Correspondence

EDITED BY MATTHEW HOTOPF

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Conflict of interest and the British Journal of Psychiatry

There has been debate in medical journals over the potential for conflicts of interest to bias scientific judgements: “we should pay attention to conflict of interest not only when it is clear that a judgement has been influenced by conflict of interest but simply when it might have been” (Smith, 1994). The BMJ requires authors to complete a detailed questionnaire regarding competing interests. Editorial staff may also be vulnerable to conflicts of interest. The editor of the New England Journal of Medicine was criticised for links with the pharmaceutical industry (Gortleib, 2000).

The drug company Wyeth sponsors the educational organisation Neuralink. Although Neuralink has educational components, it may also fulfill a marketing function. Its educational materials appear to give undue prominence to venlafaxine, manufactured by Wyeth. The Editor of the British Journal of Psychiatry is a member of the Neuralink Advisory Board as well as a member of the working party which produced the ‘depression guide’ (Neuralink Advisory Board, 2000).

The British Journal of Psychiatry has recently included a paper written by two Wyeth employees and a Wyeth consultant (Thase et al, 2001). This is a commercially valuable paper in which venlafaxine is described as having benefits compared with other antidepressants. It has already been cited in advertisements for Wyeth’s venlafaxine preparations. I believe that the paper should have contained a declaration of interest by the Editor of the British Journal of Psychiatry, making clear his links with Wyeth. Perhaps the editor of a major medical journal should not have such a prominent link with any drug company.

I hope that the Journal will strengthen its policy on competing interests, including a detailed register of interests for editorial staff, referees and authors (including authors of letters) on its website. This should include the magnitude of payments: there is a big difference between a drug company paying someone £10 travel expenses and £10 000 consultancy fees. Significant competing interests should be summarised in the published articles. At the very least, readers would learn a lot about the dependency between medical research and big business.

Declaration of interest

I am paid £2000 per year for editorial work for Schizophrenia Monitor, a review journal sponsored by the drug company Novartis.


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Author’s reply: Dr Wright correctly notes that the potential impact of ties with the pharmaceutical industry may extend to editorial decisions about whether or not a manuscript is published. This topic was addressed in a recent article in the Journal of the American Medical Association (Wilkes et al, 2001) and the authors, a group of editors of general medical journals, recommended periodic publication of the editors’ relationships with various companies. Should the Editor of the British Journal of Psychiatry choose to accept this suggestion, it would appear to address at least some of Dr Wright’s concerns.

Most of us in academic medicine have some consulting, teaching, or research relationship with the corporations that manufacture medications. I do not know Professor Wilkinson, but I assume that, like me and most others, he works with more than one company.

It is neither reasonable nor necessary to assume that any fiscal relationship with a pharmaceutical company should necessitate that the editor exclude himself or herself from the decision-making process. I do not favour the use of a specific level of income to determine whether or not there is a conflict. Frankly, some of the most blatantly biased decisions (about the scientific merit of a manuscript) that I have observed over the past 25 years have involved no money whatsoever. A monetary threshold cannot replace personal integrity or judicious feedback when one’s peers seem to be close to the edge of propriety.

With respect to our paper (Thase et al, 2001), we submitted to the British Journal of Psychiatry because of the journal’s clear commitment to evidence-based medicine. No aspect of the submission, review, revision, resubmission or acceptance process seemed to be out of the ordinary. The manuscript received very positive ‘blind’ reviews and was praised for being even-handed. The studies incorporated in our pooled analysis were randomised, double-blind trials, the data sets were ‘closed’ (i.e. they had already been subjected to external regulatory review), and the studies were not selected or excluded because of the pattern of findings. In fact, two of the studies in the pooled analysis were ‘rescued’ from the file drawer of unpublishable results. The results were robust: the findings were consistent across multiple outcome definitions and various study characteristics. The findings also were reinforced by a sensitivity analysis, which indicated that the effect was not dependent on the results of any single study.

