opinion & debate

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Choosing antipsychotic drugs in schizophrenia

A personal view†

Clinical psychiatrists are today in a position to prescribe an expanded range of antipsychotic drugs for the treatment of schizophrenia and related psychoses. The introduction of chlorpromazine in 1952 was followed by many others. They varied in potency and in side-effect profile, but they shared the capacity to cause extrapyramidal side-effects (EPS). These side-effects were produced by a mechanism intrinsically similar to that responsible for the antipsychotic effectiveness of the drug. They seemed to be the price that had to be paid for the resolution of psychotic symptoms.

This type of side-effect has a major impact on the willingness of patients to accept medication (Buchanan, 1992). Thus, the grail was to find compounds with antipsychotic potency and a reduced or absent tendency to produce EPS, a combination that might require a different basis for the antipsychotic effect.

Clozapine, which was reintroduced in 1989 in the UK, appeared to meet these requirements, and was followed by a number of the 'atypical' antipsychotic drugs during the 1990s. The term 'atypical' has been used in several different ways, but serves as a useful shorthand for drugs with diverse properties. They are generally held to have a better side-effect profile, especially in relation to EPS.

The introduction of these drugs was accompanied by several randomised controlled trials (RCTs) of their effectiveness, more with some than others. These clinical trials are compulsory requirements for drug licensing, but may not generate the information of most use to practising clinicians. Hence they are usually conducted over periods (6–8 weeks) that are extremely short in relation to the course of psychotic illness. Nevertheless, they represent a great investment of effort, and on first inspection appear to substantiate various claims made for the superiority of the new drugs over their predecessors.

Practising clinicians are faced with large amounts of information to absorb in order to be able to advise their patients about the appropriate choice of medication. Pharmaceutical companies must clearly recover drug development costs and will emphasise the selling points of their particular product. The psychiatric profession too has a valid interest in the commercial viability of pharmaceutical companies since the prospect of therapeutic advance would otherwise be blighted. However, this should not be at the expense of patients.

Nevertheless, objective and accessible evidence concerning the performance of new drugs is not easy to acquire, and claims to objectivity are easy to mistrust. The National Schizophrenia Guidelines Group (a joint initiative of the Royal College of Psychiatrists and the British Psychological Society) has attempted to summarise the available evidence (Geddes *et al*, 2000). The group conducted a meta-analysis of the available RCTs in the area, identifying 52 such trials including over 12 000 patients. All but five were short term (median follow-up 6 and a half weeks).

The original intention was to quantify the advantages of the new drugs and to investigate the possibility of identifying clinically important differences between them. To this end they carried out separate meta-analyses of the trials involving individual compounds (amisulpride, clozapine, olanzapine, quetiapine, risperidone and sertindole). The results mainly concerned symptom score reduction and drop-out rates. (Drop-out rates are an imprecise, but commonly used and relatively unbiased measure of overall acceptability.) Findings relating to EPS were usually reported idiosyncratically, and were thus often difficult to compare between studies.

The meta-analysis indicated that some of the atypical antipsychotics had slightly better efficacy and tolerability, and all had a significantly lower risk of causing EPS than conventional antipsychotics (Geddes *et al*, 2000). Evidence for specific effects on different types of psychotic symptoms was weak. Nevertheless, some of the new drugs did seem to be clearly and appreciably superior, although there was a good deal of variation (heterogeneity) in the relative effects observed in different trials of particular drugs.

However, there was a caveat. The new compounds were compared with standard comparator drugs, usually haloperidol, but in some cases chlorpromazine. Common side-effects, including EPS, are dose-related, while efficacy reaches a plateau with increasing dose (Bollini *et al*, 1994). In many RCTs of atypical antipsychotic drugs the dose of comparator was high, and well into the range likely to induce EPS. The group therefore decided *a priori* to control for comparator drug dose using the technique

