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The use of clozapine

Sir: In the audit article on the use of clozapine in South Manchester (Seabourne & Thomas, *Psychiatric Bulletin*, 1994, **18**, 618–619) 25 patients were given clozapine between 1990 and 1992 and, at the end of the trial, only ten subjects were still receiving the drug, the majority having been discontinued because of side-effects.

I am interested in why patients who have started clozapine are then terminated. Neutropenia apparently accounted for only one patient and the other side-effects noted were hypersalivation, sedation, grand mal fits, myoclonic jerks, vomiting, neuroleptic malignant syndrome, acute confusional state with cognitive impairment, slurred speech, benign hyperthermia, dry mouth, weight gain, constipation, diarrhoea, hypotension, and urinary incontinence. The clue may lie in the mean daily dose of clozapine; around 445 mg per day for responders, 633 mg per day for non-responders and 356 mg per day for the side-effect patients. This dosage is markedly above the average UK dosage of around 300 mg per day and our own dosage which is nearer to 200 mg per day.

With the experience of around 70 patients in the community on clozapine I would say that these patients were probably receiving clozapine at too high a dosage. Apart from the case of neuroleptic malignant syndrome, and of neutropenia, these side-effects are dose related. If the clozapine is combined with an oral conventional anti-psychotic then any breakthrough psychotic symptoms can be usually managed. In this way most of the side-effects would have markedly reduced and, with regards to epileptic and myoclonic side-effects that were not reduced, better control could be achieved with the addition of an anticonvulsant, e.g. sodium valproate.

With these modifications we might have seen an improvement in the high final discontinuation rate of 32%. Another benefit of lower dosage is that patients are less likely to non-comply as they perceive an enhanced life quality.

The authors mention that they are interested in maximising the response to clozapine so as to persuade the purchasers to spend more money on the drug. A spin-off from using combined clozapine therapy is that the cost is less and you can get more well patients for your money.

MICHAEL LAUNER, *Burnley Healthcare NHS Trust, Burnley General Hospital, Burnley BB10 2PQ*

Sir: We agree with Dr Launer's observation that the doses of clozapine administered to patients were high. However, King & Mills (1993) reported doses of 438 mg a day in females and 488 mg a day in males; and Meltzer (1992) recommended a target dose of 450 mg a day given as monotherapy for six months. If the response was inadequate after this time it was suggested that doses up to 900 mg a day should be tried.

Our audit showed that patients experiencing side-effects were on lower doses (356 mg) than those who responded (445 mg), who in turn were on lower doses than non-responders (633 mg). It is possible that lower doses may have been better tolerated and fewer patients would have been withdrawn from treatment. It is becoming clear that some patients can be maintained on low doses with two of our patients receiving 75 mgs and 100 mgs a day.

We dispute the logic of combining clozapine with an oral conventional antipsychotic as a way of reducing side effects. The *BNF* states that "prescribing of more than one antipsychotic at the same time is not recommended; it may constitute a hazard and there is not significant evidence that side effects are minimised". The Clozaril Patient Monitoring Service (CPMS) report that there are no absolute contraindications to combining other neuroleptics with clozapine. However, combinations should be used with care especially in early clozapine therapy as this may prolong neutropenia, particularly if depot medication is used. In our experience monotherapy is preferable, although sodium valproate was used in the two subjects who developed seizures.

We are also unaware of any cost-benefit analyses which support Dr Launer's final statement that combined clozapine therapy costs less and you can get more well patients for your money. There are cost benefit analyses which demonstrate that clozapine when compared with conventional neuroleptics significantly improves social functioning, quality of life and reduced the need for in-patient admission in the second and following

years of treatment (Revicki *et al*, 1990; Drummond & Davies, 1993). It is this evidence that should be used to educate managers and purchasers to demand that patients who suffer from treatment resistant schizophrenia receive clozapine as part of an overall treatment package for this disabling illness.

At present the prescription of clozapine is restricted to 20 patients in our district. The Department of Health, the BMA and the Royal College of Psychiatrists have all condemned this rationing of care. One possible solution to this restriction would be to vary the price of in-patient and out-patient care to take into consideration the cost of clozapine. We are looking into this possibility.

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Antidepressant prescribing by GPs

Sir: R. J. Thompson's study on antidepressant prescribing among general practitioner referrals to a community mental health unit in New Zealand (*Psychiatric Bulletin*, 1994, **18**, 461–462) and K. R. Linsley's comment (*Psychiatric Bulletin*, 1994, **18**, 703) suggested that sub-therapeutic prescribing might have to do with longer intervals between consultations related to the fees New Zealand residents have to pay to see their GP.

My survey of antidepressant prescribing among GPs referring clients to a community mental health centre in Keighley suggests that sub-therapeutic prescribing is also common in the UK where residents do not pay consultation fees (albeit many pay a fee per prescription). To determine whether GPs prescribe antidepressants in adequate dosage once they have established an indication for their use, I collected data from referral letters of 100 consecutive clients referred for depression while on antidepressants. Where dosage was not mentioned, the GP practice was contacted to clarify the dose at the time of referral.

The referrals consisted of 26.6% of a total of 376 referrals by GPs received during 18 months from April 1993. Seventy-six were women aged 17–61, and 24 men aged 22–55. Just over half were on tricyclic and related antidepressants of which the most widely prescribed was dothiepin (34/52). Applying the consensus statement of Paykel *et al* (1992), 75% (39/52) of clients on tricyclics were on sub-therapeutic doses (i.e. less than 125 mg daily), 69.2% (36/52) taking 75 mg or less. This is well after the launching of the Defeat Depression campaign, a disappointing result.

In stark contrast to Dr Thompson's sample, where few were prescribed selective serotonin re-uptake inhibitors (SSRIs), almost half of clients in Keighley were on these drugs, mostly fluoxetine (32/48). According to guidelines of manufacturers, 87.5% (42/48) of clients on SSRIs were on the minimum dose. Although this dose is said to be therapeutic, experience in psychiatric practice suggests that higher doses are frequently needed. It may be that GPs could treat many patients more effectively using higher doses of SSRIs.

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Leave for restricted patients

Sir: A letter dated 5 September 1994 and addressed to "All responsible medical officers in special hospitals, secure units and other psychiatric hospitals" from the Head of C3 Division at the Home Office indicates that the Secretary of State has "decided that ... he will normally no longer give consent for restricted patients to have escorted or unescorted leave of absence from hospital for holidays or holiday-type activities".

I read this with concern and when I discussed it with my immediate colleagues I found that this concern was shared. I would be interested in wider views of this (especially from forensic psychiatrists) and whether the forensic section of the College has any views.