

Failure to respond to treatment with typical antipsychotics is not associated with CYP2D6 ultrarapid hydroxylation

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Aims To investigate whether or not there is a correlation between failure to respond to typical antipsychotics and CYP2D6 ultrarapid metaboliser status.

Methods CYP2D6 phenotype (metaboliser status) was assigned following genotyping for gene duplication, as well as for the *CYP2D6*3*, *CYP2D6*4*, and *CYP2D6*5* null alleles in 235 treatment-refractory patients and 73 nonrefractory patients.

Results Four (1.7%) of the 235 treatment-refractory subjects were positive on the duplication assay, but, of these, two were found to represent duplications of a null allele (*CYP2D6*4*), therefore leaving only two (0.85%) positive for duplication of a wild type allele (ultrarapid metabolisers). Three (4.1%) of the nonrefractory subjects had a genotype consistent with ultrarapid metaboliser status. Fisher's exact test gave a two-tailed *P* value of 0.091, i.e. a trend towards an excess of ultrarapid metabolisers in the nonrefractory group, which was in the opposite direction to that predicted by our hypothesis.

Conclusions Although the results show a trend towards an excess of ultrarapid metabolisers in the nonrefractory group, the percentages in the two groups of patients are both within the range for ultrarapid metabolisers in Caucasian populations. Our data are not consistent with ultrarapid metaboliser status being a major cause of failure to respond to typical antipsychotics.

Keywords: CYP2D6, genotype, metabolism, pharmacokinetics, treatment-refractory, typical antipsychotics

Introduction

The cytochrome P450 enzyme CYP2D6 is a polymorphic enzyme which contributes significantly to the pharmacokinetics of most typical antipsychotics [1]. Between 0.5% and 7% of Caucasians have very high enzyme activity [2, 3] and are known as ultrarapid metabolisers, or UMs. This high enzyme activity is due to the presence of 2 or more copies of a functional *CYP2D6* allele existing in tandem on the same chromosome [2, 4–6]. At the other end of the metabolic spectrum are individuals who are homozygous for null alleles (poor metabolisers or PMs), representing about 7–9% of most Caucasian populations. The remainder of the population (excluding PMs and UMs) are known as extensive metabolisers (or EMs).

Two patients with ultrarapid metaboliser status have

been described for whom tricyclic antidepressants at doses beyond the usual therapeutic range were required in order to achieve a therapeutic response [4]. Up to 30% of patients with schizophrenia who are prescribed typical antipsychotics are treatment-resistant [7]. The term treatment-resistant includes those who are treatment-refractory (show inadequate clinical response) and those who are treatment-intolerant (exhibit adverse responses). We hypothesized that patients with schizophrenia who were refractory to treatment with typical antipsychotics would be more likely to be ultrarapid metabolisers, as compared with patients who responded to typical antipsychotics. If the hypothesis were confirmed, it could form the rationale for a preprescribing genotyping assay to predict patients who would be less likely to respond well to typical antipsychotics at standard doses, and therefore assist the process of clinical dose finding and/or the more rapid progression of such patients on to an atypical antipsychotic not subject to the CYP2D6 polymorphism.

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Received 4 November 1998, accepted 8 April 1999.

Methods

Our 235 treatment-refractory subjects came from a sample of 246 patients treated with clozapine in the United Kingdom (UK). All of these patients were resistant to treatment with typical antipsychotics, and had a diagnosis of schizophrenia or schizoaffective disorder (clozapine prescribing restrictions in the UK, UK Clozaril Patient Monitoring Service). Prescribing consultants provided data regarding whether their patients were refractory to typical antipsychotics, intolerant of typical antipsychotics, or both refractory and intolerant of typical antipsychotics. Out of the 246 patients on clozapine there were a total of 235 who were refractory, or refractory and intolerant to typical neuroleptics. The standard definition of treatment-refractory schizophrenia has been provided by Kane *et al.* [7]: (1) at least three periods of treatment in the preceding 5 years with antipsychotics (from at least two different chemical classes) at doses equivalent to or greater than 1000 mg day⁻¹ of chlorpromazine for a period of 6 weeks, each without significant symptomatic relief, and (2) no period of good functioning within the preceding 5 years. Data regarding which typical antipsychotics had been prescribed were not available. However, the most commonly prescribed typical antipsychotic prior to switching to clozapine in the UK for the period during which our sample was collected was haloperidol (Novartis, personal communication).

