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Commentary

Response to Professor Kerwin

T. R. E. Barnes

In the treatment of psychotic illness, clinicians regularly face the decision whether to prescribe a standard neuroleptic or a new, atypical drug. The relevant criteria for such a choice will vary depending on the clinical situation, and many of the data required for an informed assessment of the relative risk–benefit balance for old and new drugs are not yet available. In his essay, Professor Kerwin's guiding theme is that atypical neuroleptics are not prescribed widely enough by clinicians, a view shared by other authorities in this area (Carpenter *et al*, 1995; Meltzer, 1995). The reasons he puts forward for this underuse include the high cost of these drugs, the false perception that new drugs are dangerous, too strict a definition of treatment resistance (in the case of clozapine), and the tendency for clinicians to reserve risperidone as a second-line treatment after standard neuroleptics have failed to produce a satisfactory response. In addition, some psychiatrists prefer depot medication for maintenance treatment, the principal advantage being the avoidance of covert non-compliance (Barnes & Curson, 1995). Undoubtedly, these are all relevant factors in the degree of use of newer atypical neuroleptics. However, although it must be accepted that prescribing habits die hard, the degree to which the current reservations and caution of clinicians may be appropriate is a matter for discussion. Having been invited to comment on Kerwin's article, I would like to take the opportunity to elaborate on some of the issues raised.

Side effects and safety

Concerning safety, Kerwin concludes that "a balanced view of the adverse event profile of drugs shows that older drugs are less safe compared to carefully monitored patients on newer drugs". While this may prove to be the case, it is uncertain whether the published evidence so far would support such an assertion. With regard to clozapine, any data relating to its use in the long term would refer only to those patients who had tolerated and responded to the medication: because of the increased risk of agranulocytosis there is a strong incentive to stop the drug in any patient who has shown a less than impressive response or developed problematic side effects. This might introduce a bias when comparing safety data for a cohort of patients receiving clozapine long term with similar groups on other neuroleptics. Furthermore, although a number of serious side effects are associated with standard neuroleptics (Barnes & Edwards, 1993; Edwards & Barnes, 1993), it is the evidence of an increased risk of a specific problem associated with a particular drug that tends to cause concern and leads to greater safety monitoring or restrictions on the patient population to whom it can be prescribed. The standard neuroleptics available would generally be thought to have similar profiles for both mild and severe side effects. Any differences observed may be partly related to clinicians' preferences for specific drugs or classes of drugs in particular

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circumstances, such as emergency situations, and in particular patient groups, such as the elderly.

A further difficulty in comparing the side effect profiles of standard and atypical neuroleptics from clinical reports is that the administered dose range of the latter group is clearly defined, either as a result of clinical studies identifying an optimum dose range (risperidone) or with an upper limit partly determined by severe dose-related side effects (seizures with clozapine). However, over the last decade, the use of higher doses of standard antipsychotic drugs has become fashionable despite a lack of systematic evidence for any superior efficacy for such treatment over a medium to long-term basis (Baldessarini *et al*, 1988; Reardon *et al*, 1989). The dosage used might be judged to exceed the optimum dose in many published studies of both acute and chronic drug treatment (Baldessarini *et al*, 1988). The interpretation of data on side effects from controlled, comparative studies of an atypical and standard neuroleptic is confounded by the possible lack of equivalence between the doses of the two drugs. Given the difficulties of calculating clinically-equivalent doses for the two types of drug, perhaps the only way of ensuring comparison of optimum doses for the patient sample under scrutiny would be a multi-arm treatment design, testing a range of doses of both drugs.

Kerwin states that clozapine has a "low side effect profile". There is no mention of the particular problems of hypersalivation, weight gain (Lamberti *et al*, 1992), enuresis (Warner *et al*, 1994) and an increased risk of seizures at high dosage (Toth & Frankenburg, 1994; Pacia & Devinsky, 1994; Welch *et al*, 1994). Where clozapine, and indeed risperidone, have a superior side effect profile is a lower liability for extrapyramidal side effects and possibly tardive dyskinesia. A particular advantage is the reduction in the need for concomitant anticholinergic medication, which has its own adverse effects and hazards.

There is only passing reference to the risk of agranulocytosis. Kerwin contends that deaths from agranulocytosis with clozapine represent "far fewer deaths... than other neuroleptic deaths." This statement cannot really be substantiated on the basis of the report cited, which is a paper by Jusic & Lader (1994) which deals with a small group of selected cases of sudden, unexpected death in psychiatric patients. The aetiology of such deaths is complex and varied and the role of neuroleptic drugs remains to be established. Cardiac arrhythmias may be one cause, and the cardiotoxicity of both standard and atypical neuroleptics at therapeutic and higher doses warrants careful investigation. In respect of clozapine, potentially fatal instances of orthostatic and cardiorespiratory dysregulation have been reported. These have been attributed to concomitant administration of benzodiazepines (Sassim & Grohmann, 1988; Grohmann *et al*, 1989), but it is possible that such problems may also occur, unpredictably, with clozapine as monotherapy (Bredbacka *et al*, 1993).

