

with promising clinical improvement). We are currently engaged in a study to pursue this issue in a more scientific manner, and welcome the views of other clinicians.

Barnes, T. R. E., McEvedy, C. J. B. & Nelson, H. E. (1996) Management of treatment resistant schizophrenia unresponsive to clozapine. *British Journal of Psychiatry*, **169**, (suppl. 31), 31–40.

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Genetic polymorphism and drug-induced movement disorders

Sir: We were interested to read the paper by Armstrong *et al* (1997) on drug-induced movement disorders in relation to the *CYP2D6* genotype. We would agree that this important polymorphism may well be a contributory factor in more chronic drug-induced movement disorders.

Several lines of evidence support this. Firstly, one of the most robust findings in the whole field of tardive dyskinesia (TD) research is the link between TD and high neuroleptic dosage. Impaired clearance of antipsychotics due to the poor metaboliser genotype leads to elevated plasma levels, which has clear implications in view of the first association. Other studies have attempted to assess the problem from a different standpoint: looking at the variation in neuroleptic breakdown between those with TD and schizophrenic controls. The best study in this area is that of Yesavage *et al* (1987), which found a significant difference in standardised thioxanthine levels between 21 TD sufferers and 20 controls.

In our recent study (Bates, 1997) we used promethazine, a phenothiazine predominantly metabolised by the *CYP2D6* cytochrome, to probe metabolic clearance in 18 patients, 10 with TD and eight controls. We used a high-performance liquid chromatography technique which simultaneously assayed promethazine and its two major breakdown products, the sulphoxide and monodesmethyl metabolites. We found evidence of significant impairment of metabolism of promethazine in the TD group, with raised promethazine levels and raised promethazine to metabolite ratios, indicating this was not an effect of varying absorption or bioavailability. We will be publishing our results more fully soon.

This simple and relatively inexpensive method may prove useful in pretreatment testing to enable prediction of those likely to develop TD or concentration-dependent side-effects, and to guide dosage decisions.

Armstrong, M., Daly, A. K., Bienerhassett, R., et al (1997) Antipsychotic drug-induced movement disorders in schizophrenics in relation to *CYP2D6* genotype. *British Journal of Psychiatry*, **170**, 23–26.

Bates, G. D. L. (1997) Using Promethazine to Demonstrate Abnormalities of Phenothiazine Metabolism in Tardive Dyskinesia. MMedSc dissertation, Department of Psychiatry, University of Birmingham.

Yesavage, J. A., Tanke, E. D. & Sheikh, J. I. (1987) Tardive dyskinesia and steady-state serum levels of thiothixene. *Archives of General Psychiatry*, **44**, 913–915.

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Demography and age at onset of schizophrenia

Sir: Jablensky & Cole (1997) conclude from their analysis of the WHO 10-Country study of schizophrenia that marital status has a major effect on age at onset of schizophrenia, and that the effect of gender disappears when controlling for marital status (and other variables). However, these findings are partly due to demographic effects. To explain this artefact assume that outbreak of schizophrenia occurs (like a random event) irrespective of marital status. As is well known, married people are in our population on average older than single ones. Therefore the mean age at onset of schizophrenia will be later for married people than for single ones. This difference does not reflect a real association between schizophrenia and marriage (which was excluded by the hypothetical model) but it reflects a trival demographic effect due to the different age structures of married and single people. This applies to men and women but in a different way. In general, women marry earlier than men. Thus, in the population, married women are on average younger than married men, and unmarried women are younger than unmarried men. Let us assume that outbreak of schizophrenia is related neither to gender nor to marital status. Then because of these different age structures the mean age at onset will

be earlier for married women than for married men. The same relation holds for singles. But, as above, these differences are due to a trival demographic effect. If there is a real association between gender and schizophrenia in the sense that onset is later for women, then this difference is reduced when comparing married women with married men and single women with single men. Thus differences in the age structures between married and single persons in the population explain, at least in part, the effects of marital status and gender on age at onset, described by Jablensky & Cole. The differences in age at onset between developing and developed countries may be attributed to different demographic structures in these countries. We do not deny these effects, but to disentangle demographic effects from real effects the age structures of the underlying population must be taken into account when analysing the data.

Häfner, H., Riecher, A., Maurer, K., et al (1989) How does gender influence age at first hospitalization for schizophrenia? A transnational case register study. *Psychological Medicine*, **19**, 903–918.

Jablensky, A. & Cole, S. W. (1997) Is the earlier age at onset of schizophrenia in males a confounded finding? Results from a cross-cultural investigation. *British Journal of Psychiatry*, **170**, 234–240.

Riecher-Rössler, A., Fätkenheuer, B., Löffler, W., et al (1992) Is age of onset in schizophrenia influenced by marital status? Some remarks on the difficulties and pitfalls in the systematic testing of a simple question. *Social Psychiatry and Psychiatric Epidemiology*, **27**, 122–128.

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Author's reply: Jennen-Steinmetz *et al* suggest that “differences in the age structures between married and single persons . . . explain, at least in part, the effects of marital status and gender on age at onset, described by Jablensky & Cole”. Since the statistical analyses we use uncorrelate gender and marital status prior to examining the relationship of either variable to age at onset, Steinmetz *et al*, can rest assured that no part of our conclusions reflects a spurious correlation between marital status and age at onset of schizophrenia that is induced by those two variables' common association with gender differences in age at marriage. In the general linear model, the effects of gender (and gender-correlated differences in age at marriage) are partialled out, or controlled for, in the calculus underlying multiple regression (Mosteller & Tukey,