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Lithium: evidence reconsidered

Sir: In re-evaluating lithium augmentation studies Joanna Moncrieff (1997) quotes our study, but appears not to have read it. She writes "The largest and longest of them [lithium augmentation studies], which followed up 34 patients for three weeks, was negative (Stein & Barnadt, 1988)", whereas we actually reported on 24 patients followed up for nine weeks and that there were significant lithium augmentation effects at weeks three, six and nine.

The reason we then reported on 24 patients, which was three-quarters of the way through the trial, was the occurrence of the Second British Lithium Congress, which we regarded as an important occasion. Our final and definitive report (Stein & Bernadt, 1993) which Dr Moncrieff did not quote was of 34 patients who over a nine-week trial showed significant benefit from lithium augmentation for treatment-resistant depression. We found that when added to existing tricyclic medication, which was taken in maximally tolerated doses, lithium 750 mg per day had a greater antidepressant effect than low-dose lithium (250 mg per day), which was no better than placebo. Dr Moncrieff also states that our earlier study reported low compliance rates, but neither of our publications mentioned compliance and our impression was of good compliance. The review is also inaccurate in stating that ours is the largest lithium augmentation study in that Katona *et al* (1995) had 61 patients. Another study that should have been quoted is Dinan & Barry (1989) who showed that lithium augmentation was as effective as electroconvulsive therapy in tricyclic non-responders.

Dr Moncrieff is right to draw attention to methodological weaknesses in lithium studies. Because lithium treatment is cheap, research about it has never attracted funding of the scale lavished on the newer antidepressants and there remain important uncertainties about its clinical use.

Dinan, T. G. & Barry, S. (1989) A comparison of electroconvulsive therapy with a combined lithium and tricyclic combination among depressed tricyclic non-responders. *Acta Psychiatrica Scandinavica*, **80**, 97–100.

Katona, C. L. E., Abou-Saleh, M. T., Harrison, D. A., *et al* (1995) Placebo-controlled trial of lithium augmentation of fluoxetine and lofepramine. *British Journal of Psychiatry*, **166**, 80–86.

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Grey matter correlates of syndromes in schizophrenia

Sir: In a sample of people with schizophrenia Chua *et al* (1997) reported the interesting finding that there was a significant and positive correlation between the disorganisation score and relative volumes of grey matter in medial temporal lobe structures. They mention that this finding "may seem at odds with the reportedly reduced size of this region in schizophrenia. However, our observations were made within a group of schizophrenics, and reflected differences among schizophrenics rather than differences between schizophrenics and controls". They proceeded to discuss reasons why increased volume of grey matter in medial temporal lobe structures might result from some pathological process in schizophrenia, for example, lack of neuronal pruning.

There is another possible interpretation which may be somewhat more parsimonious. It is possible that the finding reflects normal volume of medial temporal lobe grey matter in patients with the disorganisation syndrome, and abnormal reductions of temporal lobe grey matter in other people with schizophrenia. This interpretation is consistent with many studies which have found that the volume of medial temporal lobe grey matter is abnormally reduced in schizophrenia (Suddath *et al*, 1990; Breier *et al*, 1992; Rossi *et al*, 1994; Fukuzako *et al*, 1996). It is also consistent with a previous report of an association between reduced mesiotemporal tissue volume and higher ratings of the Brief Psychiatric Rating Scale psychosis factor (Bogerts *et al*, 1993).

Hypotheses based on these alternative interpretations could be tested in future studies by including a normal comparison group.

Bogerts, B., Lieberman, J. A., Ashtari, M., *et al* (1993) Hippocampus–amygdala volumes and psychopathology in chronic schizophrenia. *Biological Psychiatry*, **33**, 236–246.

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Fukuzako, H., Fukuzako, T., Hashiguchi, T., *et al* (1996) Reduction in hippocampal formation volume is caused mainly by its shortening in chronic schizophrenia: assessment by MRI. *Biological Psychiatry*, **39**, 398–945.

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Suddath, R. L., Christison, G. W., Torrey, E. F., *et al* (1990) Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. *New England Journal of Medicine*, **322**, 789–794.

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Comorbidity of mental disorders with substance misuse

Sir: A recent editorial in the *Journal* on comorbidity of mental disorders with substance misuse proposed that staff in addiction services should be trained to identify anxiety and affective disorders in their clientele (Hall & Farrell, 1997). A third of persons with an alcohol use disorder (37%) have another mental disorder and half of those with other drug use disorders have comorbid mental disorder (Regier *et al*, 1990). Purchasers are increasingly using services provided by non-statutory agencies, which are often cheaper than those provided by psychiatric addiction services, in part because there is less emphasis on nursing and psychiatric training within the staff skills mix.

We conducted a telephone survey of facilities for treatment of patients with comorbidity in such services. Ten residential rehabilitation addiction services were contacted and admission staff questioned on their attitudes to new referrals who were on medication for comorbid psychiatric disorders. The therapeutic orientation ranged from a therapeutic community to a skills-based programme; half were based on the abstinence 12-step approach. Only one of the 10 had psychiatric input and two had general practitioner support. The other seven could call on general practitioner services when necessary. Six would not accept patients on hypnotics, anxiolytics or antidepressants; the other four would work towards the reduction of such medication. Six would accept patients on antipsychotics, four refused. Five would accept patients on mood stabilisation, five refused. All would accept referrals on anti-epileptic medication.

