Letters

Intensive insulin treatment after acute myocardial infarction in diabetes mellitus

Evidence exists from study of non-insulin dependent diabetes in Japan

EDITOR—In his editorial prompted by the publication of the DIGAMI (diabetes mellitus, insulin glucose infusion in acute myocardial infarction) trial,[1] Malcolm Nattrass states that (in non-insulin dependent diabetes) "evidence [is] still awaited for a relation between diabetic control and microvascular complications."[2] It is true that we all await with interest the results of the United Kingdom prospective diabetes study, but some evidence does already exist. Although it is not directly relevant to Nattrass's editorial, in other contexts I have been surprised that it is rarely discussed and is almost never referenced in publications written by authors working on diabetes outside Asia and Australasia.

The study to which I refer is the Kumamoto study.[3] This randomised 110 patients with non-insulin dependent diabetes (half with existing microvascular complications and half without) into a group treated with multiple injections and a group given normal care. After six years of follow up, both retinopathy and nephropathy were convincingly less common in the group treated with multiple injections—both the primary prevention cohort and the secondary prevention cohort.

While I do not necessarily advocate this trial as definitive evidence of the same effect as that in the diabetes control and complications trial in non-insulin dependent diabetes, it seems a pity that it is discussed so rarely outside Asia and Australasia. This may be due to failure on our part to take note of studies published in journals from other continents. It may also be due to reservations, on the part of those who do know about the study, about whether results obtained in Japanese patients (who were, for example, not obese) also apply to populations of patients that might have different characteristics and different therapeutic responses.

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1 Malmberg K for the DIGAMI Study Group. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. *BMJ* 1997;314:1512-5. (24 May.)
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Factors other than continued use of subcutaneous insulin may be important

EDITOR—The long term follow up data from the DIGAMI (diabetes mellitus, insulin glucose infusion in acute myocardial infarction) study confirm the data at one year follow up.[1] These data showed that diabetic patients who received an insulin-glucose infusion followed by intensive subcutaneous insulin after myocardial infarction had a lower mortality than a control group who received standard treatment. Unfortunately, this new publication adds little to previous publications of data from the same study.[2-4] In particular, the authors are unable to identify whether the improved mortality is due to the intravenous insulin given in hospital, the subcutaneous insulin given after discharge, or improvements in patients' general care. As in previous publications, the authors assert that there were no other differences between the two groups in the treatment given in hospital, but they provide no supporting data. In particular, there are no data on the use of thrombolytic treatment, β blockers, or angiotensin converting enzyme inhibitors during the acute event.

In the accompanying editorial Malcolm Nattrass emphasises the importance of these other treatments, which remain the most important factors along with cholesterol reduction in improving mortality in diabetic patients after myocardial infarction.[5] He hopes that, after the publication of the data from the DIGAMI study, clinicians will not be reluctant to introduce insulin treatment; on the basis of the results of this single study, however, this approach would be premature.

In particular, it should be recalled that half of patients could not be randomised to the study, and in most cases this was because the patient was either unwilling or unable to comply with the treatment regimen. Furthermore, the high use of insulin in the control group (49% at one year) suggests that factors other than the continued use of subcutaneous insulin may be important.

Before this intervention package can be applied in routine clinical care, further studies are necessary to identify the effective component and to determine which patients might benefit.

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Intensive insulin regimens in primary prevention should be assessed

EDITOR—The DIGAMI (diabetes mellitus, insulin glucose infusion in acute myocardial infarction) trial confirms the role of intensive control of diabetes (with insulin) as secondary prevention after myocardial infarction.[1] The results of this trial may have far

Advice to authors

We receive more letters than we can publish: we can currently accept only about one third. We prefer short letters that relate to articles published within the past four weeks. We also publish some "out of the blue" letters, which usually relate to matters of public policy.

When deciding which letters to publish we favour originality, assertions supported by data or by citation, and a clear prose style. Letters should have fewer than 400 words (please give a word count) and no more than five references (including one to the BMJ article to which they relate); references should be in the Vancouver style. We welcome pictures.

Letters, whether typed or sent by email, should give each author's current appointment and full address. Letters sent by email should give a telephone and fax number when possible. We encourage you to declare any conflict of interest. Please send a stamped addressed envelope if you would like to know whether your letter has been accepted or rejected.

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Letters will be edited and may be shortened.

reaching implications. The fact that the beneficial effects of strict glycaemic control (or the beneficial effects of insulin, or both) were greatest in patients who had not previously been treated with insulin and were considered to be at low risk requires further explanation. This group was by far the biggest, and the numbers in other groups (as low as 100) may have been too small for a treatment difference to be detected. The duration of diabetes was not given for each group, but the low risk group had probably had it for a shorter period and probably had fewer macrovascular complications at the time of entry into the study. The benefits of treatment may be related not only to the effect on glycaemic control but also to the point in the development of macrovascular disease at which insulin treatment is started. Two questions arise from this: how long should treatment continue, and when should insulin treatment begin?

From the DIGAMI trial it seems that patients with non-insulin dependent diabetes who are not already taking insulin should receive intensive insulin treatment for at least three months after infarction. It has been shown, however, that (compared with non-diabetic survivors) diabetic survivors of myocardial infarction remain at increased risk of subsequent cardiovascular events far beyond this period.[2] It could be argued, therefore, that secondary prevention with such dramatic benefits should not be stopped unless the risks or cost of treatment outweigh those of macrovascular disease. Studies comparing different durations of insulin treatment are needed.

