.4, remained significant even after correcting for the 3 clinical confounders in the logistic regression. The PgP exon 21 variant was close to reaching significance in the univariate analysis, but CYP3A5, PgP exon 26, GSTM1, and GSTT1 variants were not.

Variables Associated With Risperidone Discontinuation Due to Adverse Drug Reactions

In the univariate analyses, ADR discontinuation was associated with CYP inhibitors, CYP inducers, low risperidone dose, and coprescription of atypical antipsychotics. Among other clinical characteristics, outpatient status was significant, and typical antipsychotics, being naive to antipsychotics, and white race were close to being significant. The logistic regression clinical model included coprescription with atypical antipsychotics, CYP inhibitors and CYP inducers, outpatient status, and race (the latter 3 parameters were of borderline significance). The univariate analysis suggested that CYP2D6 poor metabolizer phenotype increased the odds of having risperidone discontinued due to ADRs by 3.0 (Figure 1). The multivariate OR was 6.0 after correcting for the clinical confounding variables in the logistic regression. White race was not significant once CYP2D6 poor metabolizer phenotype was included in the regression. None of the other gene variants were close to significance in the univariate analyses.

Plasma Concentration Ratio of Risperidone/9-Hydroxyrisperidone

Among the subjects taking risperidone for whom risperidone/9-hydroxyrisperidone ratios were calculated, 19% (53/281) had inverted ratios > 1, and 81% (228/281) had ratios ≤ 1. There are 2 obvious reasons for an inverted ratio[9]: (1) being genetically deficient in CYP2D6 (poor metabolizer phenotype) or (2) taking at least 1 powerful CYP2D6 inhibitor (fluoxetine, paroxetine, or bupropion). Those reasons were respectively present in 36% (19/53) and 44% (23/53) of subjects with inverted ratios. The remaining subjects with inverted ratios were intermediate metabolizer individuals (11%, 6/53; 2 of whom were taking other CYP inhibitors) and extensive metabolizer individuals (9%, 5/53) taking other CYP inhibitors or CYP2D6 substrates. Among subjects with normal ratios ≤ 1, 1% (2/228) were genetically deficient CYP2D6 poor metabolizers (their ratios were close to 1: 0.82 and 0.93) and 9% (21/228) taking at least 1 powerful CYP2D6 inhibitor.

In the 281 patients taking risperidone who had complete risperidone levels, an inverted ratio was significantly (OR = 2.0; CI = 1.0 to 3.8, p = .04) associated with having moderate-to-marked ADRs in the univariate analysis. The 3 variables (typical antipsychotics, outpatient status, and organic CNS lesion) that were significant in the clinical logistic model of the total on-risperidone sample were tested to develop a clinical model in these 281 patients. Organic CNS lesion had to be eliminated due to its high p value (p = .20). A logistic model having 3 variables (typical antipsychotics, outpatient status, and inverted level ratio) provided a significant adjusted OR of 2.1 (CI = 1.1 to 4.2, p = .02) for the inverted ratio. This suggested that the risperidone ratio provided additional information to the clinical model in these 281 patients.

Table 5. Variables Associated With Discontinuation of Risperidone Due to Adverse Drug Reactions in Univariate Analyses and Logistic Regression (LR)

	Univariate Analyses			LR[b] Clinical Model (blind to genotype)			LR[c] Model With Genotype		
Variable	OR	CI	p	OR	CI	p	OR	CI	p
Clinical									
High dose[a]	0.68	0.70 to 1.7	.42						
Typical antipsychotic	0.50	0.20 to 1.2	.12	NS					
Atypical antipsychotic	0.42	0.17 to 1.0	.05	0.37	0.15 to 0.94	.04	0.33	0.14 to 0.85	.02
CYP inhibitors	2.5	1.4 to 4.7	.003	2.2	1.2 to 4.1	.04	2.4	1.3 to 4.7	.008
Low dose	1.7	0.97 to 3.1	.06	NS					
Antiparkinsonian drugs[a]	1.2	0.61 to 2.4	.31						
CYP inducers	0.33	0.11 to 1.0	.04	0.32	0.10 to 1.0	.06	0.26	0.08 to 0.88	.03
Outpatient status	2.2	1.2 to 4.2	.02	2.0	0.99 to 3.9	.05	2.1	1.0 to 4.1	.04
Naive to antipsychotics	1.9	0.86 to 4.2	.11	NS					
White	2.4	0.97 to 5.8	.05	2.3	0.91 to 5.7	.08	2.1	0.82 to 5.3	.13
Genotype									
CYP2D6 poor metabolizer	3.0	0.85 to 10.6	.07				6.0	1.4 to 25.4	.02
CYP3A5 poor metabolizer[a]	1.0	0.51 to 1.9	.99						
P-glycoprotein exon 26[a]	1.1	0.61 to 2.2	.66						
P-glycoprotein exon 21[a]	0.78	0.36 to 1.7	.51						
GSTM1[a]	1.1	0.67 to 2.0	.58						
GSTT1[a]	0.71	0.37 to 1.4	.94						