Our comparison group, nonrefractory to typical antipsychotics, comprised 73 patients from the Maudsley and Bethlem Royal Hospitals NHS Trust. Sixty-six of these had been treated with various antipsychotics, mostly haloperidol (approximately 60%) or fluphenazine, at doses equivalent to at least 100 mg chlorpromazine daily for at least 12 months prior to assessment and had DSM-III-R schizophrenia. Information regarding duration of treatment was not available for the remaining seven subjects, but six had been treated with the equivalent of at least 100 mg chlorpromazine daily, while the remaining patient received 15 mg flupenthixol decanoate by depot injection fortnightly, the equivalent of 75 mg chlorpromazine daily. Six of these seven subjects had a clinical diagnosis of schizophrenia; one had a diagnosis of affective psychosis. As the patients were treated with a variety of antipsychotics, we converted all the prescriptions to chlorpromazine equivalents according to British National Formulary guidelines, in order to assess whether or not there was a relationship between the magnitude of the dose and the CYP2D6 genotype.

Ethics Committee approval was obtained for the study on all subjects, and, as there were insufficient numbers of non-Caucasians in the sample for the analysis to be informative, all non-Caucasians were excluded.

DNA was extracted from blood collected in EDTA tubes using the Nucleon II kit (Nucleon Biosciences, UK). *CYP2D6* gene duplication was detected by the long-PCR method of Løvlie and colleagues [8], using the Expand Long Template PCR System (Boehringer Mannheim, UK), and primers 5'-TCCCCCACTGAC CCAACTCT-3' and 5'-CACGTGCAGGGCAC CTAGAT-3'. The PCR was performed in a final volume of 25 µl including 2.5 µl Boehringer buffer 1, 4.5 µl of a 2 mM solution of each dNTP, 0.5 µl of each primer (10 µM solutions), and 0.25 µl of Boehringer enzyme mix (Taq/Pwo). Boehringer buffer 1 contains 20 mM Tris-HCl pH 7.5, 100 mM KCl, 1 mM dithiothreitol, 0.1 mM EDTA, 0.5% (v/v) Tween_R 20, 0.5% (v/v) Nonidet_R P40, 50% glycerol (v/v), and 1.75 mM MgCl₂. Cycling conditions were modified as follows: initial denaturation for 2 min at 94° C, 35 cycles of 93° C for 10 s, 60° C for 30 s and 68° C for 5 min, followed by an elongation step of 68° C for 7 min.

As cases have been described in which there are extra copies of a nonfunctional or null *CYP2D6* allele [8–10], it is necessary to assay for nonfunctional *CYP2D6* alleles as well as for the presence of a duplication event in order to confirm ultrarapid metaboliser status. We therefore assayed for the *CYP2D6*3*, *CYP2D6*4*, and *CYP2D6*5* null alleles. *CYP2D6*4* and *CYP2D6*5* are the most common and next most common null alleles, respectively; analysis for *CYP2D6*4*, *CYP2D6*5*, and *CYP2D6*3* should detect 90–95% of null alleles in a European Caucasian population [11–13].

