Letters

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Use of calcium channel blockers and risk of suicide

Independent studies are needed before causality is established

EDITOR—Lindberg et al suggested that the use of calcium channel blockers increases the risk of suicide.[1] Methodological problems, however, render that conclusion uncertain. In a cross sectional ecological study they found a weak but significant correlation between rates of suicide and use of calcium channel blockers, expressed as numbers of defined daily doses dispensed by pharmacies in 152 municipalities in Sweden. The defined daily dose is, however, a technical unit for studies of use of drugs[2]; defined daily doses might differ twofold or more from the daily doses actually prescribed. Therefore, when used for other purposes, such as an estimate of individuals at risk (as in Lindberg et al's paper), methods based on the defined daily dose require validation.[3]

The authors also carried out a historical cohort study of patients with an index prescription of an antihypertensive drug. They found that "five users of calcium channel blockers (three men and two women, one with uncertain intent) and four non-users (three men and one women, none with uncertain intent) committed suicide" within seven years after they bought the index drug in 1988 or 1989. A minimum requirement for applying statistics on the outcome in nine individuals is to validate exposure as well as outcome. One misclassification in this study would mean that the difference was no longer significant. One of the "suicides" in the calcium channel blocker cohort was not even a certain suicide but an undetermined unnatural death. The remaining eight cases of alleged suicide were not validated against death certificates or medical records. It is not known whether these nine patients were taking an antihypertensive drug at the time of death, whether they were depressed, etc. Potential confounders, such as the severity of hypertension, comorbidity, concomitant drug treatment, and history of depression or use of antidepressants, were not controlled for, although such prescription data are available in the database and medical records can be made available for validation purposes in this population.[4]

It is vital that the non-experimental nature of pharmacoepidemiology is recognised. If the association between calcium channel blockers and suicide can be confirmed by validation of exposure and outcome, this association has to be confirmed in independent studies before any causality is established.

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1 Lindberg G, Bingefors K, Ranstam J, Råstam L, Melander A. Use of calcium channel blockers and risk of suicide: ecological findings confirmed in population based cohort study. *BMJ* 1998;316:741-5. (7 March.)
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Drug prescriptions over longer period should have been followed up

EDITOR—Since 1988 there have been suspicions that calcium channel blockers may cause depression; these suspicions have been based on spontaneous reports, including reports of cases in which rechallenge gave a positive result.[1–3] Hallas recently found that calcium channel blockers and angiotensin converting enzyme inhibitors but not β blockers were more often prescribed before than after the start of antidepressant treatment[4]; this is another finding that needs confirmation.

In a population based prescription database Lindberg et al identified a cohort of patients who received at least one prescription of a cardiovascular drug in 1988 or 1989.[5] These patients were followed up in the mortality register until the end of 1994. Nine suicides were identified; five of the patients who committed suicide (one with uncertain intent) had been exposed to calcium channel blockers and four to other cardiovascular drugs (relative risk 5.4 (95% confidence interval 1.4 to 20.5)). The authors calculated an excess risk of 1.1 suicides/1000 users/year.

We applied this estimate to sales of calcium channel blockers and the total number of suicides among men and women aged ⩾45, and we calculated the proportion of all suicides in Sweden that might have been caused by calcium channel blockers (table).

It is highly implausible that such large proportions of all suicides would be caused by calcium channel blockers. More plausible is that the authors overestimated the risk. The significance of the estimated relative risk disappears if the one uncertain case is not taken as a suicide. The authors did not check the history of depression or use of antidepressants in the cohort. Since there is speculation that β blockers may cause depression, the cohort who had been prescribed calcium channel blockers may well have contained patients with prior depression. β Blockers are contraindicated in patients with obstructive lung diseases. This may be a confounding factor if such patients are at higher risk of suicide.

It is disappointing that the authors did not use the database to its full potential.

Proportion of all suicides among people aged ⩾45 who were taking calcium channel blockers (CCBs). Among those aged ⩾65, CCBs would account for 43% and 88% of all suicides in men and women respectively.

	No of suicides*		Patient-years of treatment with CCBs (thousands†)		No (%) of suicides by people taking CCBs	
Year	Men	Women	Men	Women	Men	Women
1988	785	378	62.6	52.7	69 (9)	58 (15)
1989	768	364	73.8	63.2	81 (11)	69 (19)
1990	796	393	86.4	72.6	95 (12)	80 (20)
1991	767	393	96.2	80.9	106 (14)	89 (23)
1992	750	373	108.6	97.7	119 (16)	108 (29)
1993	744	363	109.3	101.9	120 (16)	112 (31)
1994	714	353	121.4	117.1	134 (19)	129 (36)
1995	760	347	126.0	124.3	139 (18)	137 (39)
1996	680	352	148.2	142.2	163 (24)	156 (44)

*Including those with unclear intent. †Calculated as number of defined daily doses sold/365.

They could have followed up all the patients' drug prescriptions, including prior use of antidepressants, continuously for a longer period to get more information. Such a study could have given valuable information to confirm or refute the idea that calcium channel blockers may cause depression. Lindberg et al's paper has not helped to elucidate that important question. It has, however, contributed to the confusion of prescribers and patients over the benefits and risks of calcium channel blockers.

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Prescriptions for particular drug are influenced by numerous factors

EDITOR—On the basis of evidence from ecological analysis and a population cohort, Lindberg et al suggested that use of calcium channel blockers may increase the risk of suicide.[1] In ecological studies, findings are limited to describing differences in populations that would signal the presence of effects worthy of further investigation; this limitation is mainly because of the unavailability of data necessary for control of confounding.[2]

In an attempt to adjust for cardiovascular comorbidity the authors performed analyses in which they used partial correlation coefficients that adjusted the correlation (for each tested cardiovascular drug group) with the rate of use of the other drug groups. The authors reported a significant partial correlation coefficient (r) of 0.29 ($P<0.001$) between calcium channel blockers and suicide rates. However, the P value is determined largely by the size of the sample. The magnitude of r itself must be evaluated too. The degree of association can most usefully be expressed as r^2, the proportion of total variance in a dependent variable that can be explained by the independent variable.[3] Thus less than 9% (that is, 0.29^2) of the variance in mortality from suicide is explained by use of calcium channel blockers—a value of only moderate association, since 91% of the variation is not explained.