[a]Variable was far from being significant.
[b]Hosmer-Lemeshow goodness of fit: $\chi^2 = 6.3$, df = 6, p = .39.
[c]Hosmer-Lemeshow goodness of fit: $\chi^2 = 10.8$, df = 6, p = .10.
Abbreviations: CI = 95% confidence interval, NS = nonsignificant, OR = odds ratio.

However, when the genetic CYP2D6 poor metabolizer phenotype was added to the regression model (adjusted OR = 6.0; CI = 1.8 to 19.9, p = .003), the adjusted OR for the risperidone inverted ratio became nonsignificant (OR = 1.1; CI = 0.45 to 2.6, p = .87).

Dosing Effects

In the complete sample set, high doses were not good predictors of risperidone ADRs (Table 4) or risperidone discontinuation due to ADRs (Table 5). Mean dose values had no better predictive power and did not account for patient characteristics (naiveness, old age, or dementia). Low risperidone dosing became relevant when the CYP2D6 genotype was considered. Among the 27 CYP2D6 poor metabolizers taking risperidone, the group was split by the presence (N = 12) or absence (N = 15) of moderate-to-marked ADRs. None of the patients with moderate-to-marked ADRs were taking low risperidone doses (0%, 0/12), but almost half of the group without significant ADRs (47%, 7/15) were taking low risperidone doses (Fisher exact test, p = .007). Thus, a low risperidone dose appeared to offer CYP2D6 poor metabolizers some protection from developing moderate-to-marked ADRs. This effect was not seen in non–poor metabolizer subjects (p = .86).

In the group discontinued from risperidone, there was a trend among non–poor metabolizer subjects (p = .13) for low-dose risperidone therapy to be overrepresented among patients who discontinued therapy due to ADRs (41%, 30/74) versus those discontinued for other reasons (30%, 38/127). In the small number of 11 poor metabolizers, low doses were similar in those discontinuing risperidone due to ADRs (57%, 4/7) or for other reasons (50%, 2/4).

The Effects of Comedication

Table 3 lists CYP inhibitors and inducers according to genetic CYP2D6 phenotype. Patients discontinued from risperidone were further subdivided according to whether they were discontinued due to ADRs or not, since this variable was significantly associated with CYP inhibitors and inducers.

Table 4 shows that the presence of inhibitors (intermediate definition) in patients taking risperidone was not significantly associated with moderate-to-marked ADRs in the univariate analysis. The use of the other definitions (narrow or wide) did not appear to change the results (respectively, OR = 0.88; CI = 0.45 to 1.7, p = .61 and OR = 0.95; CI = 0.56 to 1.6, p = .86). Inducers were also not significantly associated with moderate-to-marked ADRs.

Table 5 shows that CYP inducers in patients discontinued from risperidone were associated with discontinuation due to ADRs in the univariant and multivariate analyses. Univariate analysis (Table 5) showed that the presence of CYP inhibitors (intermediate definition) was associated with discontinuation due to ADRs (OR = 2.5; CI = 1.4 to 4.7, p = .003). Use of the narrow or wide definitions instead of the intermediate definition for CYP inhibitors provided very similar significant univariate ORs (respectively, OR = 2.7; CI = 1.3 to 5.4, p = .005 and OR = 2.8; CI = 1.5 to 5.0, p = .001). Substituting the intermediate definition for the narrow or wide definition was not associated with any relevant changes in the

clinical logistic regression models. The only relevant change in the model with the CYP2D6 genotype was that the wide inhibitor definition was associated with a no longer appropriate model (i.e., the Hosmer-Lemeshow goodness-of-fit test became significant).

