Letters

Bias in meta-analysis detected by a simple, graphical test

Asymmetry detected in funnel plot was probably due to true heterogeneity

EDITOR—Egger et al report that they "found bias in 38% of meta-analyses published in four leading journals."[1] This is misleading, at least insofar as our meta-analysis of inpatient geriatric consultations is concerned.[2]

Firstly, the bias observed in our meta-analysis was not a retrospective detection of bias, as one might infer from Egger et al's statements. We knew that there was evidence of heterogeneity for the pooled effect estimates of geriatric consultation programmes and reported this finding.[2] Secondly, the asymmetry detected in the funnel plot of the meta-analysis of inpatient consultation programmes was probably due not to bias (distortion of true effect) but to true heterogeneity (true difference of effects between trials). We took the presence of heterogeneity as an opportunity to examine whether we could identify the programme elements that might have resulted in the observed effect differences between geriatric consultation programmes. Using a multivariate logistic regression approach, we found that both geriatric assessment programmes in which the consultant controlled the implementation of the recommendations and those that included long term follow up resulted in better outcomes than did programmes in which this was not the case.

Thus, the meta-analytical methods of testing heterogeneity or drawing funnel plots should not be considered absolute criteria for separating good from bad meta-analyses. Meta-analyses reporting effect estimates that may contain bias should continue to be published in leading medical journals, as long as the possibility of heterogeneity is stated and potential underlying reasons for heterogeneity are addressed. This is especially true for meta-analyses of complex interventions. Although they are methodologically difficult to deal with, variations in effect estimates give us the opportunity to disentangle the black box of complex interventions, such as of geriatric assessment, and identify what the necessary ingredients of these programmes are.[3]

A third issue concerns the "mega-trial" to which our meta-analysis was being compared.[4] This trial was different from any of the trials considered in our meta-analysis. Among other things, it was based in a health maintenance organisation system that had incorporated considerable geriatric expertise into its usual care for older people. Another important factor was that it involved four hospital sites, each with different characteristics, populations, and survival rates. If Egger et al had taken the same pains as we did in recovering unpublished data from primary trials, they would have found that the mega-trial they used in questioning our meta-analysis was a multicentre trial with unreported variability in intervention components and outcomes across study sites. Analysts must consider rigorously any methodological issues unique to each trial, particularly when considering complex interventions.

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1 Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. *BMJ* 1997; 315:629-34. (13 September.)
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Experts' views are still needed

EDITOR—Egger et al's regression analysis of funnel plot asymmetry is an interesting exercise in descriptive statistics: most fascinating is their distribution of biasedness in meta-analyses.[1] The funnel plot test that they derive, however, rests on the assumption that it is the smaller trials that are the culprits. What if the larger trials are those that were stopped judiciously at the right moment or underwent some data-analytic "massage"? As noted in the accompanying editorial, the predictive power of the test was validated retrospectively on eight specific instances and became positive only when its test boundaries were changed to a 10% value.[2] More experience with the test seems necessary.

If we accept the test, or any similar test of heterogeneity on meta-analyses, what should we conclude from it? The main message from it is that there might be a problem because the funnel plot is asymmetrical—which we also see on the plot. The real questions to which we would like an answer are: what is the cause of the asymmetry and, more importantly, which trials should we believe? The cause of the asymmetry can be anything, from publication bias, "willingness to please" during data collection, data massage in the analysis, unclear rules for stopping the trial, or downright fraud (as indicated by Egger et al); it can also be a mix of all these things. Alternatively, the source of heterogeneity might be a true difference in underlying populations. Most difficult to live with is the overall conclusion of the test that the literature is biased. If the test is positive, should we dismiss all randomised trials on the subject? This means that we discard one trial by one group of investigators because of the results of another trial by a completely unrelated group. We might try to use quality criteria, but a recent meta-analysis on homoeopathy teaches us that this will not suffice.[3]

In the end there is no escape from a return to "the expert," who tells us which trial to believe, not only on the basis of methodology but also on the basis of insights in pathophysiology, pharmacology, and perhaps type of publication (supple-

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.

We may post some letters submitted to us on the world wide web before we decide on publication in the paper version. We will assume that correspondents consent to this unless they specifically say no.

Letters will be edited and may be shortened.

ments, special interest or "throw away" journals, etc). All that we can ask from the expert is a careful explanation of what arguments he or she used in accepting or dismissing the evidence from certain trials.