A major flaw in the cohort study is the lack of adjustment for confounding effects. Only sex and age were adjusted for in the multivariate models. Other potential confounding factors associated with risk of suicide, such as socioeconomic status, comorbid conditions, severity of disease, mental status, functional status, cognitive status, and social support, were not considered. Patients receiving cardiovascular drugs are heterogeneous, and prescriptions for a particular drug are influenced by numerous other factors. Furthermore, the cohort study was based on use of prescription drugs in only one Swedish municipality between 1988 and 1989. Its generalisability to other populations and to the use of more recent calcium channel blockers is questionable. Moreover, use of death by suicide as a proxy for depression is neither sufficient nor effective in addressing the potential link between calcium channel blockers and depression. Finally, as only nine deaths from suicide occurred in the cohort it is difficult to draw causal conclusions on the basis of such a small number of outcome events without additional sensitivity analyses.

The findings of the current study probably result from ecological fallacy and an inadequate adjustment for confounding effects. Further investigations, with sufficient control for confounding effects, are needed to examine the association between use of calcium channel blockers and depressive symptoms.

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Authors' reply

EDITOR—Suicide is a major cause of premature death, particularly among middle aged people, so examining whether commonly used drugs such as antihypertensives influence risk of suicide is important. Our study suggested that calcium channel blockers increase that risk.

We agree that ecological analyses based on defined daily doses have numerous pitfalls. That is why we combined our ecological study with a population based cohort study. Both these authors and Wiholm et al seem to believe that the significance of the increased risk of suicide in the cohort study depends on one single case. Any reader can verify that this is wrong. A crude relative risk can easily be derived from published data. Exclusion of the fifth (uncertain) case of suicide leaves four suicides in 617 patients exposed to a calcium channel blocker versus four suicides in 2780 subjects exposed to other antihypertensives; this yields $P=0.041$ with Fisher's exact test (0.013 with the fifth case included). A log rank test yields $P=0.012$ (0.002 with the fifth case included), and Cox regression analysis with age and sex as covariates yields $P=0.044$ (0.013 with the fifth case included) and a relative risk of 4.22 (95% confidence interval 1.04 to 17.14).

Wiholm et al present data on the proportion of Swedish suicides that would have been attributed to calcium channel blockers if our estimates were true. They then take these calculations as evidence that our results are overestimates. However, they ignore the fact that our study population is substantially older than the national average. Of all subjects aged ⩾45 in Sweden, 43% are ⩾65. The corresponding proportion in our study population is 70%. The low number of suicides in the study population makes analyses of age differences uncertain, but in a new analysis that we undertook for this letter the risk of suicide related to calcium channel blockers appeared only among elderly subjects. Age adjustment of Wiholm et al's data, based on the assumption that the increased risk of suicide exists only among subjects aged ⩾65, shows that Wiholm et al may exaggerate the number of suicides related to calcium channel blockers by ⩾62%. Their calculations are thus deceptive.

All three letters emphasise the need for adjustments for possible confounders. We discussed this at length in our paper. It is equally important to remember that overadjustment may camouflage a genuine effect.

In the ecological study about 9% of the variance in suicide rates among municipalities seemed to be explained by use of calcium channel blockers. Unlike Chen and Makuch, we consider this to be substantial; calcium channel blockers are used by under 3% of the population.

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Practicalities of warfare required service personnel to be vaccinated against anthrax

EDITOR—Ness et al suggest that service personnel in the Gulf should be randomised to receive either active anthrax vaccination or placebo, but they fail to appreciate the issues behind the decision to give the vaccine.[1] The independent Advisory Group on Medical Countermeasures assessed that there was a real risk that, if a conflict occurred in the Gulf, service personnel could be exposed to anthrax aerosol used as a biological warfare agent. Infection by the aerosol route is associated with over 95% mortality.[2] The anthrax vaccination programme provides protection

for the individual as well as collective protection of the personnel of active service units. It is equivalent to the other methods of personal protection that enable the collective and efficient operation of a military unit. To suggest that this should be randomised is equivalent to a randomised distribution of blank and live ammunition.

Anthrax vaccine has been used widely for many years to protect civilians at risk from occupational exposure to anthrax and is regarded as safe. The 55 000 doses given to date have not been associated with any important adverse events; only minor discomfort at the injection site has occurred. This vaccine on its own is considered highly unlikely to have had any role in Gulf war illnesses. We welcome the involvement of epidemiologists, such as Ness et al, in helping to resolve the issue of Gulf war illness, but this must recognise the need to reconcile scientific rigour with the practicalities of warfare.

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1 Ness AR, Harvey I, Gunnell D, Davey-Smith G. All troops sent to Gulf should be randomised to receive anthrax vaccination or placebo. *BMJ* 1998;316:1322. (25 April.)
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European Medicines Evaluation Agency is ahead of other national licensing authorities

Editor—The European Medicines Evaluation Agency was set up in 1995, and, as the constantly updated status reports on our internet website (http://www.eudra.org/emea.html) show, it has now carried out evaluations of 100 medicinal products for human and veterinary use. As Abbasi and Herxheimer pointed out in their editorial, the creation of the agency reformed the way in which health professionals and patients can obtain information about the medicines they prescribe and use.[1]

The key reform introduced with the creation of the agency is the European public assessment report. This is made available for each medicinal product as soon as it is authorised. The report sets out the scientific assessment carried out by the agency, together with the summary of product characteristics and the patient leaflet.

The agency's commitment to transparency means that all European public assessment reports, as well as much other information, are systematically made available on the agency's website. As the editorial points out, most national competent authorities do not currently publish assessment reports, though they are now starting to follow our lead.

Such a radical concept as the European public assessment report was bound to be difficult to implement. A consultation exercise led to a workshop in October 1997 attended by all interested parties, representing patients, consumers, health professionals, and industry, and the European Union institutions. Details are available on our website. The European Medicines Evaluation Agency is currently examining an analysis by the International Society of Drug Bulletins of nine early European public assessment reports. We intend to make our response public before the end of the year, once we have consulted the scientific committee for human medicines.