There are now a number of other studies comparing venlafaxine and selective serotonin reuptake inhibitors (SSRIs), and we tabulated the grouped data of nine such trials in our paper. Additional pooled analyses are underway. Working with an overlapping data set, Freemantle et al (2000) observed a similar magnitude of advantage favouring venlafaxine (v. SSRIs) using a meta-regression approach to meta-analysis. If venlafaxine is indeed a more effective antidepressant than the SSRI class, there will be ample documentation of this effect.
Although the funding source of a research finding should be considered when reviewing and interpreting the results of a study, hopefully our field has not become so jaded or cynical that all such work is rejected out of hand.


Declaration of interest
M.E.T. is a paid consultant to Wyeth–Ayerst Laboratories.

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Response from Neurolink: The members of Neurolink were particularly disturbed by Dr Wright’s accusation that the materials produced by Neurolink are unbalanced and favour venlafaxine, manufactured by Wyeth.

Neurolink is a well-established board of 14 mental health experts who pride themselves on their unbiased, professional expertise in anxiety and depression, and their ability, as a multi-disciplinary group of health care professionals, to produce materials of practical value to other health care professionals and patients.

Neurolink is indeed supported by an educational grant from Wyeth Laboratories, and has been since 1995. Board members receive an honorarium for their attendance at Advisory Board meetings and working parties, where production of materials is discussed and agreed in the light of the existing evidence base and consensus of the members of the Board.

We would like to emphasise that the materials produced by Neurolink are balanced items that review all treatment options – including drug and non-drug options – and we refute all claims that materials give prominence to venlafaxine, or any other drug or treatment, unless there is a body of significant evidence that supports it. In the 6 years that we have been in existence, we have never previously received comments to suggest that Neurolink materials are not impartial, practical resource items.

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Editor’s response: The Journal is committed to openness and I was pleased several years ago to introduce a requirement for authors to make a declaration of their interests with regard to publication of their papers. Last year this requirement was extended to include editorials and items of correspondence (Wilkinson, 2001).

As an elected Honorary Officer (not a paid employee) of the Royal College of Psychiatrists I am required regularly to complete a Declaration of Competing Interests form. My form states that I have an annual renewal of a consultancy with Neurolink, sponsored by Wyeth (£2000 per annum). These forms are available to members of the College, and to non-members of the College at the discretion of the President, Registrar and the College Secretary.

The issues raised by Dr Wright were discussed by the Editorial Board in June 2001. To quote from the minutes of that meeting:

“It was not felt that the Editor had acted at all improperly. . . . It was agreed that a general policy of openness was desirable, but it was generally felt that a detailed on-line register of interests for all staff, referees and authors such as that suggested by Dr Wright was impractical. . . . The ‘Recommendations for publication’ form sent to all assessors would [be amended to] give the assessor the opportunity to declare an interest in the publication of the paper.”

Following that decision, since October 2001, referees have been required to state explicitly if they have an interest in the publication of any paper they are asked to assess. If that is the case, they are required to return the manuscript without assessment.

It has always been the case that when I have an interest in a paper’s publication by virtue of being a co-author, another nominated member of the Editorial Board acts as Editor for that paper. That person’s identity is not divulged to me, and I am kept blind to the peer-review process as it applies to that manuscript. Since receipt of Dr Wright’s letter (in April 2001, subsequent to the acceptance of another paper reporting work funded by Wyeth; Allgulander et al, 2001), the same procedure has been extended to any submission connected with Wyeth. Finally, in keeping with these developments, I am beginning the evaluation of open peer review as a policy from this month (i.e. all assessors will be required to identify themselves to authors).

I am doing what I can to address these important issues, and I am grateful to Dr Wright for this opportunity to clarify our procedures to our readers.


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Risk of pregnancy when changing to atypical antipsychotics