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1 Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315:629-34. (13 September.)
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3 Vandenbroucke JP. Homeopathy trials: going nowhere. *Lancet* 1997;350:824.

Graphical test is itself biased

EDITOR—Although the concept is useful, the method proposed by Egger et al to detect bias in meta-analyses is itself biased[1]: it overestimates the occurrence and extent of publication bias. This is easily shown by simulating data for a meta-analysis of a hypothetical intervention that is effective (and therefore has a negative regression coefficient by Egger et al's method) and is free of publication bias (and hence should have an intercept of zero in the regression analysis).

In our simulations, each study was of a treated group and a control group, both of equal size. For each simulated meta-analysis, studies ranging from 100 per group to 1000 per group, in increments of 100, were generated. The observed number of events in each group was generated from a binomial distribution.

Here is one example in which the true event rate is 40% in the control group and 10% in the treatment group. When the true population values (which would not be known in practice) are used to estimate precision, the regression coefficient is −1.7942 (an estimated log odds ratio equivalent to the expected value of 0.1667) and the intercept (0.0380, $P = 0.1$) is close to the expected value of zero, reflecting the lack of publication bias. However, the regression coefficient estimated when the precision is based on the observed values, as would occur using Egger et al's method, is −1.7169. More importantly, the intercept is −0.4492 and significant ($P < 0.0001$), incorrectly suggesting that there has been publication bias. In general, our other simulations suggest that the bias in the estimated intercept is greater the more effective the intervention actually is and the smaller the sample size of the studies.

This problem has several causes. Firstly, the estimates of precision are subject to random error due to sampling variability. This regression-dilution bias causes the regression slope to "tilt" around the mean of the predictor and response variables so that its coefficient is closer to zero; this in turn leads to the intercept becoming negative.[2] Secondly, the estimated standardised log odds ratio is correlated with the estimated precision. Thirdly, the precision estimated by the method that we assume Egger et al used[3] is a biased estimate of the true precision, with the degree of bias increasing as sample size decreases.[4]

Clearly, until the causes of the problems we have outlined are better elucidated and solutions developed, one cannot rely on the method proposed by Egger et al to detect publication bias.

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Test had 10% false positive rate

EDITOR—With examples of results from meta-analyses conflicting with those from subsequent large trials there is increasing need to distinguish the good from the not so good meta-analyses. To this end, Egger et al have developed a test for detecting bias in meta-analyses based on funnel plot asymmetry.[1] This test predicted discordance in meta-analyses. But, as with any significance test, there is also the possibility of falsely identifying bias when none existed. Since significance was defined by $P < 0.1$, the false positive rate of this test would be 10%. For instance, the quoted 13% (5/38) of the systematic reviews in the Cochrane Database showing bias may be attributed to chance alone.

Defining significance to be $P < 0.1$ enabled the test to predict discordant meta-analyses—the conventional $P < 0.05$ produced significant bias in only one of the four discordant meta-analyses—but resulted in a 10% false positive rate. Some may consider this rate of false positive results to be unacceptably high. Be that as it may, these findings showed the continuing need for care in the interpretation of results of significance tests. These comments, however, should not detract from the importance of looking for bias in meta-analyses and the potential benefits this test may bring to screening for such bias.

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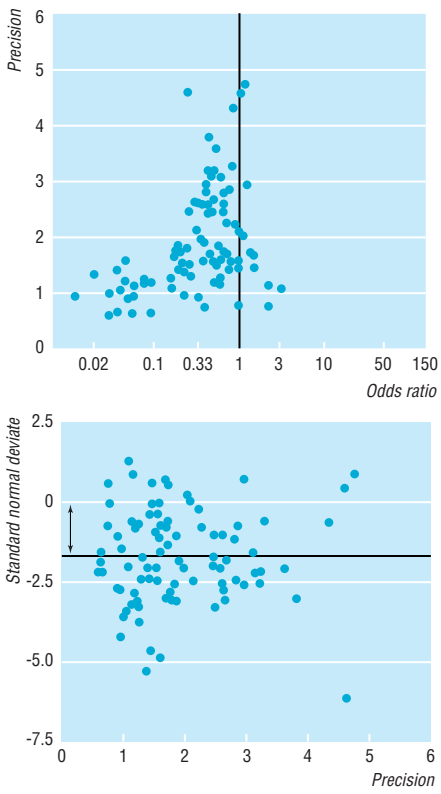
Authors' reply

