Correspondence

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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 lead to 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.

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.
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. These 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, 2002a). Is there a debate 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, 2002b). 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
dopamine transporter, and neuroimaging findings of altered brain structures including frontal lobe and striatum.

Castellanos et al (2002), for example, report the altered neuroanatomy of ADHD, with the brains of those who have never been medicated being more abnormal than those of children who have received stimulants.

Dr Double extends the debate to the question of the use of medication. A large controlled trial (MTA Collaborative Group, 1999) has shown significant advantages of medication over psychological therapy (although I believe that psychological treatment still has an important place). I should therefore like to emphasise that there are dangers in being too reluctant to diagnose and treat ADHD. Children then often receive more destructive labels. Treatment can restore normal function, so it seems to me unacceptable to withhold its benefits from individual children for the sake of a preference for a different form of society.

Declaration of interest
E.T. has an honorary National Health Service contract, and lectures at conferences receiving sponsorship from pharmaceutical companies.


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**Commissioning conundrum for custodial care**

Simon Wilson presents an editorial (2004) that questions the traditional role of the prison hospital wing. I have also questioned this over the years (Gannon, 2002). However, a factual inaccuracy in his introduction flas his conclusion.

The Health Secretary for England announced that there would be a transfer of responsibility whereby the NHS in England would become responsible for commissioning health care in prisons from April 2003. It is very different to announce 'commissioning', as distinct from 'provision' – as Dr Wilson claims. It is, I fear, less of a take-over than a make-over by the Department of Health. Primary care trusts can commission provision from a range of providers – including the current prison provider. The governor will continue to maintain control over the 'cells' in the hospital wing.

Once the reader understands the distinction between commissioning and providing, it provokes thought about the appropriate allocation of health care spending. Why spend the commissioning money twice, on the same citizen, in two different places? Why construct a parallel health care system?

Choosing to highlight capital investment on prisoners may be a public relations disaster. The general public is easily swayed by popular media headlines. Health care spending on special-care baby cots is more palatable than making the prison experience more decent for citizens.

There are hundreds of people in the secure hospitals who have been assessed as no longer requiring that level of security. Capital investment is required urgently at the lower end of the security scale – it is an illusion that more high security is required – thus creating remand beds (not cells) made directly available to courts. This is the only way to seek equivalence. Our mentally ill citizens should not be in prisons at all – we should argue for nothing less.

Eroding this principle, however well intentioned, just sanitisises society's tolerance of this essential injustice. It is all too collusive to believe that we are somehow caring more appropriately if we allow an expansion of common law – lest it just become common lore.


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Author's reply: I am pleased that my editorial has encouraged some discussion about how best to care for the mentally ill in prisons. Mr Gannon is right to point out that it is commissioning rather than providing that has moved to the primary care trusts. The reason for commissioning twice is perhaps to do with geography – people do not necessarily remain in the borough that is responsible for commissioning their health care. Prisoners are not as free to move around as other citizens and one can hardly expect a Leeds general practitioner to attend to her patient in Brixton prison, or vice versa. Otherwise, Mr Gannon and I appear to be in broad agreement – the status quo is unacceptable, and that is why I argued against any expansion of medical treatment under common law (contra Mr Gannon's assertion, and contra an earlier paper of mine (Wilson & Forrester, 2002)). I advocated an extension of the Mental Health Act 1983 to prisons precisely because that would include openness, accountability and scrutiny in a way that more use of the common law would not.

I think that it is the current system that is collusive and dishonest: the championing of equivalence (a noble idea) enables us to feel better about the reality of a failing system of hospital transfers for mentally ill prisoners. I do not, however, share Mr Gannon's optimism that more secure beds (at whatever level of security) are the solution, and it seems to me that history is on my side. At the moment we cannot even make provision within the National Health Service for the most severely mentally ill prisoners, let alone Mr Gannon's suggestion that there should be no mentally ill citizens in prison at all. I wonder whether that includes adjustment disorders, mild depression, treated schizophrenia, substance dependence and personality disorder? Peter Scott, a predecessor of mine at HMP Brixton, suggested that the nature of the walls (prison or hospital) were an irrelevant distraction as the people inside were the same in both types of institution and the treatment needed was broadly similar (Scott, 1970). I have a great deal of sympathy with this view.
Integrated in-patient adolescent services