After the transparency workshop I formulated rules on access to documents of the European Medicines Evaluation Agency; these rules are available on the agency's website. In line with the recommendation of the international transparency and accountability working group cited in the editorial, the rules provide that refusals to disclose documents are subject to appeal to the agency's management board, made up of representatives of the European parliament, European Commission, and 15 member states.

The agency's efforts towards transparency and openness continue. At a meeting on 30 September the management board endorsed my proposals to improve the transparency of opinions adopted by the agency's scientific committees before the granting of marketing authorisations, to be introduced next January. Statistics will also be made available on the number and grounds for withdrawal of applications.

The provision of quality information to healthcare professionals and patients is important to the agency. Improving what we provide, and how, remains one of our priorities.

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1 Abbasi K, Herxheimer A. The European Medicines Evaluation Agency: open to criticism. *BMJ* 1998;317:898-900. (3 October.)

Identifying asthma and chronic obstructive pulmonary disease in patients with persistent cough

Why was no control group studied?

Editor—Thiadens et al examined 192 patients presenting to their general practitioner with persistent cough—a common and challenging problem in primary care—and found a high prevalence of asthma (39%) and chronic obstructive pulmonary disease (7%).[1] I was disappointed that they did not provide a control group of asymptomatic subjects in the community.

What is the prevalence of abnormal results of pulmonary function tests in their general population? If it is high, with a prevalence approaching the prevalence found in their population of patients with cough, an alternative conclusion might be that asthma and chronic obstructive pulmonary disease are common and not significantly more common in the population of patients with cough. I encourage Thiadens et al to examine their study group further. One issue deserving scrutiny is whether these patients are still coughing after six months. Also, what diagnoses (if any) apply to the remaining (54%) patients with cough, and does their prognosis differ from that of the group diagnosed as having asthma and chronic obstructive pulmonary disease? Finally, how do these patients respond to different treatments?

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Children with cough alone should not be labelled asthmatic

Editor—Thiadens et al devised a score to estimate the probability of asthma or chronic obstructive pulmonary disease in patients who present in general practice with persistent cough[1] and report that adults with asthma may present with cough, as McFadden reported in 1975.[2] They state that the possibility of asthma or chronic obstructive pulmonary disease is rarely considered in patients with a cough, but in the past decade the symptom of cough alone has been increasingly used to diagnose asthma[3–5] and has led to children with cough receiving overtreatment with high doses of inhaled or oral corticosteroids. In a tertiary clinical practice it is not uncommon to see children who have received escalating doses of steroids prescribed for cough, which has led to some of the children becoming cushingoid.

The authors did not report on the repeatability of their question on cough. The repeatability of such questions is poor, and subjective reporting of cough is unreliable.[3] In patients with asthma and cough, the cough is usually worse at night, but in this study nocturnal cough did not reach significance as a current or a past symptom. The percentage of the patients with asthma or chronic obstructive pulmonary disease may have been high because of the definition used.

The authors also ignored increasing evidence that cough alone is a poor marker of asthma in both epidemiological and clinical studies.[4 5] When they used their devised score the probability of asthma (despite the definition) or chronic obstructive pulmonary disease in a patient with a cough and another symptom was 0.13-0.26. Thus theoretically up to eight of every 10 patients with a cough do not have asthma. Emphasising that most patients with a cough have asthma will prompt doctors to label these patients as having the disease, and escalating doses of corticosteroids will be used when the cough

does not subside. The cost to the patient and the community could be considerable.

Although the study was of adults, there is a general tendency to extrapolate such data to children. We believe that the paper should be qualified with a statement that most children with the symptom of cough alone do not have asthma.[3 5] Indeed, the only published randomised placebo controlled study that used an objective measurement for cough (a cough meter) showed that inhaled salbutamol and corticosteroids did not confer any additional benefit when compared with placebo for children with cough.[4]

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Authors' reply

Editor—Rothenberg wonders why we did not use a control group. We chose the cut off values in the pulmonary tests in such a way that only 5% of the general population might show airway obstruction by chance. Epidemiological studies have shown that bronchial hyperresponsiveness is present in the general population and that bronchial challenge testing cannot precisely separate asthmatic from non-asthmatic people in the community.[1] A paper on the prevalence of hyperresponsiveness and symptoms in the general population in the Netherlands showed that hyperresponsiveness was present in 16% of the adult population[2]; by contrast, 42% of our population had a low PD_{20} (the provocative dose causing a 20% fall in forced expiratory volume in one second).

Our population was not a general population, since they attended a general practitioner with a troublesome cough, which is not the case in population studies. In clinical medicine virtually all people with asthma show airway hyperresponsiveness (PD_{20} ≤5.6 μmol methacholine) when they have symptoms. For these reasons, a control group is not necessary. We agree with Rothenberg that follow up is important to determine prognosis for patients who cough who are and are not given a diagnosis of asthma or chronic obstructive pulmonary disease; we hope to report the results later.

We agree with Chang and Masters that in children with persistent cough overtreatment with inhaled corticosteroids is not uncommon in tertiary clinical practice. Misdiagnosis of asthma may also occur in adults in tertiary centres,[3] but in general practice underdiagnosis is probably more frequent than overdiagnosis in coughing patients.[4] It is dangerous to generalise findings from tertiary centres to primary care, since the prevalence of diseases in these settings differs. To avoid misdiagnosis, objective pulmonary function testing is necessary so that results of (methacholine) provocation tests are available to improve the diagnostic possibilities in general practice.

