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Clozapine and negative symptoms

SIR: I read with interest about the remarks made by Healy (*Journal*, January 1993, **162**, 23–29) on the superiority of clozapine over traditional neuroleptics and would like to express some reservations about this drug's ability to improve the negative symptoms of schizophrenia. Negative symptoms are ill-defined, and lack firmly established construct validity; they may be mimicked by drug-induced akinesia and depression (de Leon, 1989). The apparent improvement of negative symptoms in Kane *et al*'s (1988) study may be for a number of reasons. These include the reduction of positive symptoms, the use of a non-specific measurement scale (Brief Psychiatric Rating Scale), the relief of depression in chronic psychotic patients (clozapine is suspected of having some antidepressant property), and diminution of extra-pyramidal side-effects. The latter possibility was supported by the significantly lower scores for extra-pyramidal side-effect of the clozapine group than the chlorpromazine group from week four until the end of the trial. Perhaps a better way to prove clozapine's superiority in improving negative symptoms would be a controlled trial of treatment for 'pure negative syndrome', simple schizophrenia, or the residual negative syndrome. Until then we should be sceptical of its specificity in improving negative symptoms.

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Neuroleptic rechallenge after neuroleptic malignant syndrome

SIR: We read with interest the report by Weller & Kornhuber (*Journal*, December 1992, **161**, 855–856) on the use of the atypical antipsychotic clozapine after an episode of neuroleptic malignant syndrome (NMS). Being also concerned with the clinical management and follow-up of this syndrome, we feel it necessary to raise some points regarding the question of whether and which neuroleptic drug could be readministered as a further treatment of psychotic symptoms.

We would like to emphasise that the expression 'clozapine rechallenge' which is notified in the title of the article could lead to a potentially harmful misinterpretation. Indeed, the term rechallenge is defined as the giving of a further dose of a drug to a patient who had previously taken the same drug and in whom an adverse event, which might be due to that drug, had subsequently occurred (Stephens, 1988). Whether accidental or deliberate, the rechallenge is generally considered a major criterion in the assessment of an adverse drug reaction. The authors administered clozapine for persistent psychiatric symptoms to patients who had previously developed NMS when treated with prior neuroleptics, mainly phenothiazines and butyrophenones, but not clozapine. It is thus misleading to suggest that clozapine has been readministered after recovery of the NMS episode when this drug has just been chosen as a further and alternative antipsychotic medication. On the other hand, the authors suggest that clozapine should be considered a drug of choice for psychotic patients with a history of NMS.

However, it has been reported that clozapine by itself may be implicated in the development of NMS (Miller *et al*, 1991; DasGupta & Young, 1991). Furthermore, additional cofactors are required for the development of NMS and a number of patients may successfully tolerate careful neuroleptic re-exposure after at least two weeks of complete recovery of the index episode (Pope *et al*, 1991). How to treat subsequent psychotic manifestations in a patient after an episode of NMS is a matter of increasing attention among clinicians, and non-neuroleptic treatments such as ECT have also been considered (Bottaï *et al*, 1992). Despite the distinctive pharmacological profile of clozapine among antipsychotic drugs, it may be premature to speculate about the peculiar interest of this drug in the further management of patients with a history of NMS.

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Salivary testosterone levels and major depressive illness in men

SIR: Davies *et al*'s paper (*Journal*, November 1992, **161,** 629–632) was an interesting attempt to clarify the confusion that exists in the literature about testosterone levels in depressed men. Previous studies measured total testosterone and gave conflicting results. The authors assayed salivary testosterone, as a measure of free testosterone, and found a mean pre-dexamethasone level for the subjects of 133 pmol/l, compared with a mean of 215.1 pmol/l for the controls. Despite a sample size of 12, and the trend towards decreased testosterone observed, it was not suggested that the result could represent a type II error. This was even though they found a significant negative correlation between testosterone levels and both the Hamilton Rating Scale for Depression and the Montgomery and Åsberg Depression Rating Scale. Levitt & Joffe (1988), in a study not referenced by the authors, reported 20% lower free testosterone levels in a cohort of 12 men with major depression according to Research Diagnostic Criteria (RDC). They did consider the findings were possibly due to a type II error.

On the basis of Rubin *et al*'s findings (1989), the authors conclude that the hypothalamic-pituitary-gonadal axis seems to be normal in melancholia, and that the explanation of lower testosterone levels must be elsewhere. We feel this is stated too strongly given the available evidence. Hypercortisolaemia is the main possible explanation put forward by the authors for their findings. Cortisol and dexamethasone do suppress testosterone secretion, as evidenced by the abolition of the correlation, found by the authors, between severity of depression and testosterone post-dexamethasone.

However, although Rubin *et al* (1989) found no abnormality of basal luteinising hormone (LH) and follicle stimulating hormone (FSH), or change in LH and FSH post-gonadotrophin releasing hormone, they did find increased testosterone levels in melancholia, which is in conflict with the authors' findings. Additionally, despite the fact that cortisol suppresses testosterone secretion, testosterone has not been found to negatively correlate the sort of cortisol levels found in depression (Yesavage *et al*, 1985; Levitt & Joffe, 1988; Rubin *et al*, 1989). Similarly, we found little evidence of a corresponding positive correlation between LH and cortisol levels in depressed men ($r_s = 0.143$; Driscoll *et al*, 1991).

The authors' study was also part of an investigation during which dexamethasone suppression tests were carried out. Therefore, presumably the correlation between testosterone and cortisol can be ascertained. This would supply evidence, to either support or refute their hypothesis, that a decreasing salivary testosterone level seen with increased severity of depression is secondary to a corresponding hypercortisolaemia.

Testosterone levels decrease with age, but this phenomena has been observed to be exaggerated in depressed men (Sachar *et al*, 1973; Yesavage *et al*, 1985; Levitt & Joffe, 1988; Rubin *et al*, 1989). The authors' cohort had a mean age of 52.4 years and a large age range (s.d. 12.8 years). If their more severely depressed subjects were also more elderly, then the finding of decreased testosterone levels in severely depressed subjects may possibly be a spurious, but still interesting, finding due to the unexplained relationship between exaggerated decreasing testosterone levels and ageing in depressed men.

Testosterone secretion is stimulated by LH, and testosterone exerts a negative feedback on LH. Although Rubin *et al* (1989) and other workers have found no abnormality of LH secretion in depressed men, we have found LH levels to be significantly raised in a small sample of six men with RDC major depression ($P < 0.02$, two-tailed Mann-Whitney U Test; Driscoll *et al*, 1991). This may have been secondary to decreased testosterone levels, but insufficient serum was available to also assay for testosterone. However, LH correlated with the age of the subject ($r_s = 0.77$). Nevertheless, Whalley *et al* (*Journal*, May 1987, **150,** 682–684) found LH to be raised, with no corresponding abnormality of serum testosterone or sex-hormone-binding-globulin, in euthymic men recovered from bipolar manic-depressive illness. Given that hypothalamic endorphins and monoamines are involved in the regulation of pituitary and gonadal sex hormones, the human pituitary gonadotrophin may yet be found to be abnormal in depressed men.

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