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Asphyxia at birth and schizophrenia

In our recent paper we reported that signs of asphyxia at birth were associated with the subsequent development of schizophrenia (Dalman *et al*, 2001). Crow (2001), in his invited commentary, suggested that the birth records were assessed by midwives who were not 'blind' as to case–control status. As stated in the paper, we took care to eliminate this possibility and think it highly unlikely that the midwives became unblinded. We should add that, following the Vancouver agreement (International Committee of Medical Journal Editors, 1997), the midwives were not listed as authors as they only contributed to data gathering. We understand that Professor Crow has also adopted this policy in relation to the National Child Development Study interviews (Done *et al*, 1991).

Why were our findings so clear-cut in relation to asphyxia? There are at least two possible reasons. First, we took care to adjust for confounders and also adjusted for the association between different pregnancy and delivery complications in order to examine for an association independent of other complications. Second, by using paediatricians to examine birth records we may have been measuring birth asphyxia more accurately than with the Apgar index, which is only poorly related to asphyxia (Sykes *et al*, 1982). Most of the other large studies carried out recently have relied upon routinely available data on pregnancy and birth complications. This might have introduced a random measurement error and could have obscured important associations.

Finally, the paper by Thomas *et al* (2001) does not contradict that of Dalman *et al* (2001). Thomas *et al* (2001) were concerned only with the possibility that pregnancy and delivery complications were more strongly associated with schizophrenia in certain subgroups. The results indicated that there were no statistically significant interactions so the association between asphyxia and schizophrenia was apparent in the whole sample.

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Atypical antipsychotics, cortical D_2 receptors and sensitivity to endogenous dopamine

Xiberas *et al* (2001) report that atypical antipsychotics show a preferential cortical *v.* striatal dopamine D_2 occupancy. This finding is not without controversy as Olsson & Farde (2001) failed to find such evidence and have suggested that an apparent cortical–striatal difference may be a methodological artefact. None the less, if the finding of Xiberas *et al* can be confirmed it prompts the question of why some drugs show a higher occupancy in one brain region compared with another.

Receptor occupancy by a drug is a function of its regional concentration and functional affinity for the receptor in that region. There are no data to suggest that the atypical antipsychotics show a higher regional concentration in the cortex; therefore, the difference is likely to arise because of higher functional affinity in the cortical regions. Functional affinity is determined by the receptor protein as well as local competition from endogenous neurotransmitters – dopamine in this case. The protein structure of the D_2 receptors throughout the brain is similar and so is their *in vitro* affinity in the absence of competition (Seeman & Ulpian, 1983). This leaves one plausible explanation – that different concentrations of endogenous dopamine in cortical *v.* striatal regions may account for the difference in occupancies observed.

It has been suggested that a lower affinity and a faster off-rate (k_{off}) may make atypical antipsychotics more susceptible to competition by the high levels of endogenous dopamine in the striatum compared with the low levels of endogenous dopamine in the cortex (Seeman *et al*, 1997; Kapur & Seeman, 2001). It is interesting that of the antipsychotics reported, the one with the lowest affinity, fastest dissociation from the D_2 receptor and hence highest susceptibility to competition (clozapine) shows the greatest cortical–striatal difference, whereas the one with the highest affinity, slowest dissociation and least susceptibility (haloperidol) shows the least cortical–striatal difference. Furthermore, it seems that 5-HT_2 blockade, or a multi-receptor profile, is not necessary to achieve this cortical–striatal difference since amisulpride, a relatively specific $D_{2/3}$ antagonist, also shows this effect. Thus, a lower affinity and a faster k_{off} of the atypical antipsychotics at the D_2 receptor makes them more responsive to endogenous dopamine concentrations and may account for the cortical–striatal difference noted by Xiberas *et al*.

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Diagnosis of vascular dementia

I read Dr Stewart's article on vascular dementia (Stewart, 2002) with great interest. As a recently appointed consultant in old age psychiatry (having been trained in the 'old' way about diagnosing vascular dementia, i.e. sudden onset, stepwise deterioration, history of vascular risk factors, etc.), I started noticing a very different presentation of vascular dementia, especially in those with evidence of extensive periventricular disease on computed tomography. These cases commonly present with a range of frontal executive function deficits, with functional psychiatric symptoms of anxiety and depression and sometimes with progressive aphasia, and do not necessarily have the classical history of vascular dementia as described in textbooks.

The importance of the clinical findings is that as clinicians and educational supervisors we need to use more screening tests for frontal executive functions in routine assessments of dementia. In addition to the Mini-Mental State Examination (Folstein *et al*, 1975), verbal fluency and similarities (FAS; Thomas & O'Brien, 2002) tests are quick ways of testing frontal functions and should be encouraged among all members of a multi-disciplinary team. This has also been recognised in the new Cambridge Examination for Mental Disorder of the Elderly, Revised (CAMDEX–R; Roth *et al*, 1999).

Findings of periventricular ischaemia are controversial as far as their relevance to dementia diagnosis is concerned but patients who present with marked frontal functioning deficit and evidence of periventricular ischaemia on computed tomography should receive a diagnosis of vascular dementia. It is now known that ischaemia in periventricular areas interferes with the cortico–striato–thalamo–cortical loops which, in turn, affect functioning of frontal lobes.

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Prolonged QT interval with rivastigmine

Rivastigmine is an acetylcholinesterase inhibitor licensed in the UK since 1998 for the treatment of mild to moderate Alzheimer's disease. Prolonged QT interval in association with this drug has not been previously described in the literature.

A 78-year-old man with dementia was commenced on rivastigmine for worsening of his cognitive decline and behavioural difficulties. He was receiving the following long-term medication: diltiazem, citalopram, furosemide, aspirin and ranitidine. His urea and electrolytes showed a low-normal potassium of 3.4 mmol/l (normal 3.5–5 mmol/l). A pre-treatment electrocardiogram (ECG) showed evidence of an old inferior myocardial infarct, a QT interval of 382 ms and a QTc interval of 397 ms.

Seven days after commencement of rivastigmine a repeat ECG showed a QT interval of 476 ms and a QTc interval of 477 ms. Rivastigmine was the only recent additional medication and was therefore discontinued. No other changes were made. One week later the ECG showed a normal QT interval of 402 ms and a QTc interval of 399 ms. (An abnormal QTc interval is defined as >456 ms.) A repeat ECG 2 months later on his long-standing medication showed normal QT and QTc intervals.

Prolonged cardiac repolarisation (QT interval) is important as it may lead to potentially life-threatening ventricular arrhythmias (e.g. torsades de pointes; Thomas, 1994). Risk factors for prolonged QT intervals include: congenital long QT interval syndrome, clinically significant bradycardia or heart disease, electrolyte imbalance (hypokalaemia, hypomagnesaemia), impaired hepatic or renal function and concomitant treatment with drugs with potential for pharmacokinetic/pharmacodynamic interactions (De Ponti *et al*, 2000).

To date, rivastigmine has been associated in very rare cases with atrioventricular block (see Exelon product data sheet; Novartis Pharmaceuticals UK Ltd, 2001). A literature search failed to identify any reports of QT interval prolongation associated with rivastigmine.

Confounding factors, such as comedication, electrolyte abnormalities and underlying disease, are more likely to occur in older people, who are the most likely age group to be receiving these drugs. Case reports such as this are an important method of reporting potential side-effects, particularly in the context of a newly introduced therapy.

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From mental hospitals to community care

The statistics on mental hospital closures given by Professor Leff (2001) will surprise not only lay people. I had no idea that hardly any mental hospital beds remain.

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