It was not our purpose even to suggest that most adults with asthma or chronic obstructive pulmonary disease have cough as the predominant symptom. We tried to find the key features to identify those with these disorders in a sample of patients with a persistent cough. Thus we agree with Chang and Masters that persistent cough as an isolated symptom has low predictive value for a diagnosis of asthma. These authors state that nocturnal cough did not significantly contribute in our study because of the definitions used. This might be an explanation, but nocturnal cough is a bad predictor of asthma not only in adults but in children as well.[5]

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NSAIDs need not usually be withheld after orthopaedic surgery

Editor—We cannot let Varghese et al's letter go unchallenged. After extrapolation of rodent data they say that non-steroidal anti-inflammatory drugs should not be used after orthopaedic surgery.[1] Prompted by similar views from some of our surgical colleagues, we recently undertook a comprehensive electronic literature search of the effects of non-steroidal anti-inflammatory drugs in orthopaedics, trauma, and bone metabolism. We also asked consultant members of our trauma team for any human data to substantiate their concerns. We presented and discussed the findings at one of our main departmental meetings.

Although many studies in diverse rodent models have indeed suggested that non-steroidal anti-inflammatory drugs inhibit bone healing, many animal studies have shown no effect. In humans the published evidence seems to be limited to one non-peer reviewed abstract that reported delayed union associated with a variety of non-steroidal anti-inflammatory drugs[2] and one study that showed no adverse effect on new bone formation associated with the use of diclofenac.[3]

Unrelieved pain is dangerous and should be treated as effectively as possible in all patients for pathophysiological as well as humanitarian reasons. Drug treatment in any patient entails multiple risk-benefit analyses and all forms of pain relief have potentially deleterious effects. An evidence based overview has highlighted the need for improved management of acute pain and given guidelines on how it may best be achieved.[4] More recently the particular role of non-steroidal anti-inflammatory drugs has been clarified and promoted.[5] We recommend these documents to all staff who care for postoperative patients.

In the absence of well designed human trials showing clinically important effects on bone healing, non-steroidal anti-inflammatory drugs should not be withheld unless there are specific, proved contraindications. A more cautious approach would curtail their use only in those fractures with the highest risk of non-union, for reasons of anatomy, blood supply, or the nature of the injury.

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1 Varghese D, Kadakat S, Patel H. Non-steroidal anti-inflammatories should not be used after orthopaedic surgery. *BMJ* 1998;316:1390-1. (2 May.)
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Cost effectiveness of community leg ulcer clinics

Study compared dressing techniques in selected group of patients

Editor—Morrell et al conducted a randomised controlled trial assessing the cost and clinical effectiveness of community leg ulcer clinics.[1] We are concerned that the trial design precludes a meaningful assessment of the value of these clinics.

Sixty five patients were excluded because they were unable to travel to the clinic, and they did not undergo any formal assessment; these patients still require a home visiting nursing service. It is unreasonable to conclude that a clinic based service is more cost effective when 16.5% of those requiring treatment were excluded from the study owing to immobility. It would have been more valuable to transport half of these

patients to the clinic and include those costings in the analysis. Treatment effectiveness would be better assessed by comparing treatment with the Charing Cross bandaging technique[2] in the clinic with the same treatment in the home. The patients treated at home received a variety of other treatments.

Each patient underwent arterial pressure assessment, but there is no reference to any assessment of the venous system. A patient presenting with a venous ulcer of three months duration should at least undergo handheld Doppler assessment and ideally Duplex Doppler examination to exclude superficial venous reflux amenable to surgical correction. Isolated superficial venous incompetence may be present in 39% of those patients presenting with venous ulceration.[3] This omission may account for the lower healing rate seen in the clinic group compared with the results of other studies[2 4] and will certainly influence the recurrence rate in what is essentially a comparison of ulcer dressing techniques in a selected group of patients.

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1 Morrell CJ, Walters SJ, Dixon S, Collins KA, Brereton LML, Peters J, et al. Cost effectiveness of community leg ulcer clinics: randomised controlled trial. *BMJ* 1998;316: 1487-91. (16 May.)
2 Blair SD, Wright DDI, Backhouse CM, Riddle E, McCollum CN. Sustained compression and healing of chronic venous ulcers. *BMJ* 1988;297:1159-61.
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Study's comparison was outdated

EDITOR—Compression bandaging is the most effective form of treatment for venous leg ulcer.[1] The comparisons that really needed to have been made by Morrell et al are between the different compression bandaging systems available, not between a group receiving compression bandaging and a control group being treated with a range of what are clearly less effective interventions.[2]

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1 Compression therapy for venous leg ulcer. *Effective Health Care* 1997;3(4).
2 Morrell CJ, Walters SJ, Dixon S, Collins KA, Brereton LML, Peters J, et al. Cost effectiveness of community leg ulcer clinics: randomised controlled trial. *BMJ* 1998;316: 1487-91. (16 May.)

Trial design means useful conclusions are limited

EDITOR—Morrell et al tried to apply trial methods to the delivery of care for chronic leg ulcer.[1] Unfortunately, the trial design was such that useful conclusions are limited. Patients in the intervention group were treated in dedicated community clinics by "clinic coordinators" who had been on special training courses (in other words, specialist nurses) and used specific bandaging techniques and materials. Treatment of the ulcer was followed by a standard protocol of stocking fitting and surveillance. None of these aspects of care was available to the control group.

Outcomes were totally predictable. We already know from the Riverside study[2] and the Manchester study[3] that improved healing rates are achieved in community clinics. We also know from previous studies that multilayer bandaging improves healing rates.[4 5] Furthermore, it would be surprising if the provision of care by the same teams of specially trained nurses using optimal materials and working to protocols did not also have an impact on ulcer healing.

An important principle when designing a randomised trial is to standardise all aspects of care except the one under evaluation. The really important question—whether it is necessary to set up community clinics to improve leg ulcer care in the community—has, disappointingly, not been answered by this trial. It might, for example, be more cost effective not to treat leg ulcer patients in community clinics but simply to give all community nurses access to the best bandaging materials or simply train them properly, or both.

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1 Morrell CJ, Walters SJ, Dixon S, Collins KA, Brereton LML, Peters J, et al. Cost effectiveness of community leg ulcer clinics: randomised controlled trial. *BMJ* 1998;316: 1487-91. (16 May.)
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Effectiveness and cost effectiveness of compression bandages should be shown

EDITOR—Fletcher et al report their systematic review of compression treatment for venous leg ulcers.[1] As researchers who perform randomised trials of compression bandages, we echo their concern that the quality of research is poor in this area.