Gowers & Cotgrove (2003) correctly draw attention to the scarcity of emergency access to in-patient care for adolescents. It is therefore disappointing that they have reported the evidence from Snowfields Adolescent Unit (Corrigall & Mitchell, 2002) – the first unit in the UK to offer an all-beds, 24-hour, 7-day-a-week emergency admission service – in such a misleading way. Gowers & Cotgrove claim that the paper describes a service focused principally on responding to emergencies, but neglecting other aspects of a comprehensive Tier 4 service. This is not true. The service was designed from the outset to be comprehensive, inclusive and adapted to local needs. An emergency admission service was a necessary response to need, not an end in itself, and has not been provided at the expense of other aspects of care. Evidence in the paper demonstrating the comprehensiveness of the service includes the broad range of diagnoses covered, the wide distribution in length of stay, the high rate of admissions with learning disabilities and, most tellingly of all, the very low rate of referral on to other forms of Tier 4 adolescent service. In fact, since publication, the need to seek alternative in-patient provisions has dropped even further. In the past 3 years, out of 189 discharges, only one case has been transferred on to another type of in-patient care as a result of Snowfields being unable to meet the patient’s needs – and that individual went to a specialist adult service (the National Psychosis Unit), not a Tier 4 adolescent service.

The Snowfields approach has now been generalised to other settings, with similar principles having been successfully incorporated into new adolescent services such as the Coborn Unit in East London.

Gowers & Cotgrove call for the establishment of specialist units to complement existing services as an answer to the need for more emergency access, but a failure to rethink existing provision would be a mistake. The Snowfields and Coborn Units have shown that it is perfectly possible to provide an integrated and comprehensive adolescent in-patient service that includes emergency access.


One hundred years ago

The amendment of the lunacy acts

Sir John Batty Tuke availed himself of the vote for the maintenance of the Lunacy Commission for England and Wales in order to lay before the House of Commons the extreme inadequacy of this Commission as at present constituted and to ask for some inquiry into the subject. He pointed out that there are only three medical commissioners to supervise the treatment of 114,000 lunatics, so that, while in Scotland there is one such commissioner to every 3622, in England the proportion is one to 38,000, and he maintained that a Commission so undermanned must necessarily work in a wooden fashion, unsympathetically and without elasticity. The numerical inadequacy of which he complained was, he said, growing worse and worse, for there had been no enlargement of the Commission since its establishment in 1845, while the number of the insane had increased nearly five-fold and while a great change had come over the conception of insanity. The insane person was no longer regarded as a psychological curiosity but as a pathological subject. The nation was doing its best to stamp out tuberculosis and cancer but it was not doing its best in respect to a disease which attacked three persons out of every 1000 and which, if not arrested, consigned its victims to a living death. Sir John Tuke was well supported by other medical Members of the House, and especially by Sir Michael Foster, who declared...
that in no branch of science had there been
greater progress during the last generation
than in the knowledge of the brain and
the central nervous system. That wonderful
web of delicate fibre and cells was being
gradually unravelled and day by day a com-
mand was being obtained over the brain
which was unknown when the Lunacy Acts
were introduced. Though medical science
had reduced other diseases, lunacy, if any-
thing, was on the increase, and the main
fault was in the present state of the lunacy
laws which, if they did not hinder, certainly
did not facilitate the application of sci-
tice to the disease, especially in its early stages,
in which it was most likely to be amenable
to treatment. He proceeded to show the
necessity for changes in the present meth-
ods of notification and certification and
strongly supported Sir John Tuke’s demand
for a complete inquiry. Dr. R. Farquharson,
who followed, dwelt upon the superiority
of the Scotch method of managing what
are often described as “border cases” and
declared that there ought to be special
hospitals or special wards and special
pathological institutions. In fact, there was
a general recognition by the medical
Members of the House that the time had
come when insanity should be regarded as
a disease like other diseases and that it
should be investigated and treated by
ordinary clinical methods. The Attorney-
General, in rising to maintain on the part
of the Government that everything is for
the best in this best of all possible worlds,
“was not satisfied” that there was any
proof of increase of insanity. He has, how-
ever, presented a Bill, which was read for
the first time on Wednesday afternoon,
having for its object the amendment of the
Lunacy Acts. His somewhat unscientific at-
titude in his speech makes of his practical
action a pleasant surprise.

**REFERENCE**

Lancet, 21 May 1904, 1438–1439.

Researched by Henry Rollin, Emeritus Consultant
Psychiatrist, Horton Hospital, Epsom, Surrey

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**Corrigenda**

*Pathological Child Psychiatry and Medical-
ization of Childhood* (book review). *BJP*,
184, 282. The book reviewer’s name should
read Louise Theodosiou.

Cognitive therapy for command halluci-
cinations: randomised controlled trial. *BJP*,
184, 312–320. The last sentence under
the subheading ‘Reduction in compliance’
(p. 318) should read: Perhaps more impor-
tantly, the risk factors for compliance in the
CTCH group had reduced markedly, parti-
cularly the perceived power of the voice, its
omniscience and controllability, and the
need to appease it (14% of the CTCH
group were appeasing or complying v.
53% of the TAU group).
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D. B. Double
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References
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