Psychiatric Bulletin (1991), **15**, 617

Expert opinion

Clozapine

On several occasions in the last ten years, when interviewed by a market researcher about future developments in the treatment of schizophrenia, we have said that the biggest problem in the drug management of schizophrenia is compliance. We believed that if drug companies could manufacture an injectable neuroleptic lasting six months, then many of our problems would be over. Compared with this, the benefits of a new neuroleptic preparation appeared to be trivial.

We still think that not enough is done to ensure compliance, but were completely wrong to dismiss the advantages of a new neuroleptic. Clozapine has amazed us. The curious thing about it is that a handful of Swedish and German psychiatrists have been using it for more than a decade. One of them told us recently that he had pleaded with Sandoz not to discontinue it, which they were planning to do ten years ago. In his experience of over 100 schizophrenics resistant to conventional neuroleptics, just under 50% responded well to clozapine.

When the results of the careful trial by Kane in the United States three years ago were announced, we were immediately struck by the potential, and joined the first multi-centre trial in Britain, the results of which will be published soon.

In Kane's study one-third of treatment-resistant schizophrenics improved, in the British multi-centre trial about 40% improved significantly, and in an analysis of 20 patients treated by ourselves over the past 18 months, no less than 50% have improved.

Who improves? The sample that we treated were certainly the most severe schizophrenics that one could meet. Virtually all had been continuous in-patients for several years, most of them in and out of locked wards. Most of them had a history of violence.

What improves? The drug company lay a lot of emphasis on the improvement of negative symptoms. We are not entirely convinced that the drug has a specific effect of this kind. Apathy and flat facial expression certainly improved in most of the patients, but we were more impressed with the decrease in long-standing delusions. The increased zest for life could, therefore, be a secondary effect of experiencing a 'safer' world – i.e. feelings of persecution being less rife. This issue remains to be clarified.

What are the drawbacks? The main problem is the risk of agranulocytosis – now estimated to be nearer 2% than the 1% originally claimed for it. It was for this reason that the drug was discontinued in the 1970s. The Committee for the Safety of Medicines have granted a licence for the drug in this country provided that weekly white counts are monitored (changing to fortnightly after 18 weeks). A fall in white count to below a critical level can then be picked up, and the drug stopped, whereupon the level rises again. However, the need for blood tests may reduce the number of suitable patients, as some patients simply refuse to have a venipuncture, and one cannot practically enforce this even if the patient is compulsorily detained. One of us bribed one of the patients with a £5 note every time she agreed to have a blood test. This simple 'behaviour therapy' worked wonders. Other side-effects – hypersalivation, weight gain – occur, but are not nearly so serious. Another positive feature of the drug is its comparative lack of extrapyramidal complications. Both severe tardive dyskinesia and tardive dystonia disappeared in patients, and although the introduction of clozapine was carried out simultaneously with reduction of conventional neuroleptics, the disappearance of these movement disorders was so rapid that the drug must have played a part.

What about the economics of the drug? This is now a widely debated problem. In the United States last year the cost of a year's treatment at the standard dose of 400 mg was $9,000 per patient daily. (There is no point going above this dose in the opinion of the Swedish long-standing user mentioned). However, this amount included the drug company's obligation to arrange what they call the Clozaril Patient Management System – paying for the transport of blood sample to their own nominated laboratory, measuring the white count, communicating results to psychiatrist and pharmacy. In April of this year 29 state attorney generals won a legal injunction to 'unbundle' clozapine from this service, and the cost of a year's supply dropped to about $4,000. In Britain at least one health authority has rationed the drug to around 5% of those whom it might benefit, and here the blood monitoring is not 'unbundled'. This seems extremely short-sighted, because in our group of patients, the most striking change was the patient's improvement in general functioning. This meant that most moved up a peg in the care they needed, e.g. continuous in-patient to prospective hostel accommodation, sheltered hostel to relative independence. This must surely be cheaper.

So, in conclusion, clozapine is the first neuroleptic clearly shown to be *significantly* more effective than chlorpromazine, and in this age of cost-efficiency it could not have arrived at a more fortuitous time.

J. CUTTING
A. REVELEY

The Bethlem Royal Hospital and The Maudsley Hospital

https://doi.org/10.1192/pb.15.10.617 Published online by Cambridge University Press