The *CYP2D6*3* and *CYP2D6*4* point mutation alleles were detected by PCR followed by restriction enzyme digestion as in the method of Smith *et al.* [14], with minor modifications. For the *CYP2D6*3* assay, primers 5'-ATGAGCTGCTAACTGAGCCC-3' and 5'-CCGA GAGCATACTCGGGAC-3' were used in a total reaction volume of 25 µl containing 10 mM Tris-HCl pH 8.3, 50 mM KCl, 0.001% (w/v) gelatin, 3 mM MgCl₂, 0.2 mM each dNTP, 0.25 µM each primer, and 1.25 U AmpliTaq (Perkin-Elmer, UK). Cycling conditions were: initial denaturation at 94° C for 3 min, 30 cycles at 95° C for 1 min, 60° C for 30 s, and 72° C for 1 min, followed by final elongation at 72° C for 10 min. PCR products were digested using *Hpa*II, and analysed on a 3% agarose gel, together with a 1 kb ladder (Gibco BRL). For the *CYP2D6*4* assay, we used primers 5'-GCCTTCGCCAACCCTCCG-3' and 5'-AAATCCTGCTCTTCCGAGGC-3' and the same conditions as for *CYP2D6*3*, except a MgCl₂ concentration of 1.5 mM. PCR products were digested with *Bst*NI and analysed on a 3% agarose gel as above.

The *CYP2D6*5* gene deletion allele was assayed by long-PCR using the GeneAmp XL PCR kit (Perkin Elmer, UK) by the method of Steen and colleagues [15],

using primers 5'-ACCGGGCACCTGTACTCCTCA-3' and 5'-GCATGAGCTAAGGCACCCAGAC-3'. PCR was performed according to the manufacturer's instructions using Ampliwax[®] beads to facilitate a hot start and a 100- μ l reaction volume with 200 ng genomic DNA, 1xXL reaction buffer, 0.2 mM each dNTP, 0.3 μ M each primer, 1.1 mM Mg(OAc)₂ and 2 U of the r*Tth*/Vent[®] DNA polymerase mixture. The XL reaction buffer contains Tricine, K(OAc), glycerol, and DMSO (concentrations not given by the supplier). Cycling conditions were: initial denaturation at 93°C for 1 min, 35 cycles at 93°C for 1 min, 65°C for 30 s, 68°C for 5 min, and a final elongation at 72°C for 10 min.

Two cases were positive on both the *CYP2D6*4* and the duplication assays. These were further tested to determine whether the null or the wild type allele was duplicated as described by Sachse *et al.* [10]: a further duplication assay was performed with primers as described by Johansson *et al.* [16], giving a 10kb amplicon in cases positive for a duplication, which was then subjected to a nested PCR followed by digestion with *Hph*I. The primers for the Johansson *et al.* assay were 5'-GCCACCATGGTGTCTTTGCTTTC-3' and 5'-ACCGGATTCCAGCTGGGAAATG-3', and we modified the conditions by performing the assay with the Expand Long Template PCR System (Boehringer Mannheim, UK), using a total reaction volume of 25 μ l with 2.5 μ l of Boehringer buffer 1, 4.5 μ l of a 2 mM solution of each dNTP, 0.5 μ l of each primer (10 μ M solutions), 0.37 μ l of the Taq/Pwo enzyme mix, and 200 ng of genomic DNA. Cycling conditions were: initial elongation of 94°C for 2 min; 10 cycles of 93°C for 10 s, 60°C for 30 s, 68°C for 12 min; 20 cycles of 93°C for 10 s, 60°C for 30 s, and 68°C for 12 min with a 15 s increment per cycle; and a terminal elongation step of 68°C for 7 min. The product of this reaction was then diluted 1:5 and subjected to nested PCR using primers 5'-TCAACACAGCAGGTTCA-3' and 5'-CTGTGGTTTACCCACC-3'. The reaction volume was 65 μ l, containing 10 mM Tris-HCl pH 8.3, 50 mM KCl, 1.5 mM MgCl₂, 0.16 mM each dNTP, 0.1 μ M each primer, and 0.2 U AmpliTaq. The cycling conditions were: initial elongation at 94°C for 2 min, 25 cycles of 94°C for 30 s, 58°C for 10 s, 72°C for 1 min, and a final elongation step of 72°C for 7 min. The products were digested with *Hph*I and separated on a 3% agarose gel.