EDITOR—Bias in meta-analysis is often reflected in asymmetrical funnel plots. As we discussed in our paper, both bias and true heterogeneity in underlying effects can lead to asymmetry. Complex interventions such as geriatric consultation services may be implemented less thoroughly in larger studies, and this would explain the more positive results in smaller trials. Results of meta-analysis will then depend on how many, or how few, small or large studies are included. A thorough attempt should always be made to identify heterogeneity, and the analysis by Stuck et al is a good example of this.[1] We maintain that in these situations the combined estimate is likely to be biased and should not feature prominently in published reports. Stuck et al suggest that we should have considered differences in outcomes across centres in the health maintenance organisation trial. Post hoc analyses of effects by study centres, however, are likely to mislead, as recently shown for the β blocker heart attack trial.[2]

Vandenbroucke could have benefited from a formal analysis of funnel plot asymmetry on at least two occasions. After visual assessment of a funnel plot he suggested that publication bias may explain the association found between passive smoking and lung cancer.[3] However, we found no evidence of asymmetry ($P = 0.80$). Conversely, when he discussed a recent meta-analysis of homoeopathy,[4] significant funnel plot asymmetry ($P < 0.001$) would have lent support to his assertion that bias had produced a body of false positive evidence (fig).[5]



Asymmetrical funnel plot of clinical trials of homoeopathy[4] (upper panel) indicating presence of bias. The linear regression of the standard normal deviate against precision (defined as the inverse of the standard error) shows a significant (P<0.001) deviation of the intercept from zero (arrow). In the absence of bias, trials would scatter about a line running through the origin at standard normal deviate zero

Irwig et al claim that our method will overestimate the occurrence of bias. They simulated hypothetical trials of a treatment that reduced event rates from 40% to 10% (relative risk 0.25) with sample sizes ranging from 200 to 2000. Their example is not typical of the small effects usually examined in meta-analyses. More importantly, when performing 10 000 simulations based on the same assumptions we found that on average 4.99% of tests were significant at the 5% level and 9.63% were significant at the 10% level. Therefore, contrary to Irwig et al's contention, regression dilution bias did not produce false positive results above what was expected by chance, and the P value they quote for the intercept ($P < 0.0001$), presumably based on a large number of simulations, is misleading.

Seagroatt and Stratton are concerned about the specificity of our test. Considering the many possible biases, we think that the low sensitivity is of greater concern. When meta-analyses are based on a few small trials no test will be able to detect or exclude bias reliably. No statistical solution exists in this situation, and the results should be treated with great caution.

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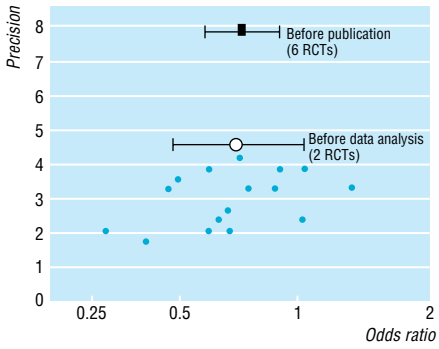
Prospectively identified trials could be used for comparison with meta-analyses

EDITOR—Egger et al's paper about bias in meta-analysis outlines the value of comparing the results of a meta-analysis of small randomised trials with those of a subsequent large definitive trial.[1] Unfortunately, in many areas of clinical practice such as stroke rehabilitation, large trials are difficult to carry out and unlikely to be available.[2]

One possible solution in this circumstance is to compare the results of meta-analysis with those of prospectively identified trials that could not have been subject to publication bias. This was possible with the recent publication of a systematic review by the Stroke Unit Trialists' Collaboration.[3] The funnel plot for several small trials can be compared with the summary result of either six trials which were identified before they were fully published or two trials (in Perth and Nottingham) which were recruited to the systematic review project before data analysis had started. The figure shows the funnel plot



Funnel plot results: odds ratio for combined adverse outcomes of death and needing institutional care versus precision of trial or group of trials
RCT = randomised controlled trial

results for individual trials and the summary results for the two groups of prospectively identified trials.

In this case the results of meta-analysis seem to be compatible with those of the prospectively identified trials. With the increasing move towards prospective registration of trials, this approach may allow some assessment of bias in meta-analyses where no large definitive trial is available.