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opinion & debate

of meta-regression. When this was done, the advantages in efficacy and tolerability of the new drugs were no longer evident. The group could not analyse EPS in the meta-regression, as too few studies reported them in a comparable way. It was, however, possible to identify three large trials describing the side-effects experienced by patients receiving risperidone (Peuskens, 1995) or sertindole (M93-098, 1997) compared with haloperidol at the relatively low fixed dose of 10 mg daily. Peuskens (1995) reported a significant benefit of risperidone (4 mg to 16 mg) over haloperidol for dystonia (P=0.0004) and dyskinesia (P=0.0499). In the trials of sertindole *v.* 10 mg haloperidol (see Geddes, 2000), we noted a 16% reduction (95% CI 10%–22%) in the incidence of akathisia attributable to sertindole. Thus, the benefit of fewer EPS was still apparent for these drugs, even at these lower doses of comparator drugs.

The apparent advantage of the new drugs therefore seems to arise because of the high dose of comparator drugs being used. No other potential explanation we examined had an appreciable effect on the results.

This was an unexpected finding, and has implications for rational prescribing. In summary, the new 'atypical' antipsychotics seem no more effective in reducing psychotic symptoms than their older counterparts. They probably have fewer EPS, but the advantage is less than that claimed. Finally, they appear to be no better tolerated, overall, than the older drugs. Thus, we have a group of new drugs with marginal but real advantage over their earlier counterparts, albeit largely restricted to the avoidance of EPS. In addition, the new drugs are understandably very much more expensive than those they seek to replace. What are we to do with this information? How should it inform our prescribing?

Before we can answer these questions, we must consider the standing of the National Schizophrenia Guidelines Group's findings. Early drafts were widely disseminated by people outside the group in advance of publication for a variety of reasons that may be imagined. While some groups welcomed the findings, others did not. Many psychiatrists have a problem with the guidelines, arguing that they fly in the face of their prescribing experience. Moreover, patient groups take a similar position, saying that their personal experience of the new drugs is very positive in comparison with the older drugs. Such statements must obviously not be taken lightly.

However, it should be pointed out that these two sorts of personal experience are based on exactly the same sorts of comparisons as were made in the RCTs, in other words, the experience of the new drugs is being compared with high doses of the older drugs.

The recent National Audit of Antipsychotic Prescribing carried out by the Royal College of Psychiatrists' Research Unit makes clear that antipsychotics are prescribed in high doses: one-fifth of patients in the UK are given them in doses exceeding *British National Formulary* (*BNF*; British Medical Association & Royal Pharmaceutical Society, 1999) limits. *BNF* limits are themselves considerably above the levels required to give EPS. In contrast, the newer antipsychotic drugs usually come with manufacturer's recommended dose ranges chosen to avoid side-effects.

The general use of high dose antipsychotic medication is understandable, and arises from a combination of therapeutic optimism and therapeutic caution. Thus it is generally held that the symptoms of psychosis can be controlled by antipsychotics. If a given dose does not work, there is always, therefore, a tendency to increase it in search of the dose that does. Once the dose has been increased, the fact that the patient still has symptoms is virtually never taken as an indication to reduce it. Thus, the impulse to increase doses is always stronger than the impulse to reduce them.

Nevertheless, there are grounds for resisting the urge towards escalating doses. First, not all people have positive symptoms that do respond to antipsychotic medication, a fact more readily acknowledged since 'treatment resistance' became a definable criterion for changing to treatment with clozapine (Meltzer, 1990). Second, the analyses of Bollini *et al* (1994) suggest that at a fairly early point increasing doses do not improve treatment response. Third, positron emission tomography studies of dopamine blockade suggest that the therapeutic effect of antipsychotic drugs commences at levels of dopamine receptor occupancy of around 65% (Farde *et al*, 1992). Most dosages in ordinary clinical practice are considerably above those required for occupancy levels of 100%. Moreover, EPS only emerge after 80% of receptors have been blocked. Thus, there ought to be a dose level that produces a treatment effect without EPS, in other words, a therapeutic window.

These findings suggest that changing the way older antipsychotic drugs are used might improve their effectiveness and tolerability. They might then be more credible alternatives to the newer drugs. Under what circumstances might we use them as such?

