Correspondence

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Contents ■ Reporting of randomised trials ■ Genetic research on cognitive ability ■ Schizophrenia-like psychosis in African and Caribbean elders ■ Attitudes to depot antipsychotics ■ Depot injections and nut allergy ■ Stigma, suicide and religion ■ Other approaches to mental and physical illness

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.


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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 Institutet, Stockholm, and was an investigator for one study centre.


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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 rai sins 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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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 substantiallyheritable.

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, 2002a). 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 2002a).

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, 2002b). 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 clearly 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 2002a). 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, 2002b). 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.


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Schizophrenia-like psychosis in African and Caribbean elders

The interesting study reported by Reeves et al (2001) draws attention to mental health service provision for ethnic minority elders. However, their findings could be misleading as they repeat common errors of cross-cultural research.

By definition, African and Caribbean elders are not a homogeneous group. Neither are they synonymous with ‘African–Caribbean’. As a population, they are of different history, ethnicity and culture. Furthermore, as migrants from different geographical regions of the world it is important that their different identities are appreciated, especially in their ‘third age’. Unlike the melting pot of second and third generations, these elders maintain distinct values that influence their social and help-seeking interactions. Migration pathways between the groups are diverse as well, ranging from long-term to recent, academic pursuit to meeting labour needs and the ‘culture-shocked’ to the assimilated.

There are also fundamental problems with defining cases by place of birth. ‘African-born’ includes Algerians, Egyptians, East African Asians and White South Africans. Similarly, ‘Caribbean-born’ persons of African, Asian and mixed-race provide a richly heterogeneous population of elders. How does one draw meaningful scientific conclusions?

The authors did not clarify the proportion of subjects from each of the African and Caribbean groups in the study. This may influence analysis and outcomes. One must also make a clear distinction between onset of illness and contact with services. First contact above age 65 years does not necessarily imply late onset of illness as alternative care pathways and help-seeking patterns may prevail (e.g. years of Pentecostal church attendance). Psychotic symptoms may go undisclosed for many years, particularly among groups suspicious or mistrusting of mental health services. On the other hand, reports of witchcraft or communication with ancestors, previously culturally sanctioned, may be mistaken for psychotic (or schizophrenia-like) experiences.

The authors argue that referral bias by primary care and community physicians is unlikely, as evidenced by low contact rates for anxiety disorders and depression. This is of concern, however, as other researchers (Abas, 1996; Shah, 1998) have reported underdiagnosis of these disorders in ethnic minority populations, with a focus on psychotic and behavioural over affective symptoms.

Although Reeves et al opine that rates may be influenced by social isolation, physical ill health and social exclusion, this was not supported by evidence from their study.

The conclusions of this study are by no means generalisable and highlight ethnic and cultural confusion, as well as the neglect of depression and anxiety disorders, in research involving African and Caribbean elders. In the words of an elderly African, ‘if the heart is too heavy with sorrow, it may disturb the mind’. As clinicians we must not ignore this cry.


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Authors’ reply: We thank Dr Ayyoninde for raising the issue of heterogeneity within ethnic groups and would fully agree that this is particularly pertinent to the comparison groups chosen for our study. Very late-onset schizophrenia-like psychosis is a relatively rare disorder and large populations would have to be surveyed to make any reasonable estimate of community incidence rates. The method we employed involved the enumeration of referrals to secondary care over a defined period and the estimation of source populations using census-derived data. In our case-note study, the ethnicity of referrals was defined by objective criteria (birthplace). However, subjective criteria were used in the 1991 census coding. For example, a person born in the Caribbean might choose to define him- or herself in their census return as Black Caribbean, Black African or Black Other. For this reason, we decided to include all African- and Caribbean-born referrals and all Black groups within the denominator populations. In fact, 96% of referrals were Caribbean-born and there are relatively few African-born people within the age ranges considered in south London.

All populations are heterogeneous, whether these are defined according to geography, culture, religion or shared ancestry. For research involving ethnic groups, the purist might argue that the only solution would be not to attempt any comparisons between categories, which will always be inadequate. This would mean that the evidence base for service provision and public health interventions would be derived entirely from the majority population. A fundamental objective of epidemiology is to describe and explain the distribution of health states across populations. Our findings suggest that incidence rates for an important disabling disorder are markedly different between two coarsely defined populations. Further research is clearly required to refine and explain this observation.

