Correspondence

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Contents ■ Need for medicine-based evidence in pharmacotherapy ■ Venlafaxine and SSRI remission data revisited ■ Meanings and causes in ADHD ■ Commissioning conundrum for custodial care ■ Integrated in-patient adolescent services ■ A new name for the *Journal*?

Need for medicine-based evidence in pharmacotherapy

As pointed out in the debate between Parker and Anderson & Haddad (2003), a gap exists between the results of randomised controlled trials (RCTs) and what is seen in daily psychiatric practice. While both parties in the debate come to more or less opposing conclusions, they agree upon the fact that the conditions in trials into the efficacy of antidepressants differ from the conditions in the field. We want to argue that these differences are often even greater than suggested in this debate and are not limited to antidepressants.

The demographics of people included in trials are skewed: men are more often included than women, children and elderly subjects are rarely investigated and participants often have a low socio-economic status. Furthermore, strict criteria for diagnosis are used and the duration of the trials is short while the compliance is high. And finally, comorbidity and comedication are most often more frequent and more severe in practice than in the conditions of a clinical trial, making the patients participating in trials virtually incomparable with the patients eventually taking the drugs in daily practice (Leufkens & Urquhart, 1994). Not surprisingly, only 14% of typical users of antidepressants would comply with the strict inclusion and exclusion criteria that are usually applied in RCTs (Zimmerman *et al*, 2002).

The gap between trials and psychiatric practice may even be bigger in other areas in psychiatry. Frequently occurring aggressive incidents in psychiatric patients are countered by a broad spectrum of psychotropic drugs as well as coercive measures to immediately reduce danger and harm (Nijman *et al*, 1997). However, evidence for these interventions is almost non-existent and mostly based on clinical experience rather than RCTs. For example, although zuclopenthixol acetate is used in 40% of the patients hospitalised on admission wards in The Netherlands (Hugenholtz *et al*, 2002), a Cochrane review concludes that 'there is a need of more RCTs' on the use of seclusion and restraint (Sailas & Fenton, 2002). However, is a call for more RCTs in patients with aggression problems realistic? Factors contributing to uninformative results of RCTs for depression (Parker *et al*, 2003) will be even more prominent in trials for aggression. Patients will be unwilling or unable to participate, compliance will be low and when coercive measures are involved randomisation is almost impossible.

How can we bridge the gap between the results of RCTs and the complicated patients we encounter in daily practice? We think that collection of valid data on treatment patterns and effects using standardised measurements in daily psychiatric practice may contribute to evidence of treatment effectiveness in patients with complex needs. Because of the lack of randomisation, dealing with confounding and other types of bias are challenges in the design and analysis of such pharmacoepidemiological studies. Pharmacoepidemiological research may provide the essential 'learning' component in the cycle that drives drug development, where clinical trials supply the 'confirming' part (Sheiner, 1997). In other words, while clinical trials may form the foundation of evidence-based medicine, one should not neglect medicine-based evidence in the pursuit of better therapy, especially in the challenging reality of psychiatric practice.

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Venlafaxine and SSRI remission data revisited

Thase *et al* (2001) suggest that venlafaxine is more likely than selective serotonin reuptake inhibitors (SSRIs) to produce remission of depression. Their article continues to be widely cited as evidence of the superiority of venlafaxine over SSRIs. While the authors identify most of the significant limitations of the study, they do not sufficiently address one of the major considerations in interpreting a meta-analysis, namely the limitations of the individual studies whose data are pooled in the analysis.

First, it is worth noting that of the 2117 patients (intention-to-treat (ITT) 2045), the data on over half (1066 patients, ITT 1028) comes from the studies that have not been published as articles in peer-reviewed journals. Indeed, the data on 278 patients, 13% of the data used in the meta-analysis, derives from 2 unpublished studies by the manufacturer of venlafaxine, Wyeth-Ayerst (Study 347 and Study 349, respectively). Thus, one cannot critically assess how such factors as study design (subject recruitment, length of study, outcome measures, dose titration, data collection and analysis, etc.) and drop-out rates may have affected the outcomes.