We also asked about attitudes to medication prescribed to help maintain abstinence. Only two of the 10 would accept clients taking acamprosate calcium or naltrexone.

Poor outcome is associated with the failure to identify and address comorbid psychiatric disorders in patients with substance use disorders. Such patients would benefit from long-term residential rehabilitation. However, this is made difficult as many rehabilitation units refuse to take patients on medication. In addition, patients may be denied the benefits of new pharmacological treatments for addiction to reduce cravings, such as acamprosate calcium and naltrexone.

Hall, W. & Farrell, M. (1997) Comorbidity of mental disorders with substance misuse. *British Journal of Psychiatry*, **171**, 4–5.

Regier, D. A., Farmer, M. E. Rae, D. S., *et al* (1990) Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) Study. *Journal of the American Medical Association*, **264**, 2511–2518.

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Sir: Hall & Farrell (1997) propose that the SCL-90 questionnaire could be used to detect probable anxiety and depressive disorders among drug-dependent persons. However, we think precaution is necessary.

We assessed the SCL-90 (Derogatis, 1994) in a Dutch population (n=56) of drug-dependent persons who have entered a clinical treatment to screen for psychopathology. The first assessment took place in a pre-detoxification intake, the second assessment took place after detoxification. Results show that all sub-scales of the SCL-90 (with the exception of the hostility scale) decrease substantially (total score diminished 18%), suggesting that high pre-detoxification scores may represent drug-related symptoms, rather than psychiatric disorders. Furthermore, in another study we found that the validity of the SCL-90 to screen for DSM–III anxiety disorders is limited. Typically, satisfactory sensitivity was accompanied by low specificity (Hendriks, 1990).

We agree with the authors that the recognition and treatment of people with comorbid mental and substance use disorders is necessary. Also, staff in addiction services should be trained to identify anxiety and affective disorders in this population. However, before implementing instruments to detect psychopathology in drug-dependent patients, thorough investigation of the psychometric properties is necessary in this specific population, in particular given the potentially drug-induced nature of the reported symptoms.

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Hendriks, V. M. (1990) *Addiction and Psychopathology: A Multidimensional Approach to Clinical Practice*. Rotterdam: Erasmus University.

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Eosinophilia, agranulocytosis and clozapine

Sir: There has been controversy in the *Journal* recently about the relationship between eosinophilia and clozapine-induced agranulocytosis (Amital *et al*, 1997; Bailey *et al*, 1997). Evidence on the predictive value of eosinophilia for subsequent emergence of neutropenia and/or agranulocytosis in clozapine-treated patients is not robust (Hummer *et al*, 1996; Ames *et al*, 1996). Undue concern about the emergence of agranulocytosis may lead to discontinuation of clozapine which may have significant impact on the future course of the disease.

A 22-year-old White male with a two-year history of paranoid schizophrenia with recurrent suicidal ideas was started on clozapine after he failed successive trials with thiothixene, haloperidol, and risperidone. The clozapine dose was gradually increased to 400 mg/day by day 18. Prior to clozapine treatment, he had a white blood cell (WBC) count of 9300 cells/mm^3, with 4.0% eosinophils (absolute count 400 cells/mm^3) and 56% neutrophils (absolute count 51 000 cells/mm^3). On day 22, the WBC count was 10 000 cells/mm^3 with 15.7% eosinophils (1600 cells/mm^3) and 59.7% neutrophils (5600 cells/mm^3). On day 27, the WBC count was 9100 cells/mm^3 with eosinophils increasing to 22.8% (2100 cells/mm^3) and neutrophils decreasing to 46.3% (4100 cells/mm^3). Clozapine was discontinued after consultation with a haematologist and the Department of Veterans Affairs National Clozapine Coordinating Center. Two weeks after the discontinuation of clozapine, the patient had a WBC count of 7300 cells/mm^3 with 18% eosinophils (1300 cells/mm^3) and 36% neutrophils (2900 cells/mm^3). All the blood cell counts returned to normal by eight weeks. Six months later he died from a self-inflicted gun shot wound to the brain while on a combination treatment with loxapine and risperidone.

Eosinophilia may occur in up to 40–60% of patients on clozapine and is usually considered transient and asymptomatic (Gerlach *et al*, 1989, Banov *et al*, 1993, Bailey, 1997). Cases of symptomatic eosinophilia associated with a decreasing neutrophil count have been reported (Galletley *et al*, 1996). Sometimes, it acts as a precursor of neutropenia; genetic differences are postulated to explain this variability (Hummer *et al*, 1996). Current guidelines from the manufacturer recommend discontinuation of clozapine if the eosinophil count goes above 4000 cells/mm^3. Galletley *et al* (1996) suggest developing guidelines for discontinuation of clozapine in patients with eosinophilia and or decreased neutrophil counts. We believe that eosinophilia is of virtually no clinical utility in predicting clozapine-induced agranulocytosis (Ames *et al*, 1996; Bailey 1997). Premature discontinuation of

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