A particular concern of ours is that—unlike pharmaceuticals—bandages, which are classified as medical devices, do not need to undergo rigorous clinical testing to establish effectiveness before being released on to the market. Moreover, provided that the product conforms to certain specifications, it may be placed on the drug tariff without trials in patients with the condition. While some manufacturers invest time and effort into performing properly controlled trials with adequate sample sizes to show statistical significance, many are dissuaded from doing so. Moreover, multilayer systems, which the paper indicates perform better than single layer bandages, are classified according to the individual bandages that make up the system rather than as a single unit.

Recently the NHS Executive called for proposals to examine methods that provide improved healing in patients with leg ulceration, and we await its decision on the allocation of funds. It is difficult to imagine, however, how appropriate trials can be performed on perhaps 10 different methods of compression, together with another five or so adjunctive treatments, without a coordinated national approach and suitable investment to achieve the quality required.

Using the results of the Stockport and Trafford study,[2] we estimate that at least £20m is spent annually on disposables for leg ulcer treatment in Britain, of which about half is spent on bandages. Clearly, evaluation is needed of the effectiveness of these treatments, which seem to offer maintenance treatment rather than healing.

We believe that, until manufacturers have to prove evidence of the effectiveness and cost effectiveness of their products in a similar way to that required of the pharmaceutical industry, they will be content to continue producing "me too" bandages, for which they know there is a market, rather than introducing innovations in bandage technology. The principal treatment for venous ulceration is high compression treatment. Now seems to be the time to evaluate the methods of delivering this treatment, with the aim of avoiding undue waste and unnecessary suffering by the use of ineffective treatments.

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1 Fletcher A, Cullum N, Sheldon TA. A systematic review of compression treatment for venous leg ulcers. *BMJ* 1997; 315:576-80. (6 September.)
2 Simon DA, Freak L, Kinsella A, Walsh J, Lane C, Groarke L, et al. Community leg ulcer clinics: a comparative study in two health authorities. *BMJ* 1996;312:1648-51.

Author's reply

EDITOR—Our study was not an explanatory trial designed to tease out, in an artificial experiment, the efficacy of different components of leg ulcer care. Rather, it was a pragmatic trial of a complex new technology in the population for whom the treatment was intended.[1] The principles of health technology assessment are to compare a new technology (in this case, new ulcer dressing technique in a clinic setting by specially trained nurses) with existing mainstream technology[2] (in this trial, routine care at home for people with venous leg ulcers by the district nursing service). To have compared other combinations such as new dressings in conventional settings (as suggested by Whatling and Galland and Platt) would have been to invent a new technology not in use in the NHS.

When our trial was commissioned (1993) four layer compression bandaging in the home was not a treatment option, being apparently more costly. Even now few district nurses have access to all the components of the four layer bandaging system,

which are not available on the drug tariff and require specific funding. Also, we did not have the benefit of the systematic review which concluded that any compression (bandaging or other) is better than none.[3]

Patients who were immobile were unable to travel, whether for the trial or for routine care, and therefore would not be included in the target population for this particular health technology. Some patients did attend in wheelchairs and used transport suited for this purpose. The costs of transport for all patients were included in the analysis.

Superficial venous incompetence may have contributed to the recurrence rate in some patients and if treated, may have produced different results. In an ideal world all patients with leg ulcers could undergo colour Duplex Doppler assessment. However, this is not current practice as few nurses have access to this expensive technique. Moreover, not all patients with superficial venous incompetence would be eligible for or would want surgical correction. We believe that such a trial should be performed.

We do not agree that the possibility of superficial venous incompetence explains the lower healing rate for patients in the clinics compared with other studies. A more likely explanation is that patients in our trial had larger and more longstanding ulcers than those in dedicated research clinics and that these patients better represent those seen by district nurses in their regular practice.

The lower costs per visit in the home group probably relate to the salary costs of the lower grade of staff who were visiting the patients (including B grades) and the higher overheads apportioned to the district nurses in Riverside (20% *v* 8%).

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1 Last A. *A dictionary of epidemiology*. Oxford: Oxford University Press, 1995.
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Terminology for early pregnancy loss must be changed

Editorial p 1028

Editor—Miscarriage is distressing, giving rise to a range of emotional experiences for both the woman and her partner. The aim of medical and nursing staff must be to reduce distress, but the distress may be increased by staff taking the wrong approach or using inappropriate terminology. The lay public tend to interpret an "abortion" as a termination of pregnancy.[1] We advise that when women are counselled about miscarriage the word abortion should be avoided.

The Royal College of Obstetricians and Gynaecologists has a study group on early pregnancy loss, which last year recommended new medical terminology that avoids the word abortion for spontaneous early pregnancy loss. The group suggests using the term "early fetal demise,"[2] but women may still find this term distressing. "Delayed miscarriage"[3] and "silent miscarriage"[4] have been suggested to replace missed abortion. We carried out a search of Medline between January 1993 and November 1997 (table). We searched for the terms spontaneous abortion and miscarriage as textwords in two general medical British publications (*British Medical Journal* and *The Lancet*) and four specialist journals (*British Journal of Obstetrics and Gynaecology*, *Journal of Obstetrics and Gynaecology*, *Ultrasound in Obstetrics and Gynaecology*, and *Fertility and Sterility*).

Results of Medline search (Jan 1993 to Nov 1997) of two general medical British journals and four specialist journals for articles that used either of two terms, "spontaneous abortion" and "miscarriage"

	No (%) of articles using:	
	"Spontaneous abortion"	"Miscarriage"
All articles in Medline	699	542 (44)
General journals	9	21 (70)
Specialist journals	43	77 (64)

This search showed that the word abortion is still widely used in the medical literature to describe spontaneous pregnancy loss. The British journals had a lower use of the word than the overall English language literature; perhaps surprisingly, the use was lower in general journals than specialist journals on reproduction. A suitable term to replace missed abortion may have slowed the change. While "delayed miscarriage" is not a complete description of the pathogenic process neither was "missed abortion." For the purposes of medical classification, all miscarriages need further description to explain the underlying pathology, such as "anembryonic pregnancy."