Studies evaluating other treatments, such as antiplatelet and lipid lowering treatment, in secondary prevention have followed a logical progression to evaluation in primary prevention. Although the cost:benefit ratio of primary prevention is not as persuasive as that of secondary prevention, it is difficult to cost the personal gain of prevention of first events. Given the risk of macrovascular disease in patients with non-insulin dependent diabetes and evidence that glycaemic control affects this risk,[3] a strong argument could be made for studies to explore the role of improved glycaemic control through intensive insulin regimens in primary prevention. Despite the financial (and other) implications of treating all patients with non-insulin dependent diabetes with insulin, the potential gain in this population is difficult to ignore.

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Breast cancer risk with cyst type in cystic disease of the breast

Consistency of cyst type needs to be known

EDITOR—The reported observations of Paolo Bruzzi and colleagues relating breast cyst type to subsequent risk of breast cancer[1] rekindles a well worn hypothesis. This, in its original form, was based on the following sequence of observations. Apocrine changes are reportedly more frequent in populations at the highest risk of breast cancer, and histological features for breast cancer may be more frequent in those with clinically palpable apocrine cysts. Thus patients with apocrine cysts (containing a high ratio of potassium to sodium concentration) will be more likely to develop breast cancer.[2] For this to hold true it would require cyst type to be consistent for an individual. We understand, however, that the original proponents of this argument now find that their data no longer support this hypothesis (J M Dixon, personal communication).

In 1988 we published in support of an alternative hypothesis.[3] While agreeing that breast cysts may arbitrarily be divided into two types, we argued that the sodium and potassium concentrations are unlikely to predict the future behaviour of the epithelium. Breast cysts develop from microcysts which are all of an apocrine type, with high concentrations of potassium and sex steroids from active cellular secretion.[4] In at least a proportion it seems that the epithelium becomes flattened and that active concentrating mechanisms may become less effective so that the contents rapidly become more like plasma. This may simply represent an aging change of a single cyst type. Dupont and Page have noted that flattened cysts are larger than apocrine cysts and suggested that flattened cysts represent a stage of development in which the active element is no longer present.[5]

Our evidence was that the type of breast cyst was not constant in individual patients. Indeed, in the report of Bruzzi et al 60 of 120 patients with multiple cysts had a mixture of type I (high potassium concentrations) and type II (low potassium concentrations) cysts.[1] Unfortunately their study does not address the alternative hypothesis further and, given the almost perfect follow up of patients in their study, we would welcome knowledge of the consistency of cyst type in their cohort.

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1 Bruzzi P, Dogliotti L, Naldoni C, Bucchi L, Costantini M, Cicognani A, et al. Cohort study of association of risk of breast cancer with cyst type in women with gross cystic disease of the breast. *BMJ* 1997;314:925-8. (29 March.)
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Larger study found no association between cyst type and breast cancer

EDITOR—Paolo Bruzzi and colleagues found that patients with breast cysts that contain fluid with a ratio of sodium to potassium concentration of >1.5—type I cysts—had a higher incidence of breast cancer than patients with type II cysts that have an electrolyte composition more like plasma.[1] We have performed a similar but larger study with a greater length of follow up and have been unable to confirm that cyst type is associated with risk of breast cancer.

Between 1981 and 1989, 1374 patients had 3041 cysts aspirated, and the fluid was analysed for sodium and potassium. All the patients were followed up through the cancer registry up to 1995. Seventy four cancers were identified in this group of patients, compared with the 17 identified by Bruzzi and colleagues. Nine patients were excluded from the analysis, two with intracystic cancer and seven who developed cancer before aspiration of the cyst. The number of expected cancers developing in these women was estimated by age specific incidence data from 1988 and the number of person years spent in each age group. The relative risk of patients with cysts developing cancer was 3.24 (95% confidence interval 2.50 to 3.24) ($P<0.0001$), which is very similar to the results obtained by other authors[2-4] and much greater than that reported by Bruzzi and colleagues.

We have also classified cysts according to fluid electrolyte composition, although a ratio of sodium to potassium concentration of 3 seems more meaningful in terms of subdividing into different types according to the histological appearance of epithelium lining and other biochemical constituents (type I <3, apocrine epithelium, high dehydroepiandrosterone sulphate concentration, and low albumin concentration; type II >3, flattened epithelium, low dehydroepiandrosterone sulphate concentration, and high albumin concentration). The confidence interval for the relative risk of developing breast cancer in patients with type I compared with type II cysts was 0.67

Relative risk of breast cancer in women of different age groups

Age (years)*	No of cancers observed	No of cancers expected	Relative risk (95% CI)
<45	11	1.61	6.83 (3.41 to 12.22)
45-49	21	6.31	3.33 (2.06 to 5.09)
50-54	22	6.59	3.34 (2.09 to 5.05)
>54	11	5.53	1.99 (0.99 to 3.56)

*Significant trend of age related to risk, P<0.05

to 1.93. (Using a cut off point of 1.5, as in the study by Bruzzi and colleagues, the confidence interval was 0.58 to 1.68.) These data, based on a much larger database, differ greatly from those of Bruzzi and colleagues' study in that type I cysts do not confer a significantly increased risk of breast cancer, although we cannot exclude the possibility of a doubling of risk.

We identified age as the main factor related to the risk of breast cancer, with patients under 45 being at greatest risk (table). The order of risk in these young women (relative risk 6.83) is similar to that in patients with a strong family history or atypical hyperplasia. Interestingly, Bruzzi and colleagues found that younger women were more likely to have type I cysts. At present, there is no useful screening method for these younger women.

Our larger study has failed to confirm any association between cyst type and risk of breast cancer but has shown that women under the age of 45 who develop cysts are at significant increased risk of breast cancer. Further studies to assess why these young women have such a high risk are clearly warranted.