We have become aware of a number of pregnancies which have occurred in women with chronic psychotic illnesses whose medication has been changed from traditional oral or depot antipsychotics to atypical drugs. This can be explained by the loss of the contraceptive side-effects produced by drug-induced hyperprolactinemia in these women. Most atypical antipsychotic drugs (e.g. olanzapine, quetiapine, clozapine) have a negligible effect on prolactin levels, whereas older drugs such as chlorpromazine and haloperidol, as well as sulpiride, amisulpride and risperidone, can cause significant hyperprolactinemia in some women. Although these should not be considered as contraceptives, there is undeniably a contraceptive effect.
We have documented four patients in our local services who have recently had unplanned pregnancies in association with this change in medication. All four women had their medication changed from older, typical antipsychotics in an effort to improve their symptoms and reduce side-effects. Three were known to have a partner at this time. Two were also known to have hyperprolactinaemia, presumably as a result of taking typical antipsychotics. All four women had an unplanned pregnancy following the change in medication and all but one then had their atypical antipsychotic medication stopped. All four of these women decided to proceed with their pregnancies. Two women became acutely ill during their pregnancies and were admitted to psychiatric hospital. All four were admitted postnatally to a mother and baby psychiatric unit, three with acute psychotic symptoms and one with less severe symptoms but with concerns about her ability to parent her child. All four women required very high levels of input from mental health and social services; despite this, only one has been able to continue to provide care for her child.

Unwanted and unplanned pregnancies are clearly undesirable and a doctor could be deemed negligent if a pregnancy results from prescribing without appropriate advice on risk and contraception, for example, in the case of antibiotics given to women on the pill. Unwanted pregnancies are of particular concern in women with chronic psychotic illnesses. Not only does the mother have a substantially increased risk of acute relapse following childbirth, but there is also clear evidence that children of parents with mental illness suffer greater social disadvantage, increased psychological and psychiatric disturbance and higher rates of emotional, sexual and physical abuse (Gregoire, 2000).

There is relatively little information available on the sexuality, contraceptive habits, fertility or beliefs and wishes about reproduction in people with severe mental health problems. It has been suggested that fertility among people with severe mental illness is similar to that of the general population (Lane et al, 1992) and there can be little doubt among clinicians that the changing patterns of care from hospital to living in the community are likely to have altered behaviour and expectations of sexuality and reproduction. Advice to people with severe mental illness about contraception is likely to be poor and they are more likely to have unplanned and unwanted pregnancies (Miller & Finnerty, 1996). Sexuality is an area of patients’ lives that psychiatrists tend to neglect even though they and their patients acknowledge its importance (Pinderhughes et al, 1972).

The cases we have been involved with illustrate what we believe to be an increased risk of pregnancy in women changing from conventional to atypical antipsychotics. The potential risks to mother and child associated with such pregnancies are clear and the lack of attention generally paid to sexuality and contraception by those caring for people with mental illnesses must therefore be a cause for concern. Based on current knowledge, we would suggest that our patients are sexually active and need advice and assistance with contraception. We recommend that the potential effect on fertility be discussed with all patients changing from a traditional to an atypical antipsychotic and that mental health professionals be active in promoting effective contraception.


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### Hospitalisation in first-episode psychosis

The paper by Sipos et al (2001) was discussed with great enthusiasm in our evidence-based journal club. We learnt that 80% of patients with first-episode psychosis were hospitalised within 3 years of first contact with specialist services. Patients with manic symptoms at presentation were admitted rapidly; those with negative symptoms and longer duration of untreated illness were admitted later. The paper concluded that community-oriented psychiatric services might only delay, rather than prevent, admission of patients with a first-episode of psychosis.

At the end of the journal club we realised that the findings from this paper cannot be generalised to our patient group without the knowledge of certain other key issues not mentioned in the paper.

(a) Availability of in-patient beds: studies have shown that the utilisation of in-patient care is determined by the supply of available beds (Saarento et al, 1996).

(b) Availability of assertive community psychiatric services: an assertive community treatment programme has shown to be effective in reducing hospitalisation compared with clinical case management programmes (Ziguras & Stuart, 2000).

(c) A study by Lang et al (1999) demonstrates that improvement in social support predicted decline in hospitalisation.

(d) History of suicidal behaviour carries a greater risk of admission in first-episode psychosis and higher readmission rates over 2-year follow-up (Verdoux et al, 2001).

(e) In clinical practice a patient’s willingness to accept treatment as an outpatient would be a factor in deciding about in-patient treatment.

In our opinion hospitalisation in first-episode psychosis would be greatly affected by the above issues and without knowledge of these issues, the findings from Sipos et al’s study cannot be generalised to patient groups in other areas/services.