Medical and nursing professionals may find it difficult to maintain one form of language for patients and another for medical notes. They should use the word miscarriage to describe all spontaneous pregnancy loss both when speaking to patients and when completing medical notes. The language culture cannot be changed without a change in the medical literature. Editors of medical journals should ensure that the word abortion is avoided when spontaneous pregnancy loss is meant. The problem seems to be confined to the English language. In French and German the medical words for termination of pregnancy and miscarriage are completely different.

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Medical and psychological effects of early discharge after surgery for breast cancer

Patients can be discharged on second postoperative morning

Editor—Bonnema et al studied medical and psychological effects of early discharge after surgery for breast cancer.[1] Their results agree with our experience of early discharge in a district general hospital in the United Kingdom.[2]

To compare the care received by the two groups it is necessary to know what facilities were afforded to the early discharge group. These details were lacking in the paper. We routinely provide domiciliary physiotherapy (which is important after axillary surgery) and specialist breast counselling to ensure that our patients at home receive the same treatment as those in hospital.

We are unsure why the authors chose four days as the discharge time for their early discharge group. After a pilot study we now routinely discharge all patients suitable for domiciliary care on the second postoperative morning. Ninety per cent of patients thought that this was an appropriate postoperative stay. Analysis of use of analgesia showed that patients required only oral analgesia at this time even after combined mastectomy and axillary surgery. What benefit is gained by the extra 48 hours in hospital?

The technique used by the authors to assess patient satisfaction is unusual. They recorded patients' preference for a longer or shorter stay rather than satisfaction with the treatment they received. The 37% who recommended early discharge without having experienced it may have been reflecting dissatisfaction with their own experience rather than perceived satisfaction with a different discharge policy. We found that 90% of patients thought that our early discharge facility was excellent.

No significant difference in postoperative psychosocial variables was noted by Bonnema et al at one and four months after surgery. At one month after surgery the early discharge group will have spent about 88% of the month at home and the delayed discharge group 72%. Any effect of prolonged hospital stay will have been masked by the time the measurements were recorded. Analysis at day 9 postoperatively—the median time of leaving hospital for the delayed discharge group—would have maximised the chance of any effect of early discharge being picked up.

Early discharge after surgery for breast cancer is feasible, safe, and popular with patients. Inevitably there will be some patients for whom it is not feasible because of lack of social support or comorbidity. For most, however, it enables them to recover within the comfort of their own home and family. We would encourage others to look into ways of establishing this service.

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1 Bonnema J, van Wersch AMEA, van Geel AN, Pruyn JFA, Schmitz PIM, Paul MA, et al. Medical and psychological effects of early discharge after surgery for breast cancer: randomised trial. *BMJ* 1998;316:1267-71. (25 April.)
2 Mander BJ, Qureshi T, Strong L, Wishart GC. The feasibility, safety, acceptability and cost analysis of early discharge following surgery for breast cancer. *Br J Surg* 1998;85:S20.

Follow up period to assess psychological morbidity was too short

EDITOR—Bonnema et al's randomised trial fails to answer the questions that the authors sought to answer. Firstly, the two groups being compared contained a mixed cohort of patients undergoing breast conserving surgery or modified radical mastectomy. The authors have therefore made the fundamental assumption that women undergoing either procedure have the same postoperative complication rate and experience the same degree of psychological morbidity. They should have been stricter in their inclusion criteria and recruited only patients who underwent the same surgical procedure. This would have made their results more meaningful.

The concept of keeping patients in hospital for 9-12 days postoperatively is archaic. In our practice, which probably reflects practice in the rest of the United Kingdom, the mean postoperative hospital stay is in the region of four days, with drains being removed on day 5, irrespective of the volume of fluid drained.

One of the authors' aims was to address the complication rate after early discharge. In their discussion they state that "the number of patients in this study was too small to detect a difference of 5% in rates of wound complication" and that recruitment of 800 patients, which is what would have been required, would not have been "feasible in this type of research." Why?

Any study examining shorter hospital stay must include a detailed analysis of costs, with a health economist participating to calculate in-hospital and community costs. This is particularly important for the United Kingdom, where NHS funding is central.

The follow up period to assess psychological morbidity is too short. At three months patients may be undergoing adjuvant treatment, locoregional radiotherapy, and systemic chemotherapy, which add to their morbidity. It is essential that such studies are designed to assess psychological morbidity at completion of treatment to provide a more meaningful result. In this study a further set of questionnaires to be completed at one year would have been necessary.

These issues are currently being addressed in a randomised trial in the Western Infirmary, funded by the Scottish Office, which will complete recruitment at the end of 1998. Results from this study should clarify all the issues raised above.

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1 Bonnema J, van Wersch AMEA, van Geel AN, Pruyn JFA, Schmitz PIM, Paul MA, et al. Medical and psychosocial effects of early discharge after surgery for breast cancer: randomised trial. *BMJ* 1998;316:1267-71. (25 April.)

Home situation is important for early discharge

EDITOR—Bonnema et al's conclusion that early discharge from hospital after surgery for breast cancer is safe and is well received by patients should be challenged.[1] Their assertion that "our randomised study has proved that shortening the length of time a patient spends in hospital after surgery for breast cancer has no adverse effects" is invalid. Altogether 139 of 173 patients were enrolled in the study. Ten of the 34 excluded women had an "unsatisfactory home situation." Do the authors contend that sending these women home early from hospital would have no adverse effects? Surely the conclusion should be that early discharge from hospital is safe and well received by a selected group of women after surgery for breast cancer.

Another point concerns the psychosocial variables. The patients randomly allocated to the short hospital stay scored higher on scales measuring depression before surgery than did those allocated to a long stay. The authors contend that this finding may be due to the uncertainty about the experimental treatment. But one would expect uncertainty to lead to anxiety and not depression. Furthermore, the authors state that the difference in depression scores disappeared after surgery but then seem to contradict this by adding that there was no decrease in mood disturbance in the short stay group at four months.