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General practitioners' workload in primary care led NHS

Workload for chronic disease management has increased substantially

EDITOR—Lone Lund Pedersen and Brenda Leese suggest that general practitioners need to carry out far more evidence based research about their workload.[1] Since 1990 the increased workload in general practice has been such that in this practice alone, and we believe elsewhere, research has taken a much lower priority than previously. We know that our workload has increased.

The authors repeatedly refer to "shared care schemes for chronic disease management for diabetes and asthma." Our work shows clearly that general practitioners care for patients with diabetes alone and that shared care and hospital care are both decreasing at a considerable rate. Our paper published in 1995 and referring to work in 1986 and 1991 clearly showed this trend.[2] Audits carried out in 1994 and 1996 (table) show the increase in this phenomenon, with 62% of patients with diabetes now being cared for by their general practitioners alone.

In Tynedale 1109 patients with diabetes are now receiving care from their general practitioner, compared with 138 ten years ago. This is clear evidence of the increasing workload of general practitioners in this field and emphasises the importance of understanding how chronic disease is now managed. Shared care schemes as repeatedly referred to by Pedersen and Lund are no longer the norm, most chronic disease management having been moved into general practitioners' workload. We are certain that colleagues with interest in other fields, both clinical and administrative, will be able to furnish similar evidence.

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1 Pedersen LL, Leese B. What will a primary care led NHS mean for GP workload? The problem of the lack of an evidence base. *BMJ* 1997;314:1337-41. (3 May.)
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Policies of comprehensive anticipatory care require extra doctors and staff

EDITOR—If we accept that hospital outpatient clinics perform work requiring staff time, then if that work is transferred to primary care it will still require staff time. There may be some savings because well organised practices already know their patients, have good databases, and do not depend on junior staff who change every six months, but this cannot reduce added workload to zero. Moreover, in good primary care, dropout rates should fall, so that although follow up would become more efficient, workload would cumulatively increase.

I don't know if Lone Lund Pedersen and Brenda Leese included studies in my practice (all before the 1990 contract was introduced) in their review.[1] These provided order of magnitude estimates of the extra staff time entailed in offering anticipatory care for hypertension and diabetes to a population of 2000: 74 added hours annually for doctors, 162 for practice nurses, 85 for receptionists, and 11.5 for our manager. With proactive search policies, we found prevalences of all major common disorders to be roughly double the values reported in the national morbidity surveys and other demand led studies, requiring at least 12% additional staff time for long term management on even the most conservative interpretations of evidence then available.[2]

In practice, we found that policies of comprehensive anticipatory care,[3] doing our own minor surgery and routinely following up all cases of chronic disorder, required two whole time equivalent doctors, one whole time equivalent practice nurse, and 1.5 whole time equivalent office staff for a population of about 2000. This was with a working week of three days from 0900 to 1930 and three days from 0900 to 1300, with a 1 in 3 on call responsibility for nights and weekends and consultations booked every 10 minutes.

Staff who have not yet lost their motivation do the best they can for their patients. They lack not incentives but resources and the imagination that comes only from confidence that resources will be found for all useful work. Researchers starting from a presumption that new work in primary care might not incur cost do little to sustain that confidence.

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1 Pedersen LL, Leese B. What will a primary care led NHS mean for GP workload? The problem of the lack of an evidence base. *BMJ* 1997;314:1337-41. (3 May.)
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Practice's consultation rates have increased by three quarters in past 25 years

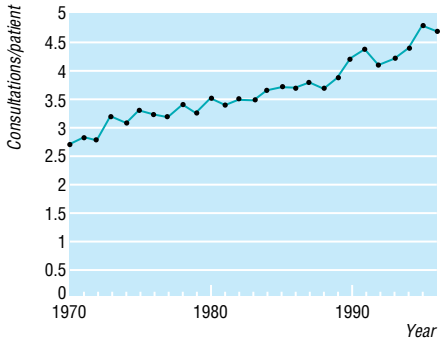
EDITOR—Lone Lund Pedersen and Brenda Leese identify the lack of evidence for an increase in general practice workload.[1] To those of us working in primary care this is perplexing, particularly as it is a point of view that seems to have been adopted by successive pay review bodies. In my practice we have been collecting data on consultation rates and visits for 25 years. The figure shows the 75% rise in consultations per patient over the period. This is not merely anecdotal. The failure of practitioners to undertake and publish the necessary studies of workload must be one reason for the lack of evidence referred to by the authors.

One reason why such evidence is not accepted as showing an increase in individual practitioners' workload is the way in which most practices cope with this inexora-

Providers of care for patients with diabetes in Tynedale, 1986-96.* Figures are numbers (percentages) of patients

	1986	1991	1994	1996
Total No of patients	328	668	1211	1299
Care provided by:				
General practitioner	115 (35)	360 (54)	724 (60)	806 (62)
Shared care	23 (7)	185 (28)	300 (25)	303 (23)
Hospital only	172 (52)	114 (17)	67 (6)	164 (13)
Not known	18 (6)	9 (1)	120 (10)	26 (2)

*In 1986 and 1991 audit was of population of 53 000 and 12 general practices; in 1994 and 1996 it was of population of 74 000 and 15 practices.



Number of consultations per patient per year

bly rising demand. Many will reduce other (often NHS) commitments, take on extra practice staff, appoint assistants, or take on additional partners. This means that an individual practitioner's workload may remain the same after such action, although his or her income and eventual pension will have decreased. I suggest that a more meaningful way to measure workload is to measure the total practice workload over a period, corrected for patient numbers.

Anecdotally, there is no doubt that such evidence of increased workload must exist in other practices throughout Britain. I would welcome the opportunity to study any such evidence that practices are able to disclose to me so that the reported lack of evidence for an increased workload in primary care can be firmly rebuffed.