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Moreover, data on some 788 subjects (ITT 762), or about 37% of the meta-analysis population, come from studies published only in abstract form (Salinas *et al*, 1997; Rudolph *et al*, 1998), and the results of each must be placed in perspective. The 8-week study with some 323 patients (15% of the meta-analysis pool) by Salinas *et al* (1997) comparing venlafaxine extended release, paroxetine and placebo found no significant difference between drugs and placebo. In addition, there was a markedly greater discontinuation rate in the paroxetine group than in the venlafaxine 75 mg group (35% *v.* 20%). In an ITT last-observation-carried-forward analysis, such a difference in discontinuation rates could significantly affect the rates of response and remission.

Another paper published only as an abstract (Rudolph *et al*, 1998) was a 6-week study with some 460 patients (22% of the meta-analysis subjects) designed to compare speed of response to venlafaxine, fluoxetine and placebo. Can data from such a brief study accurately reflect remission rates at 10 or 12 weeks? Recent work by Quitkin *et al* (2003) suggests otherwise, as a significant number of non-responders to fluoxetine at 6 weeks may show remission at 12 weeks. Thase *et al* themselves acknowledge that differences in times to response between venlafaxine and SSRIs may have contributed to their findings.

In addition, Clerc *et al* (1994) likewise reported a 6-week study, wherein almost twice as many patients taking fluoxetine as those taking venlafaxine (35% *v.* 18%) dropped out of treatment. Finally, in their study of 301 out-patients (approximately 15% of subjects in meta-analysis), Rudolph & Feiger (1999) reported an almost 50% greater drop-out rate in the fluoxetine group compared with the venlafaxine group (29% *v.* 19%).

Thus, although the meta-analysis raises the interesting possibility of differential remission rates, one should bear in mind the limitations of the component studies.

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Meanings and causes in ADHD

Eric Taylor dismisses Sami Timimi's critique of attention-deficit hyperactivity disorder (ADHD) as an oversimplified polemic (Timimi/Taylor, 2004). He admits he may have been biased because he viewed it as an antipsychiatry tract. I find it unfortunate that the threat of 'antipsychiatry' means that a serious attempt does not appear to have been made to resolve the controversy surrounding ADHD (Double, 2002*a*). Is there a dispute about the facts as well as their interpretation? For example, it is not clear whether brain differences have been shown in unmedicated children, with the protagonists stating opposite views. From the article, it is difficult to see who is correct because Professor Taylor merely quotes the chapter on ADHD from his co-edited textbook (viz. Schachar & Tannock, 2002).

Furthermore, Professor Taylor makes various statements, again with the authority of this textbook chapter, which seem to need further clarification. For example, he says there are known physical counterparts of hyperactivity in brain structure and function, and then does not say what these abnormalities are. If we know what they are, they should be stated and we can then debate their role in aetiology. Similarly, he says that some molecular genetic variations have been robustly replicated, but then does not name the genes, except to say that they especially affect dopamine systems.

There is surely an onus on Professor Taylor to justify his response to Dr Timimi's challenge that the medical model of ADHD 'offers a decontextualised and simplistic idea that leads to all of us – parents, teachers and doctors – disengaging from our social responsibility to raise well-behaved children'. Instead, Taylor proposes increased recognition of the disorder, at least in the UK, 'because there are several good ways of supporting children with severe hyperactivity'. If the central issue is the role of medication in treatment, this is clearly a matter of values (Double, 2002*b*). The recently published collection edited by Fulford *et al* (2003) argues that meanings as well as causes are essential to good psychiatric care. One way of viewing the ADHD controversy is that Dr Timimi is more concerned about the meaning rather than the physical cause of the disorder. Such a position should not be dismissed as antipsychiatry, but acknowledged as a valuable contribution to the debate about the extent to which the use of medication exploits people's emotional problems.

Declaration of interest

D.B.D. is a member of the Critical Psychiatry Network.

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Author's reply: I am grateful to Dr Double for giving me the opportunity to cite more references than are allowed in a debate; but the biological basis of hyperactivity is one of the most researched questions in psychiatry and a letter cannot do justice to it. The chapter I cited previously gives references, and interested readers might also like to consult the recent reviews cited below.

The best-established findings are probably the associations with DNA variations in genes coding for the dopamine receptor (DiMaio *et al*, 2003) and

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