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Authors’ reply: We were delighted to read that our paper was so enthusiastically discussed by Sridharan et al at their evidence-based journal club. They have spotted the main limitation to the study, which was included in our own list of limitations – namely, that our findings were “based upon only one service model and may have limited generalisability” (Sipos et al, 2001). In our paper, we cited previous work from Nottingham (Harrison et al, 1991), showing how the development of multi-disciplinary teams had coincided with a reduction in the proportion of patients with first-episode psychosis requiring hospitalisation at initial contact. In Sipos et al (2001) we went on to show that, although there is clearly a reduction in hospitalisation at first contact, the risk of admission at some point in the first 3 years after first onset has actually remained the same. Indeed, there are striking differences between those patients admitted early in the course of the disorder and those admitted later.

On reflection, we agree that the paper would have benefited from a slightly more detailed specification of service changes in Nottingham, although these have been described elsewhere and we would refer readers to Beck et al (1997). We would caution, however, against attempts to draw causal inferences from the presence, or absence, of particular ‘community’ services because our paper reported an observational study rather than a controlled one. The research community has barely begun to understand the interplay between different components of ‘community-oriented’ services and patient outcomes. The parameters mentioned by Sridharan et al are certainly pointers in the right direction but we have some way to go in describing (and measuring) factors such as the amount of ‘social support’ available, let alone evaluating their impact on outcomes.


Antipsychotics and risk of venous thrombosis

The article by Thomassen et al (2001) relates a higher risk of venous thrombosis to the use of antipsychotic drugs. As mentioned by the authors, their data cannot consequently link the risk of venous thrombosis to antipsychotic use as certain biases cannot be excluded from the autopsy date and case-control studies they analyse. However, their study adds to the numerous reports suggesting a link between this class of medication and venous thrombosis. In this debate, however, it should be noted that there is a lack of controlling for factors such as the dose of antipsychotics and the type of psychosis. Catatonia is typically a form of schizophrenia in which one could expect patients to have a higher risk of venous thrombosis (Morioka et al, 1997). Similarly, according to the dose of antipsychotic, the sediment of patients can be so intense that their movements are limited, creating predisposing conditions for venous thrombosis. It is possible that more cautious administration of antipsychotics at a dose which decreases the psychotic symptoms without inducing toxic sedation (Casey, 1997) could prevent a certain number of thrombosis cases, although low doses of antipsychotic appeared paradoxically associated with higher risk in a recent case-control study (Zornberg & Jick, 2000). Exploring the role of these potential confounding factors, particularly in cohort studies, is important to characterise the safety profile of antipsychotic drugs and to improve guidelines for the treatment of patients with psychosis.


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Use of antidepressants by nursing mothers

Hendrick et al (2001) state that the findings of their study provide no reason to discourage nursing among women taking paroxetine, fluvoxamine or sertraline at standard therapeutic doses. Comparison with previous studies is difficult, owing to the research literature consisting mainly of single case reports or small samples, difference in methods and lack of key information (as reviewed by Yoshida et al, 1999).

While I applaud the effort of studying 50 nursing mother–infant pairs, I disagree with the inclusion of all of them as study subjects for two main reasons.

First, seven were included whose prescribed doses of antidepressant were below the recommended dose (British Medical Association & Royal Pharmaceutical Society of Great Britain, 2001) for the treatment of depression (paroxetine 5 mg (n=1), paroxetine 10 mg (n=2), sertraline 25 mg (n=4)). In the case of sertraline, where 30 pairs were included, exclusion of these subjects would increase the percentage of detection of medication, including metabolites, from 24% (8/30) to 34% (8/26).

Second, Hendrick et al came to the same conclusion regarding the safety of fluvoxamine, sertraline and paroxetine, but according to their Table 1 (p. 164) only one serum sample of the five taken from mother–infant pairs where the mother was taking fluvoxamine should be taken into consideration. Of the remainder, no maternal medication concentration was obtained in three cases, and in the fourth maternal medication concentration was below the detectable range of the assays, raising
questions about compliance that will add bias to the results.