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Data on health economics of pulmonary rehabilitation programmes are needed

Editor—There are still few pulmonary rehabilitation programmes in Britain.[1] A recent meta-analysis of randomised trials strongly supports respiratory rehabilitation for patients with chronic obstructive pulmonary disease.[2] The results of further trials looking at the comparative effectiveness of hospital and home programmes are awaited; among these will be our trial in 103 patients with severe chronic obstructive pulmonary disease randomised into a hospital outpatient programme or an unsupervised programme based on education and advice about exercise. The results of this study will be available later this year.

M K Sridhar draws attention to several important issues, including the uncertainty over which patients will gain most benefit from pulmonary rehabilitation.[1] Unfortunately, most of the published studies have included patients with widely differing severity of disease, and we believe that it is important that studies should look carefully at the various subgroups.

Sridhar refers to the likelihood that rehabilitation will reduce hospital admissions and healthcare costs in patients frequently admitted to hospital with chronic obstructive pulmonary disease. Data on the health economics of programmes, however, are sparse. It is crucial that programmes should address this aspect as well as quality of life and exercise capacity. Hopefully, sufficient data will be obtained to persuade purchasing authorities to support the introduction of rehabilitation programmes.

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GPs' perceptions of tolerability of selective serotonin reuptake inhibitors and tricyclic antidepressants

Clinical assessments are liable to bias

Editor—Richard M Martin and colleagues have provided information about the rate of discontinuation of antidepressants in general practice.[1] The marked rise in new prescriptions, mainly for selective serotonin reuptake inhibitors, is noteworthy. The rise may be due to the wider range of indications for the use of selective serotonin reuptake inhibitors, though the paper focuses on a diagnosis of depression. The rise may also result from the social acceptability of these drugs and hence a much lower threshold for prescription. Prescriptions of selective serotonin reuptake inhibitors for panic disorder and obsessive-compulsive disorder, and increasingly because of patient choice, define a different population from that which is prescribed tricyclic antidepressants. Rates of discontinuation as a result of side effects will be affected by this bias in treated populations.

Although the authors controlled for the severity of depression, the measurements used were clinical assessments and hence liable to bias. With data of this kind there is concern that a circular argument is being made: that a different scale of severity is used for those patients who are prescribed selective serotonin reuptake inhibitors than is used for those prescribed tricyclic antidepressants. In practice this would mean that severe depression treated with selective serotonin reuptake inhibitors would be less severe than severe depression treated with tricyclic antidepressants.

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Research into long term use is needed

Editor—The findings of Richard M Martin and colleagues suggest that selective serotonin reuptake inhibitors are better tolerated than tricyclic antidepressants in primary care.[1] Although the authors present data on the rates of discontinuation and side effects, they do not comment on how long treatment was prescribed for or on the proportion of patients completing a recommended therapeutic course of treatment.[2] Studies have shown that general practitioners often prescribe low doses of tricyclic antidepressants for short periods.[3]

We recently audited the use of antidepressants in our practice. Using a retrospective case note review, we looked at the dose and duration of antidepressant treatment for all new prescriptions during the first quarter of 1996. Only 20 of the 46 patients started on an antidepressant during this period completed the recommended minimum of four months of treatment.[2] Of the 24 patients originally prescribed a selective serotonin reuptake inhibitor, 15 (63%) completed treatment, compared with 5 (23%) of the 22 patients prescribed a tricyclic antidepressant (numbers were too small to reach significance). This is consistent with Martin and colleagues' finding that the newer group of antidepressants is better tolerated. Additionally, four of the 24 patients started on a selective serotonin reuptake inhibitor were still taking it at one year, whereas only one of the 22 patients started on a tricyclic antidepressant was still taking it at one year. Anecdotally this seemed to be related to patients' reluctance to stop treatment with the selective serotonin reuptake inhibitor. Though there is no evidence in published studies to suggest a risk of patients becoming dependent on selective serotonin reuptake inhibitors, more research on the long term effects of these drugs is needed.

We agree with Martin and colleagues that research into the rates of the discontinuation of treatment on clinical and economic outcomes in the primary care setting is necessary. If many of those treated with selective serotonin reuptake inhibitors continue to take them over the long term this will need to be taken into account in any economic appraisal of antidepressant treatment.

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1 Martin RM, Hilton SR, Kerry SM, Richards NM. General practitioners' perceptions of the tolerability of antidepressant drugs: a comparison of selective serotonin reuptake inhibitors and tricyclic antidepressants. *BMJ* 1997;314: 646-51.(1 March.)
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Analysis should discriminate between newer and older tricyclic antidepressants

Editor—Richard M Martin and colleagues' cross sectional survey adds to the debate on the relative tolerability and efficacy of selective serotonin reuptake inhibitors as

compared with the older tricyclic antidepressants.[1] This debate has been complicated by studies comparing the relative cost effectiveness of prescribing a selective serotonin reuptake inhibitor with the cost of prescribing a tricyclic antidepressant for first line treatment of depression; an earlier report suggested that paroxetine was more cost effective than imipramine but a revised analysis suggests the opposite.[2]

Martin and colleagues point out the deficiencies of an earlier meta-analysis of the efficacy and tolerability of antidepressants.[3] This analysis failed to consider that the older antidepressants (non-selective serotonin reuptake inhibitors) comprised a heterogeneous group of drugs of variable tolerability; the findings of any study comparing selective serotonin reuptake inhibitors and tricyclic antidepressants therefore depended on whether the study included certain drugs—that is, those termed second generation, tetracyclic, and newer tricyclic drugs. These drugs (maprotiline, trazodone, mianserin, and lofepramine) are better tolerated and, with the exception of maprotiline, have also been shown to be less toxic in overdose than the older tricyclic antidepressants.