The results were analysed using SPSS for Windows and EpiInfo Version 6 (Centers for Disease Control and Prevention, USA and World Health Organization, Switzerland).

Results

CYP2D6 genotype and deduced phenotype for the 235 subjects refractory to treatment with typical antipsychotics

vs the 73 responsive to typical antipsychotics are given in Table 1. Of the 235 treatment-refractory subjects, four (1.7%) cases were positive on the duplication assay. However, two cases yielded a *CYP2D6*4/wt* result with the *CYP2D6*4* assay and a positive result with the duplication assay; these cases were found to represent duplications of the *CYP2D6*4* allele. As these cases possessed only one functional copy of *CYP2D6*, they were deduced to be phenotypically equivalent to heterozygous null cases and hence extensive metabolisers, not ultrarapid metabolisers. Therefore only two out of 235 cases (0.9%) were positive for duplication of a wild type allele. In contrast, of the sample of 73 nonrefractory patients, 3 (4.1%) were positive for the duplication assay, of which none was positive for the null alleles tested. The results were therefore in the opposite direction to that predicted by our hypothesis, but they did not reach significance: Fisher's exact test was performed, comparing the presence or absence of UM status in the two clinical groups, which gave a two-tailed *P* value of 0.091. (Chi square was not appropriate here, with the number of cases being less than 5; with Fisher's exact test the one-tailed and two-tailed values were identical, but the value is reported as two-tailed as the results were in the opposite direction to that predicted by the hypothesis).

Table 2 shows the distribution of the alleles with allele frequencies in the two clinical groups, with the results being reported under the assumption that the duplication allele is present in the heterozygous state. If this allele were present in a homozygous state in all cases in which it was found, then the frequencies of the wild type and null alleles in the treatment-refractory group would be unchanged, while that of the duplication allele would be doubled at 0.0085; the frequencies of the wild type, null, and duplication alleles in the nonrefractory group would be 0.71, 0.25, and 0.041, respectively. However, as in the paper by Johansson *et al.* none of their cases with a duplication allele was homozygous for this variant, we have assumed that all of our cases are heterozygous. The frequencies of the *CYP2D6*4*, *CYP2D6*5*, and *CYP2D6*3* alleles, respectively, in the sample of 235 and 73 were: 0.223, 0.024, and 0.018 (in the sample of 235), and 0.219, 0.02, and 0.02 (in the sample of 73). Comparing the presence or absence of the duplication allele in the two groups, Fisher's exact test gave a two-tailed *P* value of 0.10 (Table 2).

Discussion

We did not find an excess of ultrarapid metabolisers in subjects refractory to treatment with typical antipsychotics. On the contrary, only two out of 235 (0.9%) treatment-refractory cases were positive for duplication of a wild-type allele, while three out of 73 (4.1%) nonrefractory

Table 1 *CYP2D6* genotype and deduced phenotype in subjects refractory to treatment with typical antipsychotics and nonrefractory to treatment with typical antipsychotics; numbers of cases given with percentages in parentheses.

	EM (wt/wt) or (wt/mut)	PM (mut/mut)	UM (dup of wt)
Refractory to TAs (<i>n</i> =235)	220 (93.6)	13 (5.5)	2 (0.9)*
Non-refractory to TAs (<i>n</i> =73)	67 (91.8)	3 (4.1)	3 (4.1)*

TAs, typical antipsychotics, *wt*, wild type, *mut*, nonfunctional mutant or null allele (includes 2 duplications of *mut* in the EM group), dup of *wt*, duplication of wild type allele. *Two-tailed *P*-value for presence or absence of UM status in refractory vs nonrefractory group = 0.09 (Fisher's exact test); odds ratio = 0.2, 95% confidence limits 0.02–1.80.

