

We believe that the use of a single red alert coupled with careful consideration of its significance by CPMS, together with the facility for independent expert haematology review, is the optimal management system for preventing potentially fatal agranulocytosis, and is the only way in which people with severe schizophrenia can obtain the benefits of clozapine with minimal risk.

GERSON, S., *et al* (1994) N-desmethyl clozapine: a clozapine metabolite that suppresses haemopoiesis. *British Journal of Haematology*, **86**, 551–556.

SAFFERMAN, *et al* (1992) Rechallenge in clozapine induced agranulocytosis. *Lancet*, **339**, 1296–1297.

VEYS, P. A., *et al* (1992) Clinical experience of clozapine induced neutropenia. *Drug Safety*, **7** (Suppl.), 26–32.

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Obsessive-compulsive symptoms and clozapine

SIR: Eales & Layeni (*BJP*, May 1994, **164**, 687–688) report exacerbation of obsessive-compulsive (OC) symptoms with clozapine therapy within the context of pre-existing OC symptoms. These symptoms may also arise *de novo* – often shortly after beginning clozapine treatment (Baker *et al*, 1992; Buckley & Meltzer, 1994). Such OC phenomena are surprisingly recalcitrant to standard pharmacotherapy (Buckley & Meltzer, 1994). The obsessions are readily distinguishable from partial delusions and are not merely the misrepresentation of a change in either the intensity or quality of delusions consequent upon clozapine therapy. OC symptoms in schizophrenic patients in general (Rosen, 1957) and now within the context of clozapine therapy offers a glimpse of the putative neurobiological heterogeneity as it may pertain to phenomenology and treatment response. Such observations lend support to the heuristic validity of using treatment response (to typical and atypical antipsychotic drugs) to define subgroups of schizophrenic patients (Schulz *et al*, 1989).

BAKER, R. W., CHENQAPPA, K. N., BAIRD, J. W. *et al* (1992) Emergence of obsessive-compulsive symptoms during treatment with clozapine. *Journal of Psychiatry*, **53**, 439–442.

BUCKLEY, P. F. & MELTZER, H. Y. (1994) Treatment of delusional disorders with clozapine. *American Journal of Psychiatry* (in press).

ROSEN, I. (1957) The clinical significance of obsessions in schizophrenia. *Journal of Mental Science*, **103**, 773–785.

SCHULZ, S. C., CONLEY, R. R., KAHN, E. M., *et al* (1989) Nonresponders to neuroleptics: a distinct subtype. In *Schizophrenia: Scientific Progress* (eds S. C. Schulz & C. A. Tamminga), pp. 341–350. New York: Oxford University Press.

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Strength of the genetic effect in schizophrenia

SIR: McGuffin *et al*'s proposition (*BJP*, May 1994, **164**, 593–599) that schizophrenia may be a purely genetic illness is not convincing.

McGuffin *et al* realise that the major obstacle to their contention is discordance between monozygotic twins. Accordingly, McGuffin *et al* describe genetic processes – mutation, unstable DNA sequences, imprinting, and inactivation – that are not hereditary in any easily identifiable pattern. Similar mechanisms, they posit, may be at work in schizophrenia.

Yet in the various disease entities they cite, nothing near the phenomenon of 50% discordance obtaining for schizophrenia in monozygotic twins is to be found. In Huntington's disease, where an expanded tandem repeat sequence accounts for the pathology, penetrance is 88% (Gusella *et al*, 1993). In fragile-X mental retardation, penetrance for the sons of the daughters of normal transmitting males is 80% (Warren & Nelson, 1994). Penetrance for heterozygote carriers of the gene for retinoblastoma is 85–95% (Naumova & Sapienza, 1994). The random X inactivation of Duchenne's muscular dystrophy, an X-linked illness, also does not seem readily applicable to schizophrenia.

On the other hand, the hypothesis that environmental stress imposed upon a genetic diathesis may cause schizophrenia is not merely "orthodoxy". While McGuffin *et al* discuss physical stressors, psychosocial factors should not be too easily dismissed. Tienari *et al* (1994) have shown that adopted-away children of schizophrenic mothers are far more likely to develop schizophrenia if their adoptive family is characterised by emotional disturbances. Moreover, contrary to accepted wisdom, life events may often precede the onset of schizophrenia (Van Praag, 1993). These are findings impossible to explain if we limit ourselves to a purely genetic aetiology.