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1 Bonnema J, van Wersch AMEA, van Geel AN, Pruyn JFA, Schmitz PIM, Paul MA, et al. Medical and psychosocial effects of early discharge after surgery for breast cancer: randomised trial. *BMJ* 1998;316:1267-71. (25 April.)

Authors' reply

EDITOR—In the Netherlands, discharging patients one or two days after surgery for breast cancer is not yet common and length of stay is determined by the duration of wound drainage. We believe that the reduction in stay to four or five days and discharge with a drain in situ are important advances. Other studies, including the pilot study of Mander et al, show that the length of admission of the long stay group still varies between seven and nine days,[1 2] as in our study. Practices regarding hospital discharge after surgery will probably continue to change rapidly, and we are therefore interested to read of the practice at Purushotham's hospital.

We did not assess patients' satisfaction with treatment by asking them about it directly, as the answers would have been influenced by social desirability. In addition to our published findings we asked patients about several aspects of early discharge, such as being at home with the drain; the answers confirmed that the procedure was well accepted (unpublished data).

We recorded psychosocial variables one and four months after surgery, being interested in learning whether being at home earlier influenced psychosocial rehabilitation, and not in measuring a difference between being at home or in hospital. We do not agree that we should have measured psychological morbidity again one year after surgery; any effect of early discharge is unlikely to be picked up at this time, as so many stressful effects of treatment will have occurred.

Our suggestion that depression before surgery in short stay patients may be due to uncertainty remains speculative. Anxiety and depression are known, however, to be highly correlated. The difference in depression scores between short and long stay patients disappeared after surgery, which means only that mood disturbance was not significantly different between the two groups.

We do not agree with Purushotham that our inclusion criteria biased the results. Production of serous fluid after breast conserving treatment and after modified radical mastectomy does not differ,[3] and there is no strong evidence for differences in psychological outcomes between groups who receive these treatments.[4]

Sheehan is right that early discharge is safe for and well received by most patients with breast cancer, except for a small group in whom it is not feasible because of lack of social support. In our institutes it would have taken more than eight years to acquire 800 patients for our study, which we do not consider realistic in a study on discharge policies.

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Outcome of low back pain in general practice

Evidence based practice can improve outcome

EDITOR—Croft et al describe 12 month outcome in low back pain.[1] Their paper documents the disease course, but it is surprising that they do not describe patient management. The Royal College of General Practitioners has published evidence based guidelines for the management of acute back pain.[2 3] These guidelines recommend active management followed by manipulative treatment at 4-6 weeks if active management fails. An evidence based book for patients with back pain (*The Back Book*) was launched with the guidelines.[4]

We believe that evidence based management of acute back pain will improve outcome. While undertaking a prospective randomised controlled trial of manipulative treatment that aimed to compare the outcome of osteopathy and of physiotherapy we inadvertently showed the effectiveness of the college's guidelines. Two general practices in Kingston-upon-Hull participated in this study, with a total practice population of 15 000. Both practices are in deprived areas.

All patients presenting with acute non-specific back pain (defined as their first episode of back pain or an episode more than three months after a previous episode) were managed according to the college's guidelines; this ensured that patients in each arm of the trial were similar. Patients were advised on active management, minimal rest, early commencement of exercise, and rapid return to normal activity and work. All patients were given copies of *The Back Book*. They were advised to return if their symptoms deteriorated or if there was no improvement after three weeks. Patients returning to their general practitioner were entered into the trial. In the 12 month study period over 250 new patients were seen. Only five returned to their general practitioner with continued back pain. The Roland and Morris score[5] improved with manipulative treatment in all five patients.

This study showed that patients recovered rapidly when general practitioners initiated active management of back pain. *The Back Book* was introduced to these practices at the time, and we believe that it made a major contribution to the success of implementation of the college's guidelines.

The East Riding Research Ethics Committee gave ethical approval for the study. Practices participating received a small amount of funding from the Department of Health.

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1 Croft PA, Macfarlane GJ, Papageorgiou AC, Thomas E, Silman AJ. Outcome of low back pain in general practice: a prospective study. *BMJ* 1998;316:1356-9. (2 May.)
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Study's methods may have altered patients' perceptions of their pain

EDITOR—Croft et al's prospective study of low back pain in general practice reminds us that non-attendance for further care does not equal recovery.[1] They measured morbidity which often remains unrecognised, and their data counter the claim that 90% of patients with low back pain have fully recovered by one month.

This study is not methodologically robust enough to support the statement that, of the non-attenders, "most will still be experiencing low back pain and related disability one year after the [index] consultation." Detailed follow up data on patients' experience outside the surgery were available in only a minority of the original group, 170 of 463, which leaves considerable room for selection bias. Although an attempt was made to quantify this bias, the "validation group" was too small (n = 44) for findings to be conclusive. Two further factors may have exaggerated this bias. Both the original cross sectional survey and the interview process may have altered patients' perceptions of their low back pain (the Hawthorne effect).

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1 Croft PA, Macfarlane GJ, Papageorgiou AC, Thomas E, Silman AJ. Outcome of low back pain in general practice: a prospective study. *BMJ* 1998;316:1356-9. (2 May.)

Use of disease specific questionnaire may have influenced results

EDITOR—Croft et al raise the question of whether early treatment of low back pain reduces the incidence of long term pain and disability after an episode of back pain.[1] Unfortunately, they did not collect the data that might have identified a subgroup of patients who were likely to fare badly. Factors such as employment status, occupation, cigarette smoking, and physical fitness are important prognostic determinants of recovery from an episode of back pain.[2 3] The interviewees' history of back pain seems to have been ignored. Altogether 60% of those with pain and disability at initial interview had the same status at 12 months; does this group represent a homogeneous population or rather those patients with previous chronic back disability?

One important question not addressed in this study is why most (three quarters) of the interviewed cohort did not consult their general practitioner after three months despite still being in pain or disabled. The answer would have important implications when the patients with chronic back pain who consume most healthcare expenditure on this disorder are being targeted.

Caution should also be exercised when interpreting results based on a disease specific self report questionnaire. The choice of outcome measure may itself influence the reported severity of residual symptoms or functional capacity.[4] Addition of a generic health questionnaire (such as the short form 36[5]) would allow comparison with normative population data. It might also provide insights into the subtle psychosocial changes that occur with time after a period of back pain; these insights might not be reflected in a single disability score.

