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 & Berndt, 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.

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.


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Grey matter correlates of syndromes in schizophrenia

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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.

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 due to reduce cravings, such as acamprose calcium and naltrexone.

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

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.

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 risperdone. 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/mm³, with 4.0% eosinophils (absolute count 400 cells/mm³) and 56% neutrophils (absolute count 51 000 cells/mm³). On day 22, the WBC count was 10 000 cells/mm³ with 15.7% eosinophils (1600 cells/mm³) and 59.7% neutrophils (5600 cells/mm³). On day 27, the WBC count was 9100 cells/mm³ with eosinophils increasing to 22.8% (2100 cells/mm³) and neutrophils decreasing to 46.3% (4100 cells/mm³). 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/mm³ with 18% eosinophils (1300 cells/mm³) and 36% neutrophils (2900 cells/mm³). 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/mm³. 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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**References**

Comorbidity of mental disorders with substance misuse.
F Keaney, H Crimlisk and J Bearn
Access the most recent version at DOI: 10.1192/bjp.171.5.484c

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