

drug-induced prolongation of QT intervals with little risk of arrhythmia (Day *et al*, 1990). This suggests that QTc prolongation in itself is not necessarily a good indicator of risk for sudden death.

QTc dispersion is an ECG-derived measure of the difference between the longest and the shortest QTc interval on the 12-lead ECG (Slyven *et al*, 1984). While a degree of variability between leads is normal, increased QTc dispersion is an indication of more extreme variability in ventricular repolarisation. Such extreme variability could be regarded as an index of the risk of arrhythmia. QTc dispersion is gaining recognition as a predictor of sudden cardiac death in conditions as varied as idiopathic long QT syndromes (Jervell-Lange-Nielsen syndrome and Romano-Ward syndrome), diabetes mellitus, peripheral vascular disease, congestive heart failure and coronary artery disease (Campbell, 1996). Measurements taken years beforehand correlate with a patient's risk of sudden death. Warner *et al* (1996) measured QT dispersion in their in-patient survey but could not find a significant association between larger QT dispersion and antipsychotic doses in excess of 2000 mg chlorpromazine equivalent per day. (It should be noted that only 16 of their patients were in this group.) As sudden death is relatively infrequent in a population on high-dose antipsychotics, measurement of QTc dispersion may give a clearer indication of which patients are at greater risk than reliance on QTc prolongation alone.

Campbell, R. (1996) Commentary: QT dispersion may reflect vulnerability to ventricular fibrillation. *British Medical Journal*, **312**, 878–879.

Day, C. P., McComb, J. M. & Campbell, R. W. F. (1990) QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. *British Heart Journal*, **63**, 342–344.

Slyven, J. C., Horacek, B. M., Spencer, C. A., et al (1984) QT interval variability on the body surface. *Journal of Electrocardiology*, **17**, 179–188.

Thompson, C. (1994) The use of high-dose antipsychotic medication. *British Journal of Psychiatry*, **164**, 448–458.

Warner, J. P., Barnes, T. R. E. & Henry, J. A. (1996) Electrocardiographic changes in patients receiving neuroleptic medication. *Acta Psychiatrica Scandinavica*, **93**, 311–313.

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Ethnicity and clozapine metabolism

Sir: Chong & Remington (1998) have pointed out the very important influence of ethnicity on clozapine metabolism. In a recently held National Psychiatric Conference in Pakistan, a number of psychiatrists suggested that in their clinical experience their patients responded to relatively smaller doses of clozapine. This may be due to the fact that our patients attain higher plasma levels at relatively lower doses, as suggested by Chang *et al* (1993) and Chong *et al* (1997). These findings have serious implications about side-effects such as seizures, drowsiness and weight gain, etc., which are dose-related. The cost factor is equally important as in most developing countries the patients and their families have to bear the cost. If these findings can be supported by more empirical data, a costly drug such as clozapine could be made available to a larger number of patients.

However, this problem cannot be addressed by comparative studies between various ethnic groups, as suggested by Chong & Remington (1998). These studies are needed to highlight the differences pointed out by the authors, but the real need is to study the pharmacokinetics of a new drug in a particular population before recommending therapeutic doses or plasma levels in that population. It may prove very difficult, if not impossible, to get proper controls for such cross-ethnic studies in view both of differences in individual variables (e.g. body weight, height, etc.) inherent in various ethnic groups, and other extraneous factors (e.g. environmental temperature affecting body and drug metabolism). At present, dosages and plasma levels for monitoring drugs such as lithium are thought to be universally similar, mostly on the basis of data obtained in European and American populations. Professionals working in populations which have different biological parameters (which can affect drug metabolism differently) have a responsibility to ask the pharmaceutical industry to provide relevant information before experimenting with these drugs in human subjects.

Chang, W. H., Cheln, C. P., Lin, S. K., et al (1993) Elevated clozapine concentrations in Chinese patients. *Neuropsychopharmacology*, **9**, 1175–1185.

Chong, S. A. & Remington, G. (1998) Ethnicity and clozapine metabolism (letter). *British Journal of Psychiatry*, **172**, 97.

—, **Tan, C. H., Khoo, Y. H., et al (1997)** Clinical evaluation and plasma clozapine concentrations in Chinese patients with schizophrenia. *Therapeutic Drug Monitoring*, **19**, 219–223.

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Comprehensiveness of systematic review

Sir: Adams *et al* (1998) are right to take us to task for not describing our literature search parameters as clearly as we should (Lawrie & Abukmeil, 1998), but are wrong to suggest that our search strategy would have missed a sizeable number of articles of considerable or direct interest.

For the record, we searched the October 1996 Silver Platter edition of Medline using the search terms 'MAGNETIC RESONANCE IMAGING/all subheadings' and 'SCHIZOPHRENIA/all subheadings'. Articles of potential interest were then examined for suitability. As we stated (Lawrie & Abukmeil, 1998) those articles giving complete or near-complete raw volumes of one or more brain regions were included, while area studies and volumetric studies of the corpus callosum and basal ganglia were excluded as were a large number of irrelevant papers (see below). In other words, as we stated, "40 relevant volumetric MRI studies were identified" – not 40 studies in total. To demonstrate, a search on current Ovid software using our search strategy identified 333 potentially relevant studies published by June 1996, of which only 36 met inclusion criteria. The rest reported: areas (32), irrelevant volumes (22), findings in children (2) or the elderly (7), qualitative appearances (23), magnetic resonance spectroscopy (12), functional imaging (11), methodological issues (11), conference abstracts (10), uncontrolled studies/case reports (36), letters (22), review articles (51) and other matters (58).

It is far from clear that a more sophisticated search would be worth the extra effort. Adams *et al* allude to possible Medline publication bias through language, but our review included seven papers from German, Italian and Japanese research groups who had reported in English. It would, however, be interesting to establish whether a more elaborate search would identify more papers and perhaps even alter the results of our review for a pre-specified