The authors excluded these non-tricyclic antidepressants for precisely these reasons; however, they included lofepramine, which, although a tricyclic antidepressant, is relatively safe in overdose, non-sedating, and more likely to be prescribed in a therapeutic dose than other, more typical, tricyclic antidepressants.[4] Excluding this drug from their main analysis would therefore be expected to have increased the difference they found in the relative tolerability between selective serotonin reuptake inhibitors and typical tricyclic antidepressants.

A separate analysis of lofepramine comparing it with the selective serotonin reuptake inhibitors would have clarified whether there are significant differences between them. Confusingly, however, the authors group together lofepramine and dothiepin as newer tricyclic antidepressants which may be better tolerated. It is unclear how they come to classify dothiepin as such since it is an established tricyclic antidepressant with important sedative effects, has a greater propensity to impair concentration and memory than lofepramine, and is reported to be more toxic than other tricyclic antidepressants, particularly because of its proconvulsive and cardiac arrhythmic effects.[5] Analysing the rates of discontinuation of treatment for lofepramine and dothiepin together compared with the rates of discontinuation of other antidepressant classes therefore seems to be meaningless and serves only to confuse the debate.

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Authors' reply

EDITOR—Jan Grace points out that in our study the diagnosis of depression and the assessment of severity were clinical judgments. Therefore, despite our controlling for these variables in our analysis of the rates of discontinuation, a potential bias remained because general practitioners may have used different diagnostic criteria and different definitions of severity for selective serotonin reuptake inhibitors compared with tricyclic antidepressants. The problem arises because this was an observational study of what general practitioners actually do in clinical practice. We were careful to make it clear that these measurements were the general practitioners' own assessments, and we qualified our conclusions with a discussion of the potential limitations. Nevertheless, we restricted our analysis to patients with a diagnosis of depression, and the available data suggested that severity of depression was not a confounding factor in our estimates of discontinuation ratios.

Naureen Bhatti and Jonathan Graffy present data from their own practice in support of our findings. They remind us that antidepressants are often taken for an insufficient time to realise their full benefits in preventing relapse and recurrence of illness.[1]

Imad M Ali argues for an analysis of lofepramine alone against selective serotonin reuptake inhibitors. Like selective serotonin reuptake inhibitors, lofepramine has low toxicity in overdose,[2] is more likely than older tricyclic antidepressants to be prescribed at therapeutic doses,[3] but costs less.[4] While the prescribing of selective serotonin reuptake inhibitors increased dramatically during our study, the prescribing of lofepramine was relatively stable. The overall discontinuation ratio for lofepramine was 32% compared with 22% for selective serotonin reuptake inhibitors ($P < 0.0001$)(table). The discontinuation ratio for side effects was 14% and for poor efficacy 15%, compared with 11% ($P = 0.0003$) and 8% ($P < 0.0001$) respectively for selective serotonin reuptake inhibitors. While these data are subject to the potential biases previously discussed, they suggest that lofepramine is not as well tolerated in general practice as selective serotonin reuptake inhibitors.

Proportion of new courses of selective serotonin reuptake inhibitors and lofepramine that were discontinued, July 1990 to June 1995

	Selective serotonin reuptake inhibitors	Lofepramine
No of new courses	5275	1803
No (%) discontinued	1146 (22)	575 (32)
No (%) discontinued:		
Because of side effects	560 (11)	248 (14)
Because of poor efficacy	398 (8)	262 (15)

All the correspondents agree on the importance of our data. Discontinuations and switches of drugs were common and varied by class of antidepressant drug. Traditional randomised trials attempt to restrict switches of drugs and discontinuations to study clinical outcomes of a specific treatment. Prospective pragmatic trials in general practice are required to examine the effectiveness and costs of treatment.

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Anonymity for unrelated bone marrow donors should remain

EDITOR—Sally Davies raised the issue of privacy in the context of bone marrow donation between related individuals.[1] She was commenting on a case reported by the *Daily Mail* in which the sister of a woman in her 30s who had leukaemia refused to give a bone marrow donation.[2] The subsequent media debate led the donor to reconsider her position. There are wider implications for unrelated bone marrow donor registries.

The Anthony Nolan Bone Marrow Trust has reported a 6% rate of requests for second stem cell donations and a further 5% rate of requests for second blood lymphocyte donations from the same donor (S A Cleaver et al, Royal College of Physicians of Edinburgh consensus conference on unrelated donor bone marrow transplantation, 29-30 October 1996). The figures for the British Bone Marrow Registry are similar. There is therefore at least an 11% chance of being recalled for a second donation, and it should be noted that there is a small but finite risk of life threatening complications for the donor as a consequence of bone marrow harvests.[3]

If confidentiality is not broken the donor will be able to consider objectively whether to donate a second time, but if confidentiality is breached it becomes almost impossible for a request to be refused and, as in the above case, pressure may be brought to bear on the donor to comply with the second request. Obviously this precludes real consent. Conversely, in cases in which the result of the transplantation has been cure or appreciable

prolongation of life for the recipient, the donor could conceivably request a reward.

The traditional role of meetings between unrelated donors and recipients in cases of good outcome has been to recruit bone marrow donors and to raise funds. The 1996 consensus conference on unrelated donor bone marrow transplantation deemed that, although policies for anonymity for unrelated bone marrow donors vary widely throughout the world, there are good reasons to maintain strict anonymity. It was concluded that the potential problems of breaking anonymity outweigh the benefits of disclosure.

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Diagnosing and managing polymyalgia rheumatica and temporal arteritis

Sensitivity of temporal artery biopsy varies with biopsy length and sectioning strategy

EDITOR—Two recent review articles have discussed the diagnosis and management of giant cell arteritis.[1 2] Both mentioned temporal artery biopsy, but the complexities of this deserve further discussion.