DISCUSSION

The results of this study suggest the CYP2D6 poor metabolizer phenotype is associated with an increase in moderate-to-marked ADRs and increased risperidone discontinuation due to ADRs (Figure 1). Suggestions that the CYP2D6 poor metabolizer status is unimportant with regard to risperidone therapy appear unfounded in light of these consistent results. The CYP2D6 phenotype may prove useful to clinicians treating psychiatric patients with risperidone. The effect of the genetic poor metabolizer phenotype was detectable even in the uncontrolled and "noisy" clinical environment where clinicians commonly use different doses and multiple comedications.

Some researchers may feel that it is better to explore the association between CYP2D6 and risperidone response in a more restricted group of patients that have less confounding factors. Examples of more restricted subgroups are patients taking absolutely no other drugs (including no psychiatric, nonpsychiatric, or antiparkinsonian medication) or patients never treated with antipsychotics. There are 2 inherent problems with these types of restricted study designs: (1) finding an association in a very small and well-controlled subgroup will only prove that CYP2D6 genotyping may be a helpful tool in a very restricted number of patients, but will not help clinicians treating a typical patient prescribed risperidone and (2) the number of patients recruited who would satisfy these study criteria would be quite small. According to our recruitment patterns, to obtain a sample of more than 500 patients (on or off risperidone treatment) not taking any other medication would require screening more than 5000 patients willing to consent. To identify a sample of more than 500 patients (on or off risperidone treatment) never treated with antipsychotics would require screening more than 3500.

The idea that the clinical environment must be controlled in order to detect the clinical relevance of this genetic variation is a misplaced notion. When a genetic variation has a substantial impact on the clinical response to a drug (as the CYP2D6 phenotype appears to have), the influence of the phenotype may be detectable in routine clinical settings provided a sufficient number of patients are evaluated. Ultimately, the application of genetic testing to clinical practice requires proof that testing for a genetic variation has utility in the clinical setting where it is likely to be applied. The initial application of genetic testing has a far greater potential for being validated in complex patient populations when the effect of the gene variation has a substantial impact on drug elimination or response.

Relative Importance of Genetic CYP2D6 Poor Metabolizer Phenotype

Clinical confounders did not explain the CYP2D6 poor metabolizer phenotype association with moderate-to-marked ADRs or with risperidone discontinuation due to ADRs. In fact, the OR increased from 3.0 to 6.0 for the CYP2D6 poor metabolizer phenotype when confounders were considered among patients who discontinued risperidone due to ADRs. However, 2 points should be kept in mind. First, while the effect of the CYP2D6 poor metabolizer phenotype was powerful and consistent (Tables 4 and 5), it was limited to a small number of total patients. CYP2D6 poor metabolizers accounted for only 16% (12/73) of patients with moderate-to-marked ADRs taking risperidone, and only 9% (7/81) of patients who discontinued risperidone due to ADRs. Thus, the CYP2D6 poor metabolizer phenotype is not the primary cause of risperidone ADRs. Second, not every CYP2D6 poor metabolizer had problems while taking risperidone. Low risperidone dose appeared to offer CYP2D6 poor metabolizers some protection from developing moderate-to-marked ADRs. This effect was not seen in non–poor metabolizer subjects.

Comparison of Genetic CYP2D6 Poor Metabolizer Phenotype With Other Variables

The CYP2D6 poor metabolizer phenotype was the only significant variable in both logistic regression models (ADRs while taking risperidone and ADRs resulting in discontinuation of risperidone). The clinical relevance of a CYP2D6 poor metabolizer phenotype is further illustrated by the increased percentage of moderate-to-marked ADRs from a low of 19% (51/268) in non–poor metabolizers without typical antipsychotics, to 33% (10/30) in non–poor metabolizers with typical antipsychotics, and to 44% (12/27) in CYP2D6 poor metabolizers. Similarly, the increased percent of ADR-related discontinuations went from a low 30% (43/143) in non–poor metabolizers without CYP inhibitors, to 53% (31/58) in non–poor metabolizers with CYP inhibitors, and to 64% (7/11) in CYP2D6 poor metabolizers.

