Assaults on psychiatrists

Sir – O'Sullivan and Meagher[1] presented an interesting study of this important subject. They were, however, unable to find any significant factors which put psychiatrists at risk of patient-perpetrated violence. They quote a review article of mine[2] which contains an unfortunate misprint – 'decrease' instead of 'increase', although the true message is suggested thereafter: 'ie. there is a significantly higher risk of novices being attacked than veterans'. This deduction is based on a study published in the medical press[3] (ref. 40 in the review paper) wherein Tables 3 and 4 show that the bulk of assaults are concentrated in the earlier parts of a psychiatrist's career as evidenced by the lack of an increase in reported number of assaults as experience lengthens. In my study the mean number of years in psychiatric practice was 18.56 years, range 6-34 years, with a total of 1,225 years. The mean for the O'Sullivan and Meagher study was 7.2 years, range one month to 38 years.

O'Sullivan and Meagher divided their sample into 10 year age groups, finding some protective effect in the 45-54 year old group, whereas I divided up my sample on the basis of years of exposure to risk, ie. years practicing psychiatry. It would have been interesting to see what effect the latter methodology might have has on the results of the former study.

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RE: Hypertension and increased serum clozapine associated with clozapine and fluoxetine in combination

Sir – In their case report Sloan and O'Boyle[1] suggest that the elevation of serum clozapine and norclozapine with the combination of clozapine and fluoxetine is through the inhibition of the cytochrome P450 CYP2D6 isozyme, and that due consideration should be given to the genetic variation of this enzyme in clinical practice. Although an *in vitro* study[2] has demonstrated that clozapine is metabolised by CYP2D6, subsequent findings have demonstrated that there is a lack of association between clozapine metabolism and debrisoquine and S-mephenytoin hydroxylation polymorphism,[3] and that the CYP2D6 genotype does not affect clozapine clearance.[4] These studies suggest that CYP2D6 may not be involved in metabolism of clozapine *in vivo*. We would like to propose that the more likely mechanism underlying the increased serum clozapine levels is mediated by the altered activity of CYP3A4. This enzyme which is involved in the metabolism of clozapine, is also inhibited by fluoxetine and thus would lead to elevation of clozapine concentrations[5] when these two drugs are prescribed concomitantly.

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RE: Clozapine-fluoxetine and the CYP450 system

Sir – We thank Chong and Remington for their letter and interesting comments, and would like to add that there is still controversy in the literature over which of the various subtypes of cytochrome P450 are responsible for the metabolism of clozapine.[1] CYP1A2, CYP2D6 and CYP3A4 have all been found to be involved in the metabolism clozapine, and much of the evidence points toward CYP1A2 as being the most important.[1-3] CYP3A4 is not the major isoenzyme involved in the metabolism of clozapine, and while fluoxotene and its metabolite norfluoxetine have been shown to inhibit CYP3A4 this effect is minimal.[4] It is certainly possible that inhibition of this isoenzyme may have contributed to the raised clozapine and norclozapine levels, in our patient, and we accept the cited evidence indicating that CYP2D6 genotype does not effect clozapine clearance.[5] It is possible however that inhibition of the CYP2D6 system also contributed to the raised clozapine and norclozapine levels by the inhibition of a metabolic step distal to clozapine N-dealkylation ie. inhibition of secondary resulting in raised plasma levels of clozapine and norclozapine, but no change in the plasma clozapine/norclozapine ratio.[1] Furthermore the antidepressant medication nefazodone, which is a known CYP3A4 inhibitor has been shown to have no effect on clozapine metabolism.[6] Thus further clarification of the role of the different cytochromes involved in the metabolism of clozapine is warranted, and we would still advocate caution when coadministering drugs which have proven inhibitory action on the cytochrome P450 isoenzyme.

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