Firstly, temporal artery biopsy is not perfectly sensitive. Medical students learn of the existence of skip lesions and that patients should not be denied steroid treatment for giant cell arteritis that is strongly suspected despite a negative biopsy result. Sensitivity is usually measured against a gold standard test, but for giant cell arteritis no such test exists. Probably the most sensible gold standard is a persisting clinical diagnosis at long term (say, one year) follow up.

Secondly, clinicians should be aware that the sensitivity of biopsy will depend on quality, particularly biopsy length, and preparation for histological examination; a longer biopsy sample with closely spaced sections is likely to have a higher sensitivity than a short one with widely spaced sections. Supporting evidence for the various opinions about optimal biopsy length and preparation is lacking. The largest published series is from the Mayo Clinic.[3] The clinic's recommended practice is to take specimens of substantial length (mean 35 mm) with a further specimen from the artery on the other side if the first gives a negative result on frozen section; despite this, many centres still take considerably shorter specimens.[4 5]

My audit of 200 temporal artery biopsy specimens sent to the neuropathology laboratory of the Western General Hospital, Edinburgh, between 1990 and 1996 showed a median biopsy length of only 10 mm. The specimens came from various departments, and the median length did not vary between departments. However, there was a significant difference in length between samples that gave positive and negative results on histological examination (table), which suggests that longer specimens may be more likely to yield a positive result. The only way to resolve the issue is to determine the sensitivity of strategies using different biopsy lengths and sectioning policies, with long term follow up as the diagnostic gold standard.

Mean length of biopsy sample in patients in whom histological result was normal and those in whom it showed arteritis (figures in parentheses are 95% confidence interval)

Histological result	Mean log length*	Geometric mean length† (mm)
Normal (n=135)	2.14 (2.21 to 2.50)	8.6 (7.8 to 9.4)
Arteritis (n=50)	2.36 (2.04 to 2.25)	10.6 (9.2 to 12.2)

*Biopsy length logged to give normal distribution of values. Student's *t* test for difference between two means was significant (P=0.02).
†Geometric mean is antilogged value of mean log length.

Finally, occasionally the clinical suspicion of giant cell arteritis is so strong that the patient is treated with steroids whatever the biopsy result. The final diagnosis and the treatment policy in such patients depend on the clinical response to steroids, not the biopsy result. To imply that it might be considered negligent to avoid biopsy when it will clearly not alter management[1] is surely to advocate a defensive style of medicine that cannot be best for our patients.

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1 Swannell AJ. Polymyalgia rheumatica and temporal arteritis: diagnosis and management. *BMJ* 1997;314:1329-32. (3 May.)
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Oral prednisolone 40 mg daily is not adequate for temporal arteritis once vision is affected

EDITOR—A J Swannell's review of the diagnosis and management of polymyalgia rheumatica and temporal arteritis fails to address adequately the management of a patient in whom visual loss due to temporal arteritis is already established. Three such patients have been referred to me from the same rural general practice over 20 years, all of whom became totally and irreversibly blind in both eyes despite treatment with steroids.

The most recent patient was a man of 87 in previously good health who presented to his general practitioner with typical symptoms and signs. On emergency admission he had no light perception in the right eye and 6/6 vision in the apparently normal left eye. Plasma viscosity was 1.9. He was admitted and given 80 mg prednisolone by mouth daily. After 36 hours, despite great improvement in his headaches, he had become totally blind in the left eye as well, though he had not reported this to the nursing staff. Intravenous administration of 1 g methylprednisolone failed to restore vision.

His case, and results of an audit of outcome of temporal artery biopsies, were discussed by our unit audit committee. The following management guidelines were agreed:

- All patients with visual loss due to temporal arteritis should be offered admission
- 500 mg intravenous methylprednisolone should be given immediately on diagnosis
- Maintenance treatment with 80 mg prednisolone daily should be given until the situation seems stable and the plasma viscosity is falling
- Visual acuity should be monitored at four hourly intervals and administration of intravenous methylprednisolone 500 mg repeated if further visual loss occurs.

Two audits of the results of temporal artery biopsy were done in Bath five years apart. Both showed a rate of positive results of about 5%, the referrals for biopsy coming from a variety of sources. This contrasts with 10 positive cases out of 25 of polymyalgia rheumatica reported by Dixon et al.[2] There was some disagreement among the audit committee about appropriate criteria for temporal artery biopsy, but I believe that no reasonable request for a biopsy from another doctor should be refused. Temporal arteritis is a worrying and sometimes uncontrollable condition for which the patient has every right to expect our best endeavours. Oral prednisolone 40 mg daily is not adequate treatment once vision is affected.

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Urgency in giving steroids in giant cell arteritis is still not widely appreciated

EDITOR—In the comprehensive review of the diagnosis and management of polymyalgia rheumatica and temporal arteritis, A J Swannell, like other authors, persists in referring to temporal arteritis as if it was a separate clinical entity.[1] Temporal arteritis is but one of many varied manifestations of giant cell arteritis. Most authorities now link polymyalgia rheumatica and giant cell arteritis under the generic term of polymyalgia arteritica.