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Increase in studies of publication bias coincided with increasing use of meta-analysis

EDITOR—Egger et al suggest a method for testing the possible existence of publication bias, based on the assumption that larger trials are more likely to be published, irrespective of their results.[1] Stern and Simes, however, suggest that large sample size is not sufficient, because of the delay in the publication of larger studies with negative results.[2] A recent letter showed that trials published at an early stage were more likely to be positive.[3]

To test the association between the year of publication and treatment effect we identified 38 meta-analyses published in *BMJ* or *JAMA* during 1992-6 which provided summary data from individual studies. For each meta-analysis we tested the association between the year of publication and the treatment effect of the individual studies, using rank correlation analysis. We also tested the correlation between the sample size and the treatment effect. We ignored the sign of the correlation coefficient because it is often difficult to decide which group was the control when competing interventions were compared. Using 0.10 as a level of significance, we found that four meta-analyses showed a significant correlation between the year of publication and the treatment effect while 10 showed a significant correlation between the sample size and the treatment effect. In 25 meta-analyses the correlation coefficient between the sample size and the treatment effect was greater than that between the year of publication and the treatment effect. Therefore, both the delay to publication and the small sample size may be associated with the negative results but small sample size seems to be more important as a risk of publication bias.

Publication bias jeopardises the validity of meta-analysis as well as any other attempts to use published literature. A systematic approach is crucial to identify all published studies, particularly in low circulation or non-English journals and in the grey literature, and to exclude duplicate publications of positive results.[4] We agree with Naylor that "meta-analysis is an important contribution to research and practice but it's not a panacea."[5] In fact, it was meta-analysis and systematic review that highlighted the problem of publication bias. By searching Medline, we found that the number of published studies (empirical, methodological, or editorial) of publication bias was 71 during 1993 to June 1997, 41 during 1987-92, three during 1981-6, and zero during 1966-80. The increase in the number of articles coincides with an increasing use of meta-analysis. It is naive to believe that publication bias did not exist or was less important a decade ago, when medical literature review was dominated by conventional non-systematic methods.

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British renal registry is fully electronic

EDITOR—In his editorial on clinical databases Black did not mention the UK Renal Registry,[1] although it may be the most innovative and ambitious registry in the United Kingdom.

The registry was established by the Renal Association in collaboration with the British Transplant Society and the British Association of Paediatric Nephrology, and it received priming support from the Department of Health. It has been set up to collect quarterly data on patients treated for end

stage renal failure and has been carefully developed with the potential to collect data on patients with pre-end stage failure.

This registry is the only national or international renal registry to use fully electronic data extraction and transmission. Unlike the intensive care registry, which collects a single patient episode, the renal registry will collect sequential quarterly data on patients and can track patients as they move between treatments and centres. Data are collected by software links to existing clinical computer systems in renal units.

Most registries collect paper returns and transfer data to their computer systems. This slows retrieval and analysis—for example, the renal registries in the United States, Australia, and Italy are at least two years behind in analysing and reporting on the collected data. The UK Renal Registry has produced its first preliminary analysis of data this year, showing its ability to analyse and report on patient activity within six months.

The registry aims to assist renal units with both comparative audit and audit against established British standards set jointly by the Royal College of Physicians and the Renal Association. It will help health care commissioners by providing agreed purchaser datasets. The data collected should prove an invaluable resource for planning, audit, and research in renal care.

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Electronic record linkage to create diabetes registers

Impressive results can be obtained without record linkage

EDITOR—Morris et al have shown a gold standard method of compiling a community based diabetes register using record linkage of multiple data sources.[1] They conclude that this method was "more sensitive than general practice registers in ascertaining cases of known diabetes." We question the subliminal message in their paper—that with a diabetes register created from data from hospital clinics and general practices alone, effective diabetes care could not be delivered and outcomes monitored as outlined in the targets of the St Vincent declaration.[2]

Using general practice registers and the hospital clinic register in the Borders region of Scotland, we have identified 2067 live patients in the area from a total population of 106 000 (point prevalence 1.95%). We believe that we have achieved this quality of data collection by means of anonymised feedback of the prevalence of diabetes and other indicators to each practice annually. Between 1995 and 1996 this resulted in an increase in the number of known patients with diabetes from 1825 to 2067; seven of 24 practices in the area have a prevalence of diabetes of over 2%, and in one practice the prevalence is 3.5%. The recording of retinopathy screening improved from 58% in 1995 to 86% in 1996. For those patients attending only general practice diabetic clinics the mean haemoglobin A_{1c} concentration fell from 8.92% in 1995 to 6.92% in 1996. When these data were analysed further 408 sets of paired data were identified, and in these patients the haemoglobin A_{1c} fell from 7.25% in 1995 to 7.00% in 1996 ($P < 0.0001$).