Table 2 Distribution of *CYP2D6* alleles in the treatment-refractory and nonrefractory groups; allele numbers given, with frequencies in parentheses. The *CYP2D6**4 × 2 allele is included in the null alleles.

	Wild type	Null	Duplication of wild type
Refractory to TAs	343 (0.73)	97 (0.26)	2 (0.0043)
Non-refractory to TAs	103 (0.72)	37 (0.26)	3 (0.021)*

TAs, typical antipsychotics. *Two-tailed *P*-value for presence or absence of duplication allele in refractory vs nonrefractory groups = 0.10 (Fisher's exact test); odds ratio = 0.21, 95% confidence limits 0.02–1.88.

cases were genotyped as ultrarapid metabolisers. This gives a trend ($P=0.091$, Fisher's exact test) towards an excess of ultrarapid metabolisers in the nonrefractory group of patients. However, both percentages are within the range for ultrarapid metabolisers in Caucasian populations [2, 3, 6, 10]. Two cases of *CYP2D6**4 duplications were found, which is the second time this has been reported in Caucasians, Sachse and colleagues [10] having provided the first report.

The results demonstrate that ultrarapid hydroxylation by *CYP2D6* of typical antipsychotics is not a major cause of failure to respond to treatment with these agents. There are at least five possible explanations for this surprising result. Firstly, we could have failed to find a significant result when there is in fact a significant association of ultrarapid hydroxylation either with treatment-refractory status (the direction of the original hypothesis), or with treatment nonrefractory status (the direction of the trend found). The odds ratio (OR) for UM status, counting the treatment-refractory group as the 'diseased state' and the nonrefractory group as the 'nondiseased state', was 0.2, with exact lower and upper 95% confidence limits of 0.02 and 1.8, respectively (Table 1). This means that ultrarapid metaboliser status is less associated with being treatment-refractory than with being nonrefractory, with the range extending to being more associated with treatment-refractory. Of note the two patient sample

groups are unequal in size; if we had had as many in the treatment nonrefractory group and the percentage of ultrarapid metabolisers in this group had remained the same as in our current findings, then we would have found 10 ultrarapid metabolisers in the nonrefractory group, which would have given a chi square of 5.47, a *P* value of 0.019, and an OR of 0.19, with exact lower and upper limits of 0.02 and 0.92, respectively. In this scenario a significant result in the opposite direction to our original hypothesis would have been found.

Secondly, in both of our groups of subjects, the dose of antipsychotic was titrated by the prescribing consultants according to clinical effect. This could obscure any pharmacogenetic effects, i.e. ultrarapid metabolisers could be receiving doses above or at the upper end of the normal prescribed range, and then respond as if they were extensive metabolisers. However, for the nonrefractory group one of the patients with *CYP2D6* duplication was on only 30 mg flupenthixol decanoate 2 weekly (equivalent to 150 mg chlorpromazine daily, i.e. a low dose).

Thirdly, although *CYP2D6* is known to contribute to the pharmacokinetics of many typical antipsychotics [1], the specific contribution is different for different antipsychotics, and other cytochromes are involved. *CYP2D6* is involved in the first pass metabolism and systemic elimination of perphenazine [17], and the systemic elimination of zuclopenthixol [18]. For these drugs, high *CYP2D6* activity would be expected to lead to lower serum levels of the drugs, and hence possible therapeutic resistance. Although inhibition studies demonstrated that *CYP2D6* is likely to be involved in the metabolism of chlorpromazine [19, 20], Muralidhan and colleagues [21] showed that *CYP2D6* makes a relatively minor contribution to the large interindividual variability seen in plasma chlorpromazine levels.