In this study, plasma risperidone levels did not appear to add any additional information to the genotype. The clinical model in the 281 patients with available levels suggested that an inverted ratio added some additional information to the clinical model. However, the lack of significance of risperidone levels after adding the CYP2D6 genotype suggests that the main effect of the variable inverted level ratio was due to the genetic effects. Moreover, the adjusted OR of the inverted ratio was remarkably lower than the CYP2D6 phenotype OR in all analyses. This suggests that blood collection for levels may not

provide any additional valuable information to the prediction of ADRs in risperidone patients already genotyped for CYP2D6. Furthermore, risperidone level blood collection requires an early morning draw before the first dose and after steady state (at least 5 days after the last risperidone change and, optimally, without other relevant medication changes), the assumption that the patient is compliant with risperidone intake, centrifugation to extract plasma, and storage in a freezer before sending to an outside laboratory. Blood collection for genotyping can be done anytime, and the tube of whole blood can be frozen until shipped to the outside laboratory. Further advances, such as genotyping patients using buccal swabs, make this approach more attractive. In summary, although risperidone levels may add to a research study and a clinical setting with no access to CYP2D6 genotype, risperidone level collections are much more complicated to obtain than CYP2D6 genotyping for routine clinical use. Also, risperidone levels probably do not add much meaningful clinical information to CYP2D6 genotyping besides informing about drug interactions.

The lack of predictive power of high and low risperidone doses, despite the fact that we accounted for the possibility of confounding variables, such as being naive, demented, or old, was somewhat surprising. Double-blind placebo-controlled studies on healthy schizophrenia patients taking risperidone monotherapy unequivocally suggest a risperidone dosing effect on ADRs. However, in a routine psychiatric environment, the different diagnoses, multiple medical problems, and comedications may negate the relevance of such dose-related studies. This underlies a basic conundrum for clinical science: carefully controlled clinical research can identify many parameters that "could affect" clinical response, but in the complex clinical environment in which clinicians work, their importance is all too often unclear.

Our own previous high-dosing studies in a naturalistic setting suggested that high antipsychotic dosing appears to follow complex patterns.[42,43] Thus, in naturalistic studies, high dosing may be explained by some patient variables but, more importantly, by physician practices. A study on high dosing of typical antipsychotics suggested that some patient variables (e.g., age and schizophrenia diagnosis) were important, but physician variables (e.g., working in 1 of the 2 hospitals) were also found to be important.[42] We recently showed that smoking or gender did not predict high olanzapine doses (although they are reported to affect olanzapine's metabolism and disposition).[43] Instead, high olanzapine dosing was best predicted by a diagnosis of schizophrenia, physician response to the length of stay, and preferences by some individual physicians.[43]

Risperidone appears to have a narrower therapeutic window for extrapyramidal ADRs than olanzapine. This study does not suggest that risperidone dosing is irrelevant in this naturalistic setting, but that dosing effects may become more meaningful after knowing the patient's genetic CYP2D6 phenotype. Low doses definitely protected CYP2D6 poor metabolizers from moderate-to-marked ADRs, but this protective effect was not seen in CYP2D6 non–poor metabolizers. The dose effects were unclear in patients discontinued from risperidone, but it is possible that physicians tried to lower risperidone doses before discontinuing risperidone due to ADRs.

We do not have a good explanation why CYP inducers and/or inhibitors did not predict moderate-to-marked ADRs in the on-risperidone patients while they did predict risperidone discontinuation due to ADRs. However, the influence of comedications is complicated by the number of different drugs (which could not be separated into individual entities) and variable doses. Metabolic enzyme inhibition and induction are both drug and dose dependent, making the effects of group classifications more sensitive to the random variation typically encountered in a clinical environment. By contrast, the CYP2D6 poor metabolizer phenotype is always associated with absent CYP2D6 enzyme expression, regardless of what other clinical variables are present. The constancy of CYP2D6 poor metabolizer effect may explain its more predictable impact in routine clinical practice. The metabolic inhibitors and inducers may have significant therapeutic importance, but their effects appear to be less consistent.

Other Gene Variations

As expected, the GST genotypes were not associated with ADRs in patients either taking or discontinued from risperidone. The CYP3A5 and PgP exon 26 genotypes also showed no obvious risperidone ADR association. The PgP exon 21 T/T genotype did not reach significance in the univariant analyses (OR = 0.40; CI = 0.14 to 1.2, p = .08; Table 4) or in the logistic regression (OR = 0.47; CI = 0.16 to 1.4, p = .17) on the patients taking risperidone. Assuming that the T/T exon 21 variant is associated with a decrease in risperidone ADRs and OR ≤ 0.40, the sample size required to find a significant difference with a power of 80% is larger than 700 subjects on risperidone therapy. The PgP exon 21 genotype effect on risperidone discontinuation was even less promising in the univariate analysis (OR = 0.78; CI = 0.36 to 1.7, p = .51; Table 5). Assuming that the T/T exon 21 variant is associated with risperidone discontinuation due to ADRs and OR ≤ 0.78, the sample size required to find a significant difference with a power of 80% is almost 4000 subjects off risperidone. Very large risperidone studies would be needed to explore the effect of having at least an A allele on exon 21 (there were only 1%, 4/325, of subjects with A alleles among risperidone patients and 3%, or 6/212, among off-risperidone patients). It appears that even if PgP affects risperidone therapy, the effect is not as marked as the effect produced by the CYP2D6 poor metabolizer phenotype.

