



## editorial

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DAVID TAYLOR

### Antipsychotic prescribing – time to review practice<sup>†</sup>

In this issue of the *Bulletin*, three linked analyses of antipsychotic prescribing practice are published (Lelliott *et al*, 2002; Harrington *et al*, 2002*a,b*). The main findings of these studies are that high-dose prescribing and polypharmacy were commonplace at the time of the study and that generally patients were neither properly informed nor appropriately monitored. High-dose prescribing seemed to be strongly associated with polypharmacy – a practice for which there was a substantial variation in frequency between study centres.

Many will say that these studies merely quantify what is already known: that antipsychotic prescribing is less than perfect by evidence-based standards and that practice varies substantially according to patient, prescriber and institution. Nevertheless, the predictability of the findings of these studies should not detract from their importance. Nor should it prevent us from examining carefully the justification for prescribing drugs in a way which bears only a passing resemblance to the way in which they were used in efficacy studies establishing their worth.

Is 'high-dose' treatment better than 'low-dose'? Are two antipsychotics better than one? We don't know. There has been a surprisingly large number of high-dose trials conducted, but very few meet today's exacting standards for properly conducted studies. The only conclusion that can be drawn from these data is that a minority of patients may benefit from high doses (Aubree & Lader, 1980). Against this is the observation that, in recent dose-finding studies of atypical drugs, there appears to be a threshold effect. That is, above a certain dose limit all doses give rise to the same degree of response (risperidone and quetiapine are good examples). This threshold theory is supported by recent neuroimaging studies (Kapur *et al*, 2000).

Polypharmacy of antipsychotics is probably even less well supported (Davidson, 1974; Godleski *et al*, 1989), with very few available to suggest that two drugs are effective where one alone is not (Yuzda, 2000). The only exception is that of augmenting response to clozapine. This has the backing of some clinical trials and is difficult to argue against in the context of poor response to clozapine alone (Canales *et al*, 1999).

Is 'high-dose' treatment safe? Probably not. Many antipsychotics prolong the cardiac QT interval (in a dose-

dependent fashion) and may cause torsade de pointes and sudden death (Glassman & Bigger, 2001). Even moderate (but not low) doses of typical antipsychotics appear to increase the risk of sudden death (Ray *et al*, 2001).

Polypharmacy of antipsychotics also has clear adverse consequences. Most seriously, it has been suggested that polypharmacy is associated in some way with early death (Waddington *et al*, 1998). In addition, the co-prescription of typical antipsychotics with atypical drugs has been shown to increase the frequency of acute extrapyramidal side-effects to levels expected when typicals are used alone (Taylor *et al*, 1997, 2000). Presumably the risks of tardive dyskinesia and hyperprolactinaemia are similarly increased. Apart from this, there is very probably an important risk of adverse interaction when antipsychotics are prescribed together, either through inhibition of metabolism or through summation of toxic effects (such as QT prolongation).

Overall, the practices of high-dose prescribing and antipsychotic polypharmacy seem unsupported – somewhat feeble evidence supports any therapeutic benefit, while rather more robust evidence suggests adverse consequences. Why, then, do these practices continue? It is possible, of course, that for some patients two antipsychotics are more effective than one. It may be that clinical trials are unable to detect subtle but important improvements seen in patients receiving high-dose treatment. It may also be true that different antipsychotics are prescribed together because they have different effects on different symptoms of psychosis. Thus, polypharmacy may represent the optimal application of scientific knowledge and clinical experience combined.

In considering these possibilities, it would be unwise to suggest that high-dose prescribing and polypharmacy should always be avoided and always be viewed as poor prescribing. None the less, given the known and suspected adverse consequences of these practices, it does seem sensible to restrict such prescribing to patients in whom usual dose, single-drug prescribing has been satisfactorily proven to be inadequate. Recent observational studies suggest that physicians are too ready to resort to polypharmacy (Taylor *et al*, 2002*a*) and that it is used ineffectually where the use of clozapine might be a better option (Taylor *et al*, 2002*b*). More

<sup>†</sup>See pp. 411–420, this issue.



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recently still, the National Institute for Clinical Excellence (NICE, 2002) has endorsed this viewpoint by recommending that 'atypical and typical antipsychotics should not be prescribed concurrently'.

The introduction of atypical antipsychotics has, to some extent, encouraged a more scientific approach to the treatment of schizophrenia. It is to be hoped that this will eventually result in poorly supported, unsafe practice being abandoned except where there is very clear evidence of patient benefit. This is certainly the time to review prescribing practices in schizophrenia and other psychoses and to move towards a more evidence-based approach.

## Declaration of interest

None.

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**David Taylor** Honorary Senior Lecturer, Institute of Psychiatry and Chief Pharmacist, South London and Maudsley NHS Trust, Pharmacy Department, Maudsley Hospital, Denmark Hill, London SE5 8AZ