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.

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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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