Limitations and Strengths

The number of CYP2D6 ultrarapid and intermediate metabolizer subjects was too small to assess the effect of these phenotypes; however, they did not appear to have as much clinical importance as the CYP2D6 poor metabolizer phenotype.

The recruited total sample was rather large, but the CYP2D6 poor metabolizer phenotype subsamples were relatively small. To decide if this sample size is a limitation or strength, one needs to compare it with prior published studies. After excluding case reports,[11,12] the published risperidone samples relating ADRs and CYP2D6 phenotypes after CYP2D6 genotyping are rather small. The respective numbers of poor metabolizer/genotyped individuals in these types of studies were 5 poor metabolizers among 32 risperidone-treated subjects in our pilot study,[9] 3 poor metabolizers among 42 patients in a Danish study,[13] 1 poor metabolizer among 35 in a Spanish study,[14] and 0 poor metabolizers among 11 in a Japanese study.[15] These 4 studies total 9 poor metabolizers among 120 subjects; without our pilot study, the total is 4 poor metabolizers among 88 subjects. The current analyzed samples had 27 poor metabolizers of 325 taking risperidone and 11 poor metabolizers of 212 discontinued from risperidone after excluding some subjects (2 poor metabolizers/17). Although the risperidone discontinuation sample is relatively small and included only 11 poor metabolizers, this number of poor metabolizers is higher than in all published samples combined, including our pilot study. In summary, relatively small study samples like this one are not uncommon in published pharmacogenetic studies in the psychiatric setting. For example, a frequently quoted pharmacogenetic study of 2 antidepressants that explored CYP2D6 genotype included 16 poor metabolizers of 246 genotyped geriatric patients.[44]

Future Studies

Many other potential risk factors for risperidone ADRs must exist in the typical clinical setting. No cause was found for risperidone problems in approximately half of the patients. The CYP2D6 poor metabolizer genotype, typical antipsychotics, or organic CNS lesions were absent in 41% (30/73) of patients with moderate-to-marked ADRs. CYP2D6 poor metabolizer genotype and CYP inhibitors were absent in 53% (43/81) of patients discontinued from risperidone due to ADRs. This may suggest that pharmacodynamic variation (receptor response) may play as great or greater a role in risperidone-induced ADRs as genetic or environmental metabolic variations.

Like a prior relatively large retrospective survey,[45] this cross-sectional study suggests that the genetic CYP2D6 poor metabolizer phenotype is clinically important. However, a large prospective study should be performed to verify that the CYP2D6 poor metabolizer phenotype is associated with risperidone discontinuation due to ADRs. Extremely large samples, perhaps of 1000 or more patients taking risperidone, are required to assess the clinical importance of CYP2D6 intermediate or ultrarapid phenotype on risperidone treatment. Newly identified gene polymorphisms associated with antipsychotic ADRs should also be tested in similar, large-scale, clinical environments to assess their value in helping clinicians identify patients at risk for ADR-related risperidone discontinuation.

The prediction that genetics will be part of the standard patient clinical management by 2015[2] may be a bit optimistic, in view of the translational research yet to be done before this information can effectively be translated into routine clinical practice.[18,46] However, testing for gene variations in metabolic enzymes like CYP2D6 that play a major or important role in the elimination of many psychiatric drugs seems an appropriate initial target application for psychiatry. The implication of this enzyme variation on drug dosing is relatively straightforward[47] and modifications in dosing regimens based on genetic polymorphisms in this and other metabolic enzymes have already been proposed for numerous drugs.[48–51]

Drug names: amantadine (Symmetrel and others), bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Tegretol, and others), celecoxib (Celebrex), citalopram (Celexa), erythromycin (Ery-tab, E-base, and others), escitalopram (Lexapro), felbamate (Felbatol), fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), nefazodone (Serzone and others), nortriptyline (Aventyl, Pamelor, and others), olanzapine (Zyprexa), paroxetine (Paxil), phenytoin (Dilantin and others), primidone (Mysoline and others), risperidone (Risperdal), sertraline (Zoloft), valproic acid (Depakene and others).

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