These decisions clearly involve clinicians in value judgements. What ethical positions might be appropriate to facilitate such judgements? I can identify three: the first is one based on considerations of utility, the second uses cost-effectiveness and the third relies on the precautionary principle.

If we focus on the overriding undesirability of EPS, the utility principle would lead us to prescribe the new antipsychotics as first-line drugs. On the other hand, under the cost-effectiveness principle, the high acquisition costs of the new drugs might lead to a decision only to use the older, cheaper alternatives. Weight would be given to the opportunity costs of prescribing. This leads to very difficult ethical situations. Thus, clinicians have an obligation not to withhold from individual patients a treatment that they think would benefit them. At the same time, all health services are cost-limited, and thus the acquisition costs might lead to cuts elsewhere. Psychiatrists might be less keen to prescribe new antipsychotics exclusively if the cost was met by the removal of two community psychiatric nurses from their community mental health team. And yet, that consequence might only affect patients other than the one for whom they are in the process of prescribing. Difficult.

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The final ethical position is one that I favour – it involves the precautionary principle, currently topical in other contexts. This acknowledges the novelty of the new drugs. The introduction of a new drug presages a period in which experience of its use is built up and in which unsuspected disadvantages may become apparent. This has been the case with a number of the new compounds, and led to the voluntary withdrawal of sertindole and worries about the effect of olanzapine on weight gain and glucose metabolism.

Thus there are arguments for using drugs that seem to bring advances but for using them carefully. This requires a due consideration of the properties of all the available drugs, new and old, in the light of the particular needs and susceptibilities of individual patients. It is morally imperative to involve patients as much as possible in these considerations, but also clinically advantageous. Involving patients can only be done if they are provided with information.

Taking this position is clinically facilitative. It implies that in our current state of knowledge we are entitled to choose from the whole list of antipsychotics, conventional and atypical. On this basis, one should consider using the established products for front-line treatment, but with a readiness to opt for a newer compound if it seems appropriate. I have marshalled arguments for limiting dosage of conventional antipsychotics to levels that do not produce EPS. Thus, if in moderate doses the initial treatment does produce side-effects, or seems ineffective, there should be a rapid switch to one of the novel antipsychotics.

This general approach should, however, be modified in the light of particular and individual considerations: a knowledge of patients' individual preferences and characteristics, and their known or likely susceptibility to given side-effects. If discussion with the patient is not possible because of the acute nature of the illness, it should be done later.

Pharmacological treatment of schizophrenia and related psychoses is usually for the long-term, and depends on patients' willingness to take medication when unsupervised. This is far more likely in the context of a good therapeutic relationship (Ley, 1982; Hanson, 1986; Bebbington, 1995). While there are many components in the development of a good relationship, frank discussion about medication is essential. Central to this is a commitment to take seriously, and to respond to, complaints about side-effects. The available compounds differ in their side-effects. Those particularly incommoding to patients include EPS, but also weight gain and effects on sexual function (Silverstone *et al*, 1988; Pfeiffer *et al*, 1991).

My own approach is to avoid EPS as much as possible. In some cases this means accepting the continued experience of positive symptoms: even if they persist, medication usually causes them to be much less intrusive and distressing, and there are other ways of helping patients to deal with residual psychotic symptoms. The overall target of prescribing is improved quality of life and this may sometimes be optimised when some positive symptoms are the price accepted for an absence of side-effects. This approach is the one most likely to ensure that patients will agree to take medication consistently over prolonged periods. This in turn is a considerable guarantor of quality of life: relapse rates in schizophrenia are up to 3× higher than they would be if all patients prescribed neuroleptics actually took them (Kissling, 1994). The choice of antipsychotic is intrinsically important, but it is much more so as part of the overall negotiation about treatment between patients and their clinical advisors.

Declaration of interest

P.B. has received fees for presentations at meetings sponsored by various pharmaceutical companies who manufacture antipsychotic drugs. In addition, he is one of the lead investigators of the European Schizophrenia Cohort, funded by Lundbeck A/S.

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