Polymyalgia rheumatica is relatively benign but may later progress to giant cell arteritis—a multisystem pathological process. Giant cell arteritis may also present without an antecedent history of polymyalgia rheumatica.[2] One must view with concern, as do Karanjia et al, that in 66 patients with giant cell arteritis admitted to a

district general hospital there was an average delay of more than six weeks from the onset of symptoms and diagnosis; this was the case even when eight patients in whom the disease presented insidiously over periods longer than six months were excluded.[3]

The urgency in treating patients with giant cell arteritis with steroids is still not widely appreciated. A delay of even a few hours in starting treatment may result in irreversible visual failure. If untreated, some 30% of patients develop serious visual complications due either to obliteration of the central retinal artery or, more commonly, to ischaemic optic neuropathy as a direct result of the ciliary arteries supplying the optic nerve and disc being similarly affected. An elderly patient presenting with sudden loss of vision in one or both eyes should be given an intravenous injection of 10 mg dexamethasone before admission to hospital and before the erythrocyte sedimentation rate or, preferably, plasma viscosity is known. Abandoning measurement of the erythrocyte sedimentation rate in favour of measurement of plasma viscosity has been advocated. This would be premature until viscosity can be measured whenever necessary, 24 hours a day.[4]

With initial high doses of steroids, toxic effects, such as iatrogenic Cushing's syndrome and osteoporosis, may rarely occur. This, however, is surely a small price to pay compared with permanent blindness in one or both eyes. Monitoring of the acute phase response is essential. Once taking a low maintenance dose of steroids, patients must be warned that any exacerbation of symptoms, particularly sudden deterioration of vision, demands that the dose should be increased immediately. Details of this procedure should be given to the family doctor.[5]

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Repeated measurements of erythrocyte sedimentation rate are not efficient use of time or resources

EDITOR—A J Swannell has provided a comprehensive review of polymyalgia rheumatica and temporal arteritis.[1] The author's own policy is to review patients monthly, titrating the dose of prednisolone against symptoms and the erythrocyte sedimentation rate. I believe that repeated measurements of the erythrocyte sedimentation rate are not an efficient use of time or resources.

To exclude other diagnoses such as malignancy, it is important to monitor the erythrocyte sedimentation rate to ensure that it returns to normal after the initial presentation. The dose of steroid can then be reduced, as suggested by Swannell and by others,[2] but only using symptoms as a guide to the severity of disease. If a relapse occurs then the erythrocyte sedimentation rate should be remeasured to confirm the relapse. In a prospective study of 74 patients, however, the erythrocyte sedimentation rate was normal in 48% of relapses.[3] The same study reported that the rate was normal in 80% of visits before a relapse. The authors concluded that the erythrocyte sedimentation rate was not useful in predicting relapse.

As Swannell mentioned, there is little evidence for the various dosing and monitoring schedules. Few studies have taken place in general practice, where most of the patients are treated. For a condition in which side effects of treatment are common,[4] it must be time for a large trial to try to define the optimum management schedule.

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Patients starting steroids should be given advice on risk of osteoporosis

EDITOR—The review of polymyalgia rheumatica and giant cell arteritis correctly concentrated on the clinical presentation, diagnosis, and treatment with corticosteroids.[1] We wish to reinforce the author's brief comment about the risks of osteoporosis.

Polymyalgia rheumatica and giant cell arteritis occur in the aging population, when the risk of fractures is already rising. Corticosteroid treatment, by causing an early loss in bone mass, leads to a further increase in the risk of fracture. The effect is important, especially as the dose of steroid can be high and treatment prolonged, with over half the patients being treated for over two years. Many patients may also be managed by specialists not fully aware of the risks of osteoporosis.

An audit of practice in one ophthalmology department showed that little consideration was given to the problem of osteoporosis and that little or no advice was given to the patients starting corticosteroids.[2] We recently conducted a survey of all British ophthalmologists, with a response rate of 81%.[3] While three quarters of respondents regularly prescribed prednisolone in doses of over 5 mg for at least three months, only one quarter gave patients advice on osteoporosis. A recent government report recommended that at this dose bone densitometry should be considered.[4] Few consultants in our survey used bone densitometry.

We believe that all practitioners prescribing corticosteroids should beware of the risk of osteoporosis, especially in the aging population. All patients starting to take corticosteroids should receive basic advice on dietary calcium and exercise. Postmenopausal women should consider hormone replacement therapy, especially if they have had a hysterectomy. Treatment with calcium and vitamin D_3, cyclical etidronate, and calcitriol have been shown to have some effect in preventing bone loss in patients taking corticosteroids.

Our audit has raised local awareness so that patients starting corticosteroids now receive advice as well as referral to an appropriate clinician if they are to remain on treatment for many months.

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1 Swannell AJ. Polymyalgia rheumatica and temporal arteritis: diagnosis and management . *BMJ* 1997;314:1329-32.
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Doctors should be trained in lifting patients

EDITOR—Julia Smedley and colleagues found that back pain was more common in nurses who lift and move patients frequently without the use of mechanical aids, and they conclude that prevention may lie in improved ergonomics.[1] Nurses undertaking these tasks, however, have been trained in safe handling and thus are better able to perform them repeatedly without sustaining injury. In addition, nurses are now advised to consider using hoists, sliding aids, or other specialised equipment when most or all of a patient's weight has to be lifted.[2] Few doctors in training have such skills, and yet many will have tried to lift patients when suitably trained staff are not available. Injury to both doctor and patient may arise from poor lifting methods.

We undertook a telephone survey of 55 junior hospital doctors in medicine, surgery, orthopaedics, and casualty. We asked them about personal injury, training, and their approach to lifting a patient with a dense stroke in casualty. Thirty eight doctors had tried to lift patients alone, and 52 had tried with the help of another medical colleague. Fifty one had at some time found it difficult or had abandoned the attempt. Ten had sustained injury as a consequence, all of which were back injuries; eight of the 10 were female. Only 26 doctors had had any instruction, which was usually informal from the nursing staff. Forty nine, however, thought that specific training would be helpful, 29 believing that this should be given before qualification, 12 that it should be given after qualification, and eight that it should be given both before and after qualification. Fifty two doctors said that they would try to lift a patient with a dense stroke,

but none described a safe approach.[3] All were potentially at risk of injuring the patient or themselves.