**Reforming the Mental Health Act – recruitment and retention issues**

Having recently read the Royal College of Psychiatrists’ response (see http://www.rcpsych.ac.uk/college/parliament/wp.htm) to the Government White Paper on the reform of the Mental Health Act (Department of Health, 2000), there were a number of issues I felt needed raising. First, I believe that the College’s response to the white paper would broadly be welcomed as helpful by my junior colleagues. However, there are some additional points I would like to comment on from the perspective of a junior doctor working on a busy general psychiatry ward. These include the matters of recruitment and retention of junior grade doctors, the erosion of the autonomy of the profession, the changes required for junior doctor training and the implications for the use of ‘holding orders’ by senior house officers (SHOs).

The College expresses concern that recruitment to the profession may be adversely affected by the implementation of the Government’s proposals. Early retirement of consultant grade staff is also mentioned. In addition, I would like to draw attention to the increasing problem of retention of junior doctors at SHO grades who do not complete training and are lost to psychiatry, or to medicine generally.

Arguably, junior doctors will feel the greatest impact from the changes proposed. The prospect of working with a new Mental Health Act that is considered contentious, on both ethical and legal grounds, is bound to lower morale. This is equally true of the Government’s further emphasis on the coercive aspects of patient management and the erosion of the rights of confidentiality for patients. The inevitable deterioration in the relationship between doctors, patients and user groups will further reduce job satisfaction.

Psychiatry, unlike any other medical specialty, is affected on a day-to-day basis by changes to statute law. At the same time, SHOs are perhaps more aware of their counterparts in other disciplines. Recently, the divide between psychiatry and the rest of medicine has seemed to be shrinking. However, this is likely to be reversed by legislation that separates physical illness and mental disorder so completely in terms of individual capacity and patients’ best interests.

The College’s views are so evidently at odds with the Government’s plans and yet it appears that the Government is driven predominantly by media opinion and public fears. Despite widespread misgivings it appears that psychiatrists will have to grudgingly embrace risk-management and ‘dangerous and severe personality disorder’ (DSDP). It seems psychiatry is unable to resist the external pressure to move from dealing with mental disorder to policing the population for social deviancy. Junior doctors will become increasingly aware that the job they chose and trained for may be radically different in the future.

There are questions that need to be answered regarding SHOs’ role in the management of DSDP patients. If they are to be involved in the day-to-day management and assessment of such patients, who are widely regarded as unmanageable and disruptive on general wards, then a great deal of thought needs to be given to appropriate training. Currently, there are few placements specialising in the management of people with personality disorders. More emphasis will also have to be given to training in group therapies and therapeutic communities and this will require considerable time and resources. It could also be argued that time spent managing but not ‘treating’ DSDP patients will necessarily dilute trainees’ experience of ‘treatable’ mental illness. A massive expansion in all grades of post, including SHOs, will be required. It is doubtful how achievable this is given current recruitment difficulties.

Further clarification is required regarding the role of trainees in the emergency detention of informal in-patients under any new legislation. If similar measures remain to those currently prevailing under section 5(2), more rigorous policies for emergency detention will need to be made. It is likely that the perception of detention will change significantly – from the viewpoints of staff, patients and the community at large. Further, the consequences of applying a holding order will need to be considered, especially if this leads to a chain of events that may not be in the best interests of the patient.

**Author’s reply**

Dr Agell rightly points out that seven of the nursing women in our study were taking paroxetine and sertraline at doses lower than are usually recommended for the treatment of major depression. We disagree, however, with his conclusion that these mother–infant pairs were not valid subjects for the study. These women are representative of many new mothers who choose to take the lowest dosage of medication that will benefit them for the duration of their nursing. Further, we considered the range of subjects’ doses in our correlation analyses of the relationship between maternal dosage of antidepressant and infant serum concentration of medication. In fact, one of the primary goals of our study was to identify the dosage of medication that was likely to produce a detectable level of medication in the infants.

Dr Agell also points out that fluvoxamine cannot be deemed safe in the same manner as paroxetine and sertraline, given the smaller number of fluvoxamine exposures. We agree with this observation and recommend that, whenever possible, nursing women be prescribed antidepressants for which the most extensive safety data are available.

**Declaration of interest**

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Risk of pregnancy when changing to atypical antipsychotics
A. Gregoire and S. Pearson
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