Correspondence

EDITED BY LOUISE HOWARD

Haematological monitoring with clozapine therapy in India

Sir: Clozapine was introduced in India in 1995 and some brands of the drug are now available for the equivalent of around £0.25 for 300 mg clozapine. Unfortunately, affordability is still a problem for many people with schizophrenia, as added to drug costs are the costs of weekly haematological monitoring (£0.25–0.75) and travel. The frequency and duration of haematological monitoring are factors that influence the cost and acceptability of therapy.

Studies from the USA (Alvir *et al*, 1993) and the UK (Atkin *et al*, 1996) reported a drastic fall in the incidence of agranulocytosis or neutropenia after the first 12 months of clozapine treatment. Long-term haematological data from India are lacking, but surveillance over four years in the UK (Atkin *et al*, 1996) did not find Asians from the Indian subcontinent to be at increased haematological risk. The UK study also found the risk of agranulocytosis in the second year of clozapine (0.07%) to be similar to that reported with phenothiazine treatment (0.08%), where counts are checked only on clinical indication.

Recommendations on long-term monitoring vary widely, from weekly monitoring in the USA (American Psychiatric Association, 1997), to fortnightly or monthly monitoring in Europe (Alvir *et al*, 1993). In India many centres monitor counts weekly for the first 18 weeks of clozapine therapy. Thereafter, counts are checked monthly for the duration of therapy, though some centres check counts fortnightly between 18 and 24 weeks. Early detection and management of neutropenia and agranulocytosis before sepsis supervenes is crucial in preventing mortality (Krup & Barnes, 1989). While weekly haematological monitoring for the duration of clozapine therapy would aid early detection of low counts, it is questionable whether monthly monitoring would achieve this.

With the available data, indefinite routine monitoring does not appear to be justified. I therefore invite comment from your readers on the proposition that routine haematological monitoring be discontinued after 16–18 months of clozapine therapy, except in those at higher risk such as the elderly.

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Chromosome 22q11 deletions and aggressive behaviour

Sir: We read with great interest the work by Murphy *et al* (1998) on the prevalence of velo-cardio-facial syndrome (VCFS) in a population of subjects with idiopathic learning disability. In both case reports of patients with 22q11 microdeletions described by Murphy *et al*, aggressive behaviour was a significant feature of the clinical presentation. Patients with deletional forms of VCFS are hemizygous for the gene encoding catechol-O-methyltransferase (COMT). A codon 158 polymorphism encodes common high and low COMT enzyme activity variants found in humans (Lachman *et al*, 1996*a*). Hemizygosity for the low-activity allele is associated with ultra-rapid cycling bipolar disorder that occurs in a subset of VCFS patients (Lachman *et al*, 1996*b*). Most of these rapidly cycling patients are difficult to manage because of increased aggressiveness.

Strous *et al* (1997) recently showed that the low-activity COMT allele is associated with increased violent behaviour in people with chronic schizophrenia. This finding is consistent with previous studies showing that dopaminergic and noradrenergic stimulation increase aggressive behaviour in animals (reviewed by Volavka, 1995). These observations suggest that the low-activity COMT allele could be the common denominator that leads to increased aggression in VCFS and other psychiatric conditions.

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Well-being in the families of people with schizophrenia

Sir: In this wide-ranging discussion it was encouraging that Szmukler & Bloch (1997) considered the importance of the well-being of the family, not just the risk of violence on the part of the person with psychosis. When the psychosis first manifests itself, family members suffer. Their hurt and bewilderment lowers their self-confidence, which may be further undermined by psychiatric staff not listening to them nor trying to answer their questions. Their own health may deteriorate to the point where they may abandon their relative or become incapable of supporting her/him.

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While families would agree that the prime focus of the psychiatric team must be the mental health of the patient, organisations such as ours would argue that a supportive family provides a large contribution to the short- and long-term health of the patient, whether the latter eventually lives in the family home or not.