Junior doctors often lift patients. We believe that, to prevent morbidity in both the patient and the doctor, it is essential that doctors are trained in safer handling procedures if they are to continue with this practice. Most of the doctors we surveyed would welcome formal instruction.

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Cognitive dysfunction may complicate assessment of pain in elderly patients

EDITOR—Henry McQuay and colleagues' inclusion of the biopsychosocial model of pain (the model that describes pain as having affective, cognitive, and behavioural dimensions) is of particular interest in the acute setting.[1] In drawing attention to the difficulties of assessing pain in babies and unconscious patients, however, they seem less concerned about another group—namely, those elderly patients in whom cognitive dysfunction complicates the assessment of pain. The problems of elderly patients are seen as ones of pharmacology alone.

The International Association for the Study of Pain has focused recently on the specific problem of managing pain in elderly patients, publishing a monograph[2] and several articles in its journal, *Pain.* These go beyond the purely pharmacological approach and invite readers to consider the effects of cognitive impairment and culture on elderly people's experience of pain.

The message we should be heeding from the International Association for the Study of Pain is that elderly patients, like babies and unconscious patients, may suffer silently. Unlike the two other groups, however, elderly surgical patients are not yet looked after by specially trained staff in high dependency units. There are far too many of them for such an ideal to be practical.

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1 McQuay H, Moore A, Justins D. Treating acute pain in hospital. *BMJ* 1997;314:1531-5. (24 May.)
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EU directive on bovine spongiform encephalopathy will not affect drugs

EDITOR—In his letter Alan Earl-Slater states that if certain European proposals go ahead then, with effect from 31 December 1997, certain categories of drugs will not be allowed on the market in the European Union.[1] He goes on to name two of my company's products, Hyalase and Hypurin (insulin). This is not the case. Both products will continue to be available in Britain and in the rest of the union.

The commission's proposal to amend directive 75/318/EEC (not 75/18/EEC, as stated in the letter) has been suspended. This directive is specific to pharmaceuticals. A broader commission decision on the use of materials in the food chain presenting risks in relation to transmissible spongiform encephalopathies was adopted on 29 July 1997. This decision referred to the banning of the use of specified risk materials, defined as the skull, including the brains and eyes; tonsils; and spinal cord of cattle, sheep, and goats over 1 year of age, and the spleens of sheep and goats over 6 months of age. Additionally, the use of the vertebral column of cattle, sheep, and goats for the production of mechanically recovered meat is banned from 1 January 1998.

Hypurin (beef and pork insulins) and Hyalase (hyaluronidase) are derived from beef or pork pancreases (Hypurin) and sheep testes (Hyalase). None of these organs are included in the commission's recent definition of specified risk materials. Furthermore, it is unlikely that any future amendment to directive 75/318/EEC, if indeed there is one, will encompass these organs. Incidentally, Earl-Slater's conclusions on the impact of the proposed legislation on gelatin will also not apply: gelatin will continue to be available for pharmaceutical use. Only the use of specified risk materials in the manufacture of the gelatin will be limited.

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1 Earl-Slater A. Bovine spongiform encephalopathy threatens drugs in European Union. *BMJ* 1997;315:426.

In the issue of 9 August, in the cluster on obstructive sleep apnoea, we published an authors' reply from John Wright and Trevor Sheldon (p 369). Unfortunately, we printed an early version of their letter, and we apologise for this. The correct version of the letter is published here.

Obstructive sleep apnoea

Authors' reply

EDITOR—These letters show the uncertainty about sleep apnoea. The common claim of significant associations of sleep apnoea with premature death and vascular morbidity[1 2] is reiterated by John Shneerson and Ian Smith, and Allan I Pack and Terry Young; however, J R Stradling and R J O Davies, and G J Gibson and K Prowse, agree with us that the evidence is weak. Patients will be reassured that assertions about associations between sleep apnoea and disability and death are unfounded or premature.

Uncertainty also exists over the role of weight reduction. Shneerson and Smith suggest that weight loss is the first line of treatment, yet Gibson and Prowse believe that patients should begin treatment with continuous positive airways pressure immediately. The strong statistical association suggests that sleep apnoea is frequently a symptom of obesity. Surely it is logical to tackle the cause rather than the symptom, particularly in view of the other health benefits derived from weight loss. A review has shown that weight loss can be maintained.[3]

Our systematic approach ensures a rigorous and scientific review of the evidence. All data from relevant studies are shown in the tables so readers can derive their own conclusions. This is an advance on the more ad hoc surveys such as that by the Royal College of Physicians referred to by S J G Semple and D R London[2] or those reviews by enthusiasts who often selectively quote research which supports their view and ignore methodological quality.

Pack and Young show this lack of rigour by their failure to appreciate not only the importance of adjusting for confounding but also the fact that brief rises in blood pressure have not been shown to be a significant risk factor for vascular morbidity. Hopefully, the longitudinal studies in progress are better designed than the relatively poor research available.

We did not say that treatment with continuous positive airways pressure is unjustified. We stated that there can be large benefits but that these predominantly seem to occur in patients with severe sleep apnoea. This is echoed in the Australian report, which supports our conclusions about the paucity of good epidemiological research and finds that there is "very little evidence of effectiveness" of continuous positive airways pressure for patients with sleep apnoea of mild to moderate severity.[4]

We acknowledge the support from Pack and Young for our call for further trials on treatment with continuous positive airways pressure. Clinicians, and their professional organisations, have a responsibility to determine in which patients treatment is beneficial and cost effective. To suggest, as some of these authors do, that the NHS should invest extensively in services for 2-4% of the middle aged population on the basis of a case report or a new trial of 16 patients is irresponsible.[5]

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