We cannot exclude from our data the possibility that a specific referral bias existed in relation to psychotic symptoms in African- and Caribbean-born individuals. However, for this alone to have accounted for the observed differences, the bias would need to have been at least ten times greater for African and Caribbean individuals. This would not accord with our experience of referral patterns to an old age psychiatry service in south London.

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Attitudes to depot antipsychotics

Walburn et al (2001) are correct to place their conclusions regarding patients’ favourable attitude to depot antipsychotic medication in the context of the paucity of studies using unselected patient samples. Indeed, depot preparations tend often to be used for patients who are otherwise unlikely and/or unwilling to accept antipsychotic medication, and a true reflection of patient attitudes to depot antipsychotics can be established only from research based on representative samples of patients with psychotic illnesses.

In Australia, the study of Low Prevalence (Psychotic) Disorders (Jablensky et al, 2000), conducted in 1997–1998, allowed an arguably more accurate evaluation of patients’ attitudes to depot medication. In this study, 998 persons with a non-organic psychosis were randomly selected from all
patients in contact with services during an index month, as well as selected groups who were not in contact with services in the index month, but had been in the previous 3 years. Also included was a group ascertained through ‘marginal’ services, such as homeless shelters.

The study established diagnoses, symptoms, disability and service utilisation for each participant. In terms of medication, around half were on ‘typical’ antipsychotics, with half of these being administered in depot form. A further 8.3% were on clozapine, 13.3% on risperidone and 8.8% on olanzapine. Demographic and illness parameters did not distinguish medication groups, although usage varied across different service providers. Clozapine tended to be used in patients with a long illness duration, compared with other agents.

Patients reported a mean of around 3.5 of a possible 14 medication side-effects. Some 83% of those using depot medication reported side-effects, compared with 79% of those using typical oral medication. Patients on depot preparations of typical antipsychotics reported the highest rates of akathisia, and were also least likely to perceive their medication as helpful; indeed, 17% rated it as ‘not helpful’ v. 12% of those on oral typical antipsychotics, 10% of those on olanzapine/risperidone and 5% of those on clozapine.

Thus, in unselected patient populations, patient perception of depot medications appears less favourable than the studies reviewed by Walburn et al might lead us to believe. Clinicians should attempt to enhance adherence to antipsychotics by means other than necessarily resorting to depot medication.


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**Depot injections and nut allergy**

Many clinicians may be unaware of the use of nut oil as a vehicle within antipsychotic depot preparations. We report a case of possible coconut hypersensitivity which occurred during treatment with fluphenixol decanoate.

An elderly woman with a diagnosis of paranoid schizophrenia was commenced on a 3-weekly depot of fluphenixol decanoate (20 mg). After 5 months (seven injections), she complained of soreness and swelling around the injection site. The depot was subsequently administered at a different site and in a lower volume of oil. Within 1 hour, she experienced intense local irritation and a generalised pruritus. Her systemic symptoms began to resolve within 24 hours, but continued scratching at the injection site led to a localised infection. Since then she has refused further depot medication and is hostile towards psychiatric services. Enquiries revealed that all depot preparations of fluphenixol contain coconut oil.

The symptoms described by the patient might be attributable to a late hypersensitivity reaction to fluphenixol decanoate, but they may also be a manifestation of a previously undiagnosed coconut allergy. The patient has refused to be tested for specific immunoglobulin E antibodies to coconut and is guarded when questioned about her dietary habits. Although coconut hypersensitivity is relatively rare, coconut allergens show immunological cross-reactivity with both soy and walnut proteins (Teuber & Peterson, 1999). The prevalence of allergies to peanut and tree nut (e.g. walnut, brazil nut) is increasing (Sicherer et al, 2000). Similarly, the number of reported cases of hypersensitivity to sesame seed and sesame oil has risen in recent years (Levy & Danon, 2001). In sensitised individuals, non-ingestion exposure to food allergens results in less-severe reactions than are observed following inhalation or ingestion (Sicherer et al, 1999).