Cost

The cost-effectiveness of clozapine and risperidone is discussed by Kerwin, partly with reference to American studies. Prospective, controlled studies of the cost-utility of these drugs in the UK will be valuable (Healy, 1993; Matheson *et al*, 1994; Aitchison *et al*, 1995). In the absence of any such prospective health economic studies, Davies & Drummond (1993) analysed data from a US cost-effectiveness study of clozapine (Revicki *et al*, 1990), in the light of UK clinical practice. They concluded that the use of clozapine would be cost-saving or cost-neutral compared with standard neuroleptic therapy. Although the cost-effectiveness methodology for clozapine remains to be established (see Bosanquet & Zajdler, 1993; Fitton & Benfield, 1993), the emerging view seems to be that the cost of treatment with clozapine is similar to that of other neuroleptics (Hirsch & Puri, 1993). Nevertheless, calculation of the total impact on the mental health budget is currently hampered by the lack of precise data on the frequency of poor response to standard neuroleptic treatment. Also relevant is the uncertainty regarding the duration of an adequate trial (Carpenter *et al*, 1995), which is perhaps unsurprising as this question is largely unresolved for standard neuroleptics (Keck *et al*, 1989). Further, appropriate psychosocial treatment and rehabilitation services are essential to optimise the response to clozapine (Viner *et al*, 1994; Carpenter *et al*, 1995), and cost-benefit analysis should take account of the need for such resources. Psychosocial interventions can play an important adjunctive role, particularly for those patients who are confronting the prospect of returning to living in the community after a long illness. The initial effects on psychotic symptoms and cognitive function may be relatively subtle in some patients, although their ability to participate in and benefit from rehabilitation efforts has been significantly enhanced. As has been seen with standard neuroleptics (Barnes *et al*, 1983; May *et al*, 1988), the improvement in social functioning consequent upon achieving a stable remission may develop over months or years. This may partly explain some of the reports of an apparent delayed therapeutic response to clozapine.

Treatment resistance and clozapine

Addressing the issue of treatment resistance, Kerwin suggests that clozapine should be used

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earlier in patients unresponsive to standard medication, there being little value in testing a high-dose neuroleptic regime. While there is a body of evidence to support the latter point (Hirsch & Barnes, 1994), there are few, if any, controlled studies comparing clozapine with adjunctive electroconvulsive therapy, lithium or carbamazepine, and very little published work on the value of switching from one standard neuroleptic to another in unresponsive patients. With regard to this last treatment strategy, Shalev *et al* (1993) examined the proportion of patients with acute exacerbation of their schizophrenia who remained unimproved by consecutive administration of haloperidol, chlorpromazine and perphenazine, administered in random order. The overall improvement rate was 95%, with the frequency of good responses to the first, second and third drug being 67%, 55% and 67% respectively. These figures contrast with more disappointing levels of response in a similar group of patients investigated by Kinon *et al* (1993). In an open study involving a four-week trial of a standard neuroleptic, 78 (68%) out of 115 acutely-ill schizophrenic patients were considered to be non-responders in that they were judged clinically to have failed to achieve a good or complete recovery. Subsequently, these non-responsive patients were randomly allocated to a four-week, double-blind treatment of either continuing on the original neuroleptic unchanged, a higher dose of the same neuroleptic or a different class of neuroleptic. Response was only seen in 9% of the subjects entering this second phase of the study.

Risperidone: first or second line treatment

Kerwin's review also deals with risperidone, and what he judges to be the illogicality of reserving this drug as a second or third line treatment in first-onset schizophrenia. Although there is good evidence for its efficacy in acute exacerbations of schizophrenia, there are as yet no data on its efficacy and cost-benefit in first-episode patients compared with a standard neuroleptic. Comparison of an atypical and standard neuroleptic in such circumstances presents several methodological challenges, and the design of many of the studies with risperidone has been innovative. The use of multiple doses of risperidone provides useful, controlled data on the optimum dose range. However, the administration of a single, fixed dose of comparator drug, either haloperidol 20 mg or 10 mg a day in most of the published studies, is not ideal for comparing two active drugs (Kane, 1994). It would be of interest to see a study comparing the optimum dose of risperidone with a lower dose of haloperidol, such as 5 mg a day. It is hard to know whether, in clinical practice, risperidone's relative lack of sedative properties will prove a limitation in the treatment of acute psychotic episodes. Clinicians seeking a sedative action might tend to increase the dose above the recommended optimum range, and perhaps lose the advantage of a lower liability for extrapyramidal side effects.

Compliance and new drugs

The last section of Kerwin's review deals with compliance, listing two major barriers to compliance: extrapyramidal side effects and insight into the illness. However, the problem of compliance is generally considered to be complex and multifactorial (Bebbington, 1995), with comorbid substance use being one of the most consistent predictors of poor compliance. With regard to atypical drugs, although they may be better tolerated and more acceptable to patients, as yet little evidence has been presented that this translates into improved compliance. With regard to studies with clozapine long term, the point made above with regard to a selection bias in patients staying on clozapine also applies here. Those patients who complied poorly with either the blood tests or taking the tablets in the early stages of treatment would not have continued on the medication. Further, only those patients who show an impressive clinical response are likely to continue to receive clozapine, and by virtue of the monitoring service, they will be closely supervised, receiving their drug supply every two weeks, at least for the first year of treatment. In such circumstances it would be reasonable to expect good compliance.

Comment

The clinical profiles of clozapine and risperidone have raised expectations of superior antipsychotic drugs with fewer side effects and beneficial effects on a broader range of symptoms, including negative symptoms. Whether clozapine has a direct impact on primary negative symptoms or only those secondary to positive psychotic symptoms, extrapyramidal side effects and depression is a matter of debate (Carpenter *et al*, 1995; Meltzer, 1995). For any new neuroleptic introduced, it may be difficult to establish convincingly that it possesses a genuinely superior, atypical profile until it has been tested in long-term prospective studies. A clinical consensus on the value of a particular drug and its indications is unlikely to emerge before it has been widely prescribed over some years. Nevertheless, clinical practice in this area is changing, and the critical issues raised by Kerwin relating to the relative advantages and disadvantages of new

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antipsychotic agents will need to be continually revisited as more controlled data become available and clinical experience grows.

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