Correspondence

EDITED BY MATTHEW HOTOPF

Reporting of randomised trials

Allgulander *et al* (2001) evaluated the efficacy of venlafaxine extended release (ER) in patients with generalised anxiety disorder and reported that all doses of venlafaxine ER showed significantly higher treatment response rates compared with placebo. We read this double-blind, randomised study with great interest and wish to raise concerns about the recruitment of the subjects. Randomised controlled trials are always cited as the gold standard for detecting the efficacy of results. However, they often can be flawed in design and are not immune to bias. Large-scale multi-centre trials often include hundreds of patients from a large number of centres located in different countries. The clinical relevance of such studies has been criticised on the grounds of selection bias.

Healy (2001) stated that company-sponsored randomised controlled trials invariably recruit samples of convenience, which by definition do not really sustain extrapolation to normal clinical practice. These trials also make use of restrictive inclusion criteria in order to ensure the greatest possible homogeneity of the sample studied. This creates a problem when attempting to generalise the results from available trials to more everyday patient populations.

In this context, the Consolidated Standards of Reporting Trials (CONSORT) guidelines, which state that all patients assessed for the trial should be accounted for and that the report should be accompanied by a diagram which explains what happened to all the patients involved in the trial (Begg *et al*, 1996), should be followed. Allgulander *et al* failed to follow the CONSORT guidelines. The information about recruitment of the subjects is lacking. We do not know how many subjects were initially assessed, how many were excluded and why. We also do not have any idea of the response rate or the participation rate, which have implications for generalisability and future research. Also, patients with significant depressive symptomatology were excluded, which raises concerns over whether these results are relevant to general patients.

Allgulander C., Hackett D. & Salinas, E. (2001) Venlafaxine extended release (ER) in the treatment of generalised anxiety disorder. Twenty-four-week placebo-controlled dose-ranging study. *British Journal of Psychiatry*, **179**, 15–22.

Begg, C., Cho, M. & Eastwood, S. (1996) Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA*, **276**, 637–639.

Healy, D. (2001) Evidence biased psychiatry? *Psychiatric Bulletin*, **265**, 290–291.

A. K. Jainer, S. Acharya St Michael's Hospital, St Michael's Road, South Warwick Combined Trust, South Warwick CV34 5QW, UK

Authors' reply: We thank Drs Jainer and Acharya for drawing our attention to the CONSORT statement, which has in fact been updated more recently (Moher *et al*, 2001). We find that our report adopts almost all of the recommendations in the CONSORT guidelines, and are therefore left to speculate whether there has been some misinterpretation of the objectives of our study. In reporting this study, we were at pains to ensure that the nature of the studied population was transparent. We describe the total number of randomised patients, the number who met the criteria for the intent-to-treat (ITT) population for analysis of efficacy, the definition of the ITT population and the reasons for discontinuation of *every* randomised patient (not only the ITT population), and we report in detail the inclusion and exclusion criteria applied in the protocol to obtain patients for the study. We do acknowledge, however, that we did not report in the manuscript the number of patients who were assessed for eligibility for randomisation and not finally selected for the study (i.e. screen failures).

With respect to generalisability of the results, we note the limitations of this in the appropriate section of the report. However, this study was intentionally designed and executed as a well-controlled explanatory trial rather than a pragmatic study (Schwartz & Lellouch, 1967). The objective was to prove the efficacy of venlafaxine extended release in the treatment of generalised anxiety disorder. If we had included patients with 'significant depressive symptomatology', as Drs Jainer and Acharya suggest, such a trial would have confounded the aims of the study by being incapable of determining whether the efficacy observed was due to an effect on symptoms of generalised anxiety disorder rather than on symptoms of depression. Now that we know that venlafaxine is effective in generalised anxiety disorder (as well as in depression), we may start to consider its efficacy in mixed states. Indeed, one of the more pragmatic aspects of this trial, the recruitment of patients across a wide range of centres, is also subject to criticism: surely the results would be less rather than more generalisable if the patients had been recruited from only one or two centres. Some other points of criticism are difficult to understand: response rates as well as recruitment procedures are described in the paper.

We recommend to Drs Jainer and Acharya that in order to advance the generally valid points they raise with respect to the reporting of randomised trials, they do so systematically and perform a general review of such trials in this area, both psychotropic and psychotherapeutic, in order to place within context the findings of our particular study, which we stand by as a well-conducted and well-reported trial. In the treatment of generalised anxiety disorder, benzodiazepines have been widely and traditionally used. Beta-blockers and even antipsychotic treatments are also widely given to these patients in practice. We believe that the findings in our study advance the knowledge base for the rational treatment of patients with this disorder.

Declaration of interest

This study was funded by Wyeth-Ayerst Research, of which D.H. and E.O.S. are employees. C.A. is an employee of the Karolinska Instituet, Stockholm, and was an investigator for one study centre.

Moher, D., Schulz, K. F. & Altman, D. (2001) The CONSORT statement: revised recommendations for

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improving the quality of reports of parallel-group randomised trials. *JAMA* **285**, 1987–1991.

Schwartz, D. & Lellouch, J. (1967) Explanatory and pragmatic attitudes in therapeutic trials. *Journal of Chronic Diseases*, **20**, 637–648.