The systemic elimination of haloperidol has been shown by Llerena and colleagues to be dependent on *CYP2D6* activity [22], and although early reports showed that *CYP2D6* catalysed the oxidation of reduced haloperidol back to haloperidol [23, 24], other work was not consistent with this [25], and recent reports [26, 27] have demonstrated that *CYP3A4* is the primary enzyme involved in this step in the metabolic pathway. The steps

in the metabolism of haloperidol in which CYP2D6 is involved are at present unclear, but, consistent with the results of Llerena and colleagues [22], Nyberg *et al.* showed that a CYP2D6 poor metaboliser had higher concentrations of plasma haloperidol throughout a 4-week treatment period with haloperidol decanoate as compared with 7 CYP2D6 extensive metabolisers [28]. Although none of the subjects in the study of Nyberg *et al.* was an ultrarapid metaboliser, it would be logical to assume that a UM would have low plasma haloperidol levels. Suzuki and colleagues [29] studied the correlation between CYP2D6 genotype and steady-state plasma concentrations (C_{ss}) of haloperidol and reduced haloperidol in a group of 50 Japanese patients with schizophrenia. They found that the mean C_{ss} of haloperidol was significantly higher ($P < 0.05$) in the patients with 1 mutant allele compared with those with no mutant alleles, and that the mean C_{ss} of reduced haloperidol was significantly higher ($P < 0.05$) in the patients with 1 or 2 mutant alleles compared with those with no mutant alleles. They therefore suggested that the C_{ss} of reduced haloperidol was more dependent upon CYP2D6 activity than the C_{ss} of haloperidol. However, although they did not find a significant difference between the mean C_{ss} of haloperidol in patients with 2 mutant alleles compared to those with no mutant alleles, it is of note that in this study the patients with 2 mutant alleles were either homozygous for the *CYP2D6*10* allele ($n = 4$), which is associated with reduced but not absent CYP2D6 activity, or were compound heterozygotes for the *CYP2D6*10* and *CYP2D6*5* alleles ($n = 2$). Hence no patient actually had 2 CYP2D6 null alleles. Lane *et al.* [30] examined the relationship between CYP2D6 phenotype (as measured by dextromethorphan/dextrorphan metabolic ratio) and haloperidol disposition in 18 newly hospitalized Chinese patients with schizophrenia. Despite the fact that no PMs were found in this study, significant correlations between the metabolic ratio and plasma haloperidol concentration, reduced haloperidol concentration, and reduced haloperidol/haloperidol ratios were found. In a preliminary report of a larger study, Schmider *et al.* [31] investigated therapeutic drug monitoring data in 178 patients *vs* CYP2D6 genotype and found that PMs had significantly higher reduced haloperidol but not haloperidol concentrations compared with patients with one or no mutant alleles. The suggestion of Suzuki *et al.* [29] that CYP2D6 affects reduced haloperidol levels at steady-state to a greater extent than haloperidol levels might therefore be correct. However, Suzuki *et al.* also suggested, based on the work of Tyndale and colleagues [24], that CYP2D6 catalyses the oxidation of reduced haloperidol back to haloperidol. As already outlined above, more recent work is not consistent with this [25–27], although the precise step in the metabolism of reduced haloperidol in which

CYP2D6 is involved is at present unclear. Young *et al.* [25] showed that reduced haloperidol was the preferred form in the plasma after the administration of a single dose of either haloperidol or reduced haloperidol to healthy volunteers. A negative correlation between clinical response and reduced haloperidol levels or reduced haloperidol/haloperidol ratios has been observed [32]; it is possible that ultrarapid metabolisers of CYP2D6 could have lower reduced haloperidol levels and hence a better clinical response. This would be consistent with the trend that we have found for an excess of UMs in the nonrefractory group. However, Lane *et al.* [30] did not find a correlation between response and reduced haloperidol levels, reduced haloperidol/haloperidol ratios, or haloperidol levels. This is consistent with analyses by other authors [33, 34].

