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 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.


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. 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 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, 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

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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
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 flims 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 intended, just sanctifies 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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A new name for the Journal?A new name for the Journal?
Do our patients have loves, hates, hopes, fears, passions, fantasies, beliefs, hobbies, sports? A steady reader of the Journal would have no hint that they ever had. Consequently, if the new Editor wonders what improvements he might contribute, I suggest a more suitable name, the British Mausoleum of Psychiatry, unless there be changes in the Journal far more radical than in name.
Dr Williams (2004) urges him to bring back the case report instead of monotonously publishing academic research, the gains that offers to clinical practice being ‘doubtful’, he says. Doubtful is the wrong word – the research is in volumes; the gains in practice are few and seldom visible. Meanwhile, a statistical analysis of 20 different ways of scratching one’s bum is more likely to be published in the Journal than an interesting case report.
Certainly bring back case reports, but also bring back the human being centre stage – the patients; families; psychiatrists; nurses; art, movement, group, and other psychological therapists; the whole therapeutic community, and people’s lives. After all, why not? What else is the day-to-day practice of psychiatry about?

Integrated in-patient adolescent 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

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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

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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 command was being obtained over the brain which was unknown when the Lunacy Acts were introduced. Though medical science had reduced other diseases, lunacy, if anything, 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 science 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 methods 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, however, 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 attitude 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

Corrigenda

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

Cognitive therapy for command hallucinations: randomised controlled trial. BJP, 184, 312–320. The last sentence under the subheading ‘Reduction in compliance’ (p. 318) should read: Perhaps more importantly, the risk factors for compliance in the CTCH group had reduced markedly, particularly 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).
Commissioning conundrum for custodial care
S. Gannon
Access the most recent version at DOI: 10.1192/bjp.184.5.454

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