C. Allgulander Neurotec/Psychiatry, M57 Huddinge University, S-14186 Huddinge, Sweden

D. Hackett Wyeth-Ayerst Research, Paris, France

E. O. Salinas Wyeth-Ayerst Research, Collegeville, Pennsylvania, USA

Genetic research on cognitive ability

I would like to comment on the article regarding genetic locus associations with cognitive ability (Plomin & Craig, 2001). The use of *g* as a measure of 'intelligence' or 'cognitive function' is controversial and far from universally accepted. Significant criticisms of *g* have been put forth (Gould, 1996) and *g* has been used to promote some rather objectionable eugenic views in the past (Hernstein & Murray, 1994). Admittedly, that still leaves the task of explaining the alleged positive correlation between a high *g* score and some genetic loci.

First, I would hope that any common racial/cultural prevalence found in the 'high' *g* group compared with the 'average' *g* group has been controlled for, as this would otherwise tend to produce a number of false positives simply due to genetic homogeneity.

Second, despite the claim that the expected number of chance false positives in such a DNA pooling study were exceeded, I challenge the authors to use a real-world control rather than a mathematical calculation to prove this assertion. This could be calculated quite simply by randomising the initial sample without regard to *g* scores and determining the number of positive linkages found. The same randomisation could then be performed for the second sample and a replication attempted. Presumably, any replicated linkages would be false positives unless you wanted to track down the study subjects and find something that they had in common (e.g. finding raisins to be tasty or some such thing). This could be repeated several times to give a true expected false positive rate. I suspect that, on average, the randomised groups will have as many positive linkages as those found in the initial study.

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Hernstein, R. J. & Murray, C. (1994) *The Bell Curve*. New York: The Free Press.

Plomin, R. & Craig, I. (2001) Genetics, environment and cognitive abilities: review and work in progress towards a genome scan for quantitative trait locus associations using DNA pooling. *British Journal of Psychiatry*, **178** (suppl. 40), s41–s48.

S. J. Pittelli Atascadero State Hospital, Department of Psychiatry, PO Box 7001, Atascadero, CA 93423-7001, USA; e-mail: Pittelli@aol.com

Authors' reply: Although *g* may be controversial in the media, it is no longer controversial among scientists or science journalists (Neisser *et al*, 1996), as seen for example in the reaction to a recent report linking individual differences in grey matter density in the frontal cortex with *g* (Thompson *et al*, 2002). Such research shows that *g* has a biological basis. As mentioned in our review, more genetic research has been amassed about *g* than any other trait in the biological or behavioural sciences and all of that research converges on the conclusion that individual differences in *g* are substantially heritable.

The evidence for a substantial genetic basis to *g* is so overwhelming that there is no longer any need for studies that merely demonstrate yet again the heritability of *g*. One direction for future research is to identify the specific environmental influences on *g*. Genetic research on complex traits provides the best available evidence for the importance of environmental influences and helps to identify specific environmental factors using genetically sensitive designs that can disentangle the effects of nature and nurture. Another direction for research is to attempt to identify some of the specific genes responsible for the substantial heritability of *g*. As part of our review, we reported our work in progress along these lines.

Pittelli hopes that our cases and controls do not differ. The second sentence of our method section states that all subjects were of European descent and non-Hispanic so that differences in marker allele frequencies between the groups were less likely to be due to ethnic differences. We also included a paragraph about ethnic stratification in our Conclusion, in which we note that we are adding a within-family component (parent–child trios) to our design in order to control for any remaining effects of stratification. In addition, we have subsequently applied the genomic control method (Pritchard & Rosenberg, 1999) to pooled DNA and found no evidence for stratification in our samples (Plomin *et al*, 2002*a*). Pittelli proposed randomising subjects to provide an empirical false positive rate. We cannot do this because our genotyping data are based on pooled DNA for the groups. However, genomic control analyses are relevant to establishing an empirical false positive rate. Contrary to Pittelli's prediction, we do not find more than the expected chance number of results using the genome control method (Plomin *et al* 2002*a*).

It is now generally recognised that progress has been slow in identifying specific genes associated with most complex dimensions and disorders, probably because the effect sizes of individual genes is smaller than expected (Plomin *et al*, 2002*b*). Research on *g* is no exception. The in-progress research described in our review has led to a genome scan using nearly 2000 markers in which we find no associations with *g* that cleanly replicate in two case–control samples (each twice as large as the samples described in our review) as well as in a parent–child trio sample (Plomin *et al* 2002*a*). Although the many hurdles that we set for acceptance of a quantitative trait locus association may have been too high, it is important to be conservative in light of reports of associations with complex traits that do not replicate (Plomin *et al*, 2002*b*). None the less, we are following up several promising leads, as well as applying new approaches that capitalise on methodological and substantive advances from the Human Genome Project.

Neisser, U., Boodoo, G., Bouchard, T. J., Jr, *et al* (1996) Intelligence: knowns and unknowns. *American Psychologist*, **51**, 77–101.

Plomin, R., Hill, L., Craig, I., *et al* (2002*a*) A genome-wide scan of 1842 DNA markers for allelic associations with general cognitive ability: a five-stage design using DNA pooling. *Behavior Genetics*, in press.

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R. Plomin, I. Craig Social, Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry, King's College London, De Crespigny Park, Denmark Hill, London SE5 8AF, UK

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