For the family to be able to support the patient, they must have the understanding and information necessary to provide appropriate care. Ideas on confidentiality need to be re-thought. On admission to hospital, the patient may say 'no' to informing the family, but during their hospital stay and before discharge, they should be asked again. They may well have changed their mind, especially if staff have helped them to understand that sharing their problems with carers makes living with their illness easier (Carstairs *et al*, 1985). When the patient is discharged, staff should be quite sure that the patient is adamant about not informing his/her family. If s/he is adamant but intends to see the family even occasionally, s/he could be told that the family must get some minimum information, essentially phone numbers for emergencies and crises. The release of further information could be negotiated with the patient.

Ways of giving information which do not breach confidentiality (Atkinson & Coia, 1995) include the use of voluntary organisations such as National Schizophrenia Fellowship (Scotland) which can provide support and general information about treatments, the pros and cons of medication and tips on how best to help the user.

Where the family members are going to give support, they need accurate and well-balanced information on both the illness and the individual patient. If they do not get this from the psychiatric team, they may look elsewhere for enlightenment. They may then get suggestions of how to proceed which are neither relevant nor helpful to that particular patient, such as stopping medication and using alternative therapies, going back to work or college or taking up activities which put the person under stress and increase the possibility of relapse.

It is necessary that all psychiatric staff understand that discharging patients without providing information to their family could be detrimental to the patient's welfare. People with severe mental illnesses are looked after in hospital by highly trained professional staff with their own professional support systems. Discharging these patients into the community where families, the unpaid informal carers, are given no support and information, is potentially a recipe for disaster. It simply does not make sense.

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5-HT_2 neurotransmission in major depression

Sir: I read with interest the neuroendocrine challenge study by Sargent *et al* (1998). The conclusion that potentiation in 5-HT_2 neurotransmission is unlikely to be responsible for the antidepressant effect of selective serotonin reuptake inhibitors (SSRIs) is consistent with platelet studies suggesting that up-regulation of 5-HT_{2A} receptors may be a trait phenomenon of major depression (Hrdina *et al*, 1997). However, some additional points should be made to clarify the role of 5-HT_2 neurotransmission in depressive disorder.

First, concurrent use of cyproheptadine, a 5-HT_2 antagonist, to treat sexual dysfunction resulted in a reversal of the antidepressant effect of fluoxetine (Feder, 1991), supporting the role of 5-HT_2 neurotransmission in the antidepressant effect of SSRIs in some depressed patients. Second, short-term lithium treatment appears to reverse the deficit state in an animal model of depression by activating post-synaptic 5-HT_{1C} (current terminology 5-HT_{2C}) receptor sites (Aulakh *et al*, 1994). Further, it seems to enhance cognitive and motivational process by increasing 5-HT_2 neurotransmission (Harrison-Read, 1998). Hence, it is possible that initial increase in 5-HT_2 neurotransmission may account for the improvement in some symptoms of depression and/or for the augmenting effect of lithium carbonate in the treatment of refractory depression. Third, considering the findings that neurotransmission at 5-HT_2 receptors may be a trait marker of major depression (Hrdina *et al*, 1997), the down-regulation of 5-HT_2 receptors with long-term treatment with SSRIs might be responsible for prevention of recurrences of depression (this awaits further investigation). In sum, the participation of 5-HT_2 receptors in major depressive disorder appears to be multifarious and complex.

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Active placebos in antidepressant trials

Sir: Moncrieff *et al* (1998) highlight a methodological flaw in many placebo-controlled studies; anticholinergic side-effects are readily identifiable so it is not possible for these studies to be blinded and they are therefore liable to observer bias. This is the rationale for a meta-analysis of studies that used an active placebo in the form of atropine. Nine studies were identified and a smaller effect size for tricyclic antidepressant (TCA) efficacy was identified, relative to analyses pooling studies that used an inert placebo. They conclude that TCAs may not be as effective as previously assumed and that active placebos are necessary for valid double-blind studies.

In the discussion, Moncrieff *et al* acknowledge that the decreased efficacy of TCAs identified in their analysis may arise if atropine had antidepressant properties *per se*. This is dismissed on the evidence that a study by Gillin *et al* (1995) failed to demonstrate antidepressant efficacy of a centrally acting anticholinergic agent relative to a peripherally acting anticholinergic. However, the centrally acting anticholinergic studied was biperidan, a relatively selective M1 antagonist. In contrast, atropine is a competitive antagonist at all

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