Correspondence

Sir: Some patients given neuroleptics after recovering from neuroleptic malignant syndrome (NMS) have not experienced a recurrence of the syndrome (Meltzer, 1973; Rosebush et al, 1989; Pope et al, 1991), although others have (Buckley et al, 1991). The risk of recurrence of NMS may be reduced by allowing two weeks between the episode of NMS and the reintroduction of neuroleptics, by the gradual titration of neuroleptic dosage, and by termination with early signs of a recurrence. The choice of neuroleptic drug is less clear, and rechallenge with the same typical neuroleptic drug, or an agent of a different chemical structure, appears unrelated to the risk of recurrence of NMS (Buckley et al, 1991).

While the recent report by Weller & Kornhuber (Journal, December 1992, 161, 855–856) concerning the absence of an NMS recurrence in eight of their nine patients treated with clozapine as a rechallenge agent is encouraging, it is nevertheless premature to suggest that NMS, by itself, provides sufficient clinical indication for clozapine therapy. This is not a sufficient reason to justify a trial of clozapine. Treatment-resistance and intolerance of any neuroleptic drug (e.g. severe tardive dyskinesia or dystonia) are the key indications in schizophrenia for clozapine therapy.


Firstly, the comparisons with other treatments are not really relevant. Coronary artery bypass surgery is no longer a dilemma. It was introduced before the advent of calcium-channel blockers and orally absorbable long-acting nitrates and indeed, for a while, was an expensive but realistic option for treatment. With the advent of pharmacological alternatives, no cardiologist would advocate such expensive treatment in advance of cheaper drug treatment, unless there was an immediate life-threatening indication (e.g. main stem disease). Similarly, the analogy with newer oncological drugs is misplaced. The circumstances surrounding their use means, unlike clozapine, they are essentially untested treatments often tried as a last resort. At best, they may go through open familiarisation trials in very sick patients. It is usually late on in the drugs’ lifespan that they would go through rigorous testing.

Perhaps more meaningful comparisons would be with a ‘budget-busting’ drug such as cyclosporin,

Clozapine and NMS

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Perhaps more meaningful comparisons would be with a ‘budget-busting’ drug such as cyclosporin,
which has many similarities. It was hailed as a
dramatic breakthrough in immunosuppression, is
expensive, was greeted with scepticism, and has life-threatening side-effects (interstitial fibrosis)
which require close supervision. Despite this it has
gained universal acceptance and has made trans-
plantation more widely available and has improved
survival. No one begrudges its cost. Another possible useful comparison could be made with
warfarin. This gained universal acceptance by virtue
of the fact that it is obviously good. There is not a
single clinical trial anywhere on warfarin in the
literature. The point here is that Dr Healy
chooses to ignore the very valuable anecdotal, but
now extensive, clinical experience that clozapine
is an improvement on previous treatments.
Both academics (Cutting & Reveley, 1991) and clinicians (Launer, 1991) attest to the drug’s
superiority.

Turning to the Kane et al trial, (1988); Dr Healy’s
post-hoc criticism of this excellent piece of work is
uncharitable. Firstly, it is not fair to say the patients
had 1800 mg of chlorpromazine. This was a flexible-
dose-ranging regime, 1800 mg/day being the most
any one patient received. Furthermore, doses greater
than 1000 mg were only allowable in the second half
of the trial, to guard against possible over-treatment.
Secondly, the patients were recruited from elsewhere
having already fulfilled established criteria for resis-
tance, and then underwent a further trial of resistance
with haloperidol. It is not credible to suggest that the
patients were systematically worsened by over-
treatment at each and every stage of this filter.
Thirdly, to pick over the details of whether Dr Kanes’
patients were truly resistant or not misses the general
point of the exercise. Clozapine is effective across the
board in schizophrenia, and the point of its use
is really whether there is a subset of particularly
disabled patients, for whatever reason (treatment
refractory or neuroleptic-sensitive), in whom the
drug may justify the risk of agranulocytosis (with
monitoring, of course). The dismissive comparison
with insulin-coma treatment is illogical. This is the
‘It’ll never fly’ argument. To condemn something
on the basis of past failure smacks of intellectual
nihilism, implicitly suggesting all research endeavours
are a waste of time.

In my opinion, Dr Healy is one of the UK’s leading
psychopharmacologists and he has valuably adopted
a reasonable posture as a buffer to the evangelising
about clozapine. My own stance would be that the
eye early clinical-trial data is unequivocal, the Kane et al
trial is indisputable, and the clinical impression of
clozapine from its now numerous users are unambiguously impressive.

There have been a number of these exercises cautioning the use of clozapine (see also Lancet
(1992)) and it invokes a hazy recollection of a
Guinness commercial in the 1960s ... something
about not liking it, but never having tried it!

Psychiatric Bulletin, 15, 617.
the treatment resistant schizophrenic. Archives of General
Psychiatry, 45, 789—796.
15, 223—224.

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Clozapine, cognition, and schizophrenia
Sir: Goldberg et al (Journal, January 1993, 162,
43—48) argue that the cognitive deficits of schizo-
phrenia are independent of the psychosis and as such
do not respond to clozapine. They go on to postulate
that the cognitions may actually deteriorate on
clozapine and this may be due to the drug’s anti-
cholinergic properties. They subjected the patients to
ten neuropsychological tests, some on two occasions,
and used the Brief Psychiatric Rating Scale (BPRS)
and the Clinical Global Impression scale (CGI) to
rate their clinical change.

On the surface this seems totally exhaustive and an
important development until we look at the 15
patients more closely. Six patients were on lithium
before the clozapine phase and six were on lithium in
the clozapine phase: four of these were the same
patients continued on lithium so, in all, eight patients
had received lithium either before or after clozapine.
Of the seven patients who had never received lithium,
one patient had received lorazepam and two had
received anticonvulsants.

Lithium carbonate is described in the data sheet as
being associated with memory impairment during
long-term use and there is a theoretical risk of
neuroleptic malignant syndrome possibly due to
antidopaminergic actions when it is used with
clozapine, and so the lack of change in the cognitions
is not so simple to explain. In addition, many
clinicians feel that benzodiazepines in long-term use
may damage cognitive functions and the use of anti-
convulsants, if given for epileptiform conditions (we
are not told about this in the paper), may indicate
long-standing brain damage.