Depot preparations consist of an ester of the antipsychotic drug in a solution of coconut oil (fluphenixol, zuclopenthixol) or sesame oil (haloperidol, pipothiazine, fluphenazine). Currently, the British National Formulary (British Medical Association & Royal Pharmaceutical Society of Great Britain, 2001) provides no information regarding the oils used in depot preparations. Individual drug datasheets can also be misleading: coconut oil is referred to as ‘vegetable oil’ in the fluphenixol datasheet. Although guidelines regarding the labelling of food products are sometimes seen as overinclusive, they allow consumers to make an informed choice. Depot medications are in widespread use, particularly in patients with a history of non-compliance (Adams et al, 2001). To avoid further alienating such patients from psychiatric services, it is essential that both clinicians and patients are able to make informed treatment decisions. This can only occur if the constituents of depot preparations, particularly those relating to nut and seed products, are more clearly labelled.

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**Stigma, suicide and religion**

A comment by Tadros & Jolly (2001) that ‘Hinduism and Buddhism, among other Eastern religions, have not had a traditionally negative view of suicide’ is not totally correct. According to Hinduism, ‘The law of action is inexorable and inescapable. It is not bound by the chain of time. If you
commit suicide now, you may get the circumstances in the next birth which are worse than those at the present’ (Bhatia, 1991). Sikhism propagates, ‘Suicide in the face of misery and misfortune implies lack of faith in the goodness and righteousness of God’ (Bhatia, 1985). Jainism advocates that the killing of any living being is unethical and a sin (Bhatia, 1991). The view of Islam about suicide is ‘Do not commit suicide and make your hands the instrument of your destruction’ (Bhatia, 1991). Aristotle, Pythagoras, St Thomas Aquinas, St Augustine, Jesus Christ, Guru Nanak and Socrates also considered suicide as unlawful and a sin.

Because of the stigma attached to suicide, the practice of Sati (a custom practised by Hindu women after the death of their husbands in which they used to burn themselves on their husband’s pyre) has been discarded by society and is now regarded as a crime (Chadda et al., 1991). Religiosity in India bears a negative correlation with suicide rate and is, in fact, a preventive factor against suicide (Bhatia, 2000). It is appropriate to suggest that scientific approaches and spiritual approaches can work together to eliminate the stigma attached to communication of suicidal ideas and attempts and to encourage timely professional help-seeking.


Other approaches to mental and physical illness
Kendell’s (2001) editorial on the distinction between mental and physical illness was illuminating of the present predicament of modern psychiatry and medicine. However, he did not do justice to other systems of knowledge and medicine, loosely known as ‘complementary’ medicines, which are widely used around the world. For example, the Ayurvedic tradition (with its linkage to the early Vedic civilisation and systems of thought in India, around 1700 BC), as described in the classical texts of Susratha and Caraka (200 BC–400 AD), avoid a strict body–mind dualism and instead emphasise their interaction in the causation of the human condition (in health and disease) (Ranamchandra Rao, 1990). Clinical features of ‘insanity’, depression and epilepsy are described, with aetiological roles for both mental and physical processes and interactions. The Buddhist traditions (600 BC) take a similar position and state that ‘the mind and body are neither separate nor identical, not even alternatives, but inseparable…like two bundles of reeds supporting each other’ (Goonatilake, 1998).

These systems therefore preserve the unitary nature of body and mind, and approach problems in a more holistic manner, without Cartesian dualism. Meditation, ‘noble’ living and ‘good’ emotions are often included in their therapies. Interestingly, these ideas are being confirmed in certain fields of molecular biology and immunology. Contemporary research has shown the impact of emotions on the immune system and the effect of disease on the mind (Dantzler et al., 1999). The intermediary appears to be cytokines, which are able to regulate the functioning of several organ systems (Licinio & Wong, 1999). Similarly, meditation has led to the search for new psychologies to reduce stress and in the treatment of other disorders (Goonatilake, 1998). Delving into these systems of knowledge and moving away from dualism may reveal novel therapeutic modalities (e.g. meditation) and areas for further research.

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Genetic research on cognitive ability
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