Although we applaud the authors' efforts in confirming the prolonged disability after an episode of back pain, many unanswered questions remain regarding the aetiology in these patients.

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Authors' reply

EDITOR—Deane and Crick are correct in stating that our paper was not about the management of back pain in primary care. As they point out, since our study was carried out guidelines have been published on the primary care management of low back pain. They are wrong to suppose that their findings provide evidence that treatment according to these guidelines helped their patients. Acute new episodes of back pain can get better quickly,[1] but non-return to the general practitioner is no measure of that improvement. This was the starting point of our study, the purpose of which was to identify pain and disability independently of consulting behaviour. Future cohort studies with a similar design to ours will be able to assess whether changes in treatment in general practice result in lower rates of recurrence and chronicity.

Hay suggests that selection bias explained the poor progress in the patients followed up in our study. We discussed this possibility in detail and pointed to the similar consultation rates for low back pain among non-responders and responders. We should also point here to a study, not cited in our paper, carried out in primary care in the United States.[2] Cherkin et al carried out a one year follow up of 90% of patients with low back pain recruited to a trial of early treatment and found that 61% still had symptoms and disability related to back pain—figures similar to our own. We accept that participation in data collection may have influenced outcome, but this is unlikely to have explained our results. It is difficult to envisage a design for a "methodologically

robust" prospective study that does not require data collection from patients.

We agree with Kothari et al that history is an important predictor of outcome, as studies in the literature have reported.[3] The other indicators that they mention, however, have repeatedly been shown to be weaker predictors of outcome in primary care than psychosocial factors.[4] Kothari et al also raise the issue of outcome measures. There is a growing literature on generic versus specific instruments in regional musculoskeletal pain, including a specific back pain instrument derived from the short form 36.[5] The general conclusion is that disease specific measures are more discriminating and more sensitive to change than generic measures alone. The issue, however, is to choose a sensible instrument for the particular question that you wish to address. Our study's objective was to chart the course of low back disability over time, not to compare this disability with other conditions.

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1 Coste J, Delecoeuillerie G, Cohen de Lara A, Le Parc JM, Paolaggi JB. Clinical course and prognostic factors in acute low back pain: an inception cohort study in primary care practice. *BMJ* 1994;308:577-80.
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Successful treatment of toenail mycosis with terbinafine and itraconazole gives long term benefits

EDITOR—In 1995 we published a study comparing treatments with terbinafine and itraconazole for tinea infection of the toenail.[1] Three years after the end of our one year study we carried out a follow up assessment in the patients who were cured. The study was double blind and assessed 26 patients from the terbinafine group and 21 patients from the itraconazole group. All patients had cured target nails, and none had applied antimycotics prophylactically on their toenails. The time to follow up was 3.1 (SD 0.2) years in the terbinafine group and 3.2 (0.2) years in the itraconazole group.

At follow up six (23%) of the patients in the terbinafine group had clinical signs of relapse on the target nail compared with five (24%) in the itraconazole group. Clinical infection of other nails could be detected only in patients treated with itraconazole (seven (33%)). Clinical signs of nail infection in at least one nail were seen in six (23%) patients in the terbinafine group and 12 (57%) in the itraconazole group ($P = 0.033$). As patients were primarily chosen because they had cured target nails, those with mycotic changes on other nails may have entered this follow up study. At baseline the average number of affected nails was 0.6 in the terbinafine group and 0.7 in the itraconazole group; this had increased to 0.8 and 2.0 respectively ($P = 0.009$) after three years.

Our findings agree with the results of two other recent studies. In one study only one of the 18 patients treated with terbinafine had a clinical or mycological recurrence of onychomycosis two years after effective treatment, whereas all three responders from the itraconazole group had a relapse.[2] Another study investigated 47 patients with toenail mycosis who were mycologically cured two years after the end of treatment. The relapse rate was 17% (2/12) in the group treated with 250 mg terbinafine, 8% (1/13) in the group treated with 500 mg terbinafine, and 36% (7/36) in the group treated with 400 mg itraconazole.[3]

Although all three investigations had small numbers of patients, the differences in long term benefit are consistent and impressive. Additional studies are needed to investigate the long term outcome of antifungal treatment of onychomycosis.

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Post-exposure prophylaxis against HIV infection is hard to supply for expatriate staff

EDITOR—Gilks and Wilkinson raise important issues on nosocomial HIV infection.[1] Healthcare workers planning to work overseas must be fully briefed about the risks of HIV infection and what to do. At the time of my own needlestick injury in 1993[2] I was reassured by the quoted risk of seroconversion of 0.3%. I did not know that my coeliac disease, along with other autoimmune conditions, might confer an increased genetic susceptibility to HIV. Seroconversion later occurred.

I had two subsequent exposures to blood from terminally ill patients with AIDS on to small cuts on my hands, from which I had removed gloves in order to feel collapsed veins. At that time the place of zidovudine in prophylaxis had not been clearly established, and the drug was not available. Surgeons may sustain more needlestick injuries than physicians, but physicians, and nurses, are at greater risk of seroconversion,[3] probably because of a larger innoculum from hollow needles and because they care for more terminally ill patients, with high viral loads.

The moral and ethical case for providing post-exposure prophylaxis is strong, but the practical obstacles are great. Gilks and Wilkinson quote a figure of £456 for a four week course of triple therapy. In some sub-Saharan African countries the total annual spending on health is less than £3 a head. The short shelf life of these drugs (five years for zidovudine, two years for lamivudine, 18 months for indinavir) would require frequent replenishment of stocks, which adds to the prohibitive costs. Dedicated supplies, from whatever source, for expatriate staff might cause justified resentment among local workers and is ethically questionable. Could manufacturers be persuaded to donate relatively small quantities of their drugs to individual healthcare facilities in the Third World?

The small risk of nosocomial HIV infection should not deter health professionals from working overseas. Confidence will be boosted by a full and open debate leading to appropriate guidelines for post-exposure prophylaxis.

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