In the case of thioridazine, CYP2D6 catalyses the formation of mesoridazine, a metabolite *with antipsychotic activity* [35], and may be involved in the generation of another active metabolite, sulphoridazine. Extensive metabolisers have been shown to have higher peak levels of mesoridazine and sulphoridazine than poor metabolisers after a single oral dose, with lower levels of thioridazine [35]. The total serum concentrations of substances with antipsychotic activity at steady state will be determined by the relative magnitudes of the equilibrium constants of all the reactions in the metabolic pathway; these equilibrium constants and the relative antipsychotic potencies of the different active metabolites are unknown. It is therefore difficult to predict the effect of ultrarapid metaboliser status on clinical response to thioridazine.

Both of our groups of patients had been treated with various typical antipsychotics; it is therefore possible that we failed to show a correlation in one direction or the other as effects with some antipsychotics *vs* other antipsychotics cancelled each other out. Furthermore, it is possible that some patients in the treatment-refractory group were treated with agents whose levels are not significantly affected by CYP2D6 genotype (such as chlorpromazine). However, we would emphasize that a significant result would be unlikely to be obscured by either of the above possibilities as the numbers of individuals with duplications is *very low in both* the treatment-refractory and nonrefractory groups. It is also of note that the subject on zuclopenthixol who is an ultrarapid metaboliser is clinically stable on a low dose.

Fourthly, several of the above studies (especially those on normal volunteers) were single-dose pharmacokinetic analyses; single dose effects may differ markedly from those seen at steady state in a situation of pharmacological adaptation [36]. However, the work of Nyberg *et al.* [28], Suzuki *et al.* [29], Lane *et al.* [30], and Schmider *et al.* [31] was conducted on patients at steady-state. Furthermore, Jerling *et al.* [37] conducted a study on

patients during continuous treatment and CYP2D6 genotype was shown to predict significantly the oral clearance of perphenazine and zuclopenthixol (patients with 2 CYP2D6 null alleles having a significantly lower clearance than those with one or no mutant alleles).

Finally, other factors may contribute towards non-response to medication, including noncompliance, pharmacodynamic factors, other biological factors, and psychosocial factors. Non-compliance occurs in up to 50% of patients on neuroleptics [38]. Pharmacodynamic factors have been implicated in the clinical response to clozapine, an atypical antipsychotic [39]; it may be that other pharmacodynamic factors (e.g. D₂-receptor variants) are involved in the response to typical antipsychotics. Lieberman and colleagues [40] and Van Os *et al.* [41] have reviewed predictors of outcome in psychotic illness and concluded that factors such as longer duration of untreated illness, and structural brain abnormality on CT or MRI predict unfavourable outcome, while living in a low 'expressed emotion' environment is one of the predictors of a favourable outcome.

We have not found an association between ultrarapid metaboliser status and being treatment-refractory to typical antipsychotics. On the contrary, we found a trend towards an association between ultrarapid metaboliser status and being nonrefractory to typical antipsychotics, which could have reached significance had our nonrefractory group been equal in size to our refractory group.

Nonetheless, we have not excluded the possibility that ultrarapid metaboliser status could lead to failure to respond to a standard dose of some typical antipsychotics. But as only 0.5% to 7% of Caucasians are ultrarapid metabolisers, unless ultrarapid metaboliser status were associated with the psychotic illnesses for which the antipsychotics were prescribed (in this study, mainly schizophrenia), then as treatment resistance occurs in up to 30% of cases of schizophrenia, this factor would be unlikely to account for the majority of cases of treatment resistance. In summary, our data are not consistent with ultrarapid metaboliser status being a major cause of failure to respond to typical antipsychotics, and are consistent with ultrarapid metaboliser status being weakly associated with response to typical antipsychotics, especially in the case of haloperidol.

We thank Dr A.K. Daly for the provision of a CYP2D6*5 positive control. Katherine J. Aitchison is a Wellcome Trust Clinical Training Fellow. Christoph Sachse is supported by BMBF grant 01EC9408.

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