Our experience suggests that active participation in and ownership of a diabetes register between hospital clinics and general practices can achieve equally impressive results. We would encourage district diabetologists and general practitioner colleagues to continue to refine their data collection on these patients and not to be discouraged by the lack of electronic record linkage or sophisticated monitoring facilities.

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Non-insulin dependent diabetes is being missed

EDITOR—Morris et al highlight one of the fundamental difficulties associated with meeting the targets of the St Vincent declaration: identifying all diabetic patients.[1] It is hard to see how these targets can be met if the baseline diabetic population is uncertain.

An audit in Scotland of patients who had had a leg amputated, carried out by the Scottish Physiotherapy Amputee Research Group, found that 30% of amputations were in patients known to be diabetic.[2] This figure was low compared with that in other studies.[3] Therefore the research group, in collaboration with the Scottish Vascular Audit Group, conducted a three month prospective study of the diagnosis of diabetes in 146 patients presenting for lower limb amputation in Scotland.[4] The study found that over half of the "non-diabetic" patients tested (21/36) had fasting blood glucose concentrations above 5.5 mmol/l. The positive predictive value of the fasting plasma glucose test is increased in this high risk group of patients, and an oral glucose tolerance test would probably confirm the diagnosis of diabetes in most cases.

Cases of non-insulin dependent diabetes are clearly being missed even in a group of elderly patients with vascular problems of sufficient severity to warrant amputation. Selective screening of high risk patients is one solution to the problem of reducing the level of undiagnosed diabetes, and the Scottish Vascular Audit Group intends to extend its screening programme to include all vascular patients. Whether earlier diagnosis of non-insulin dependent diabetes is of clinical benefit is still open to debate,[5] and maybe a system such as that described by Morris et al could be used to study the effect of early diagnosis on clinical outcome.

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Registers constructed from primary care databases have advantages

EDITOR—Morris et al report having joined those areas in Tayside that have developed diabetes registers and their use of electronic record linkage.[1] It is now clear from the literature that a comprehensive dataset can be collected by a variety of means, either centrally led or built up from primary care.

The suggestion in Morris et al's paper that general practice diabetes registers are not comprehensive is not supported either by their own regional data or by comparisons with other areas. The sensitivity of general practice registers in their study was 0.91 compared with 0.96 for electronic linkage. This would seem comparable, given the cost and effort entailed in producing a register by means of electronic linkage.

The prevalence of diabetes is increasing both through improved recognition and through increased morbidity. Comparison of point prevalence in Tayside in 1996 with point prevalence from previous studies is therefore invalid. Our own experience over 13 years of maintaining a district register has been of a steady increase in the prevalence of diabetes over time. Morris et al selectively cited the prevalence in North Tyneside in 1991 (1.18%) while omitting the prevalence in 1994 (1.8%) quoted in the same paper.[2] This has since risen to 2.2% in 1997, a figure that compares favourably with the prevalence in Tayside in 1996 (1.94%). Figures from South Glamorgan support a similar rise in the prevalence of diabetes over time based on a district register generated by general practices.[3]

Other factors must also be taken into account. Although Morris et al claim to have shown "how clinical information can be

harnessed electronically and exploited for the benefit of patients," they have failed to state what benefit patients with diabetes in Tayside have derived from their register. Since a variety of methods are equally effective in data collection, perhaps the choice of method should reflect the effect that the method itself has on the commitment of those involved, their feelings of ownership, and its usefulness. Diabetic registers constructed from primary care databases are not constrained by the problem of confidentiality associated with electronic linkage and are therefore free to fulfil the purpose for which they exist. They are therefore used extensively for patient recall, the gathering of clinical data, screening, audit, and research. Any presumed gain in sensitivity from electronic record linkage cannot compete with this overwhelming factor.

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Under half of senior house officers in Anglia in 1997 were United Kingdom graduates

EDITOR—The senior house officer grade in Britain has seen the effects of the new deal on junior doctors' hours and conditions, recent rapid expansion,[1] problems in recruitment, and an imbalance of people and places.[2] To find out the present make up of the grade, the Anglian postgraduate dean's database of 3 July 1997 was analysed.

Of 682 trainees in post, 469 held nationality or residence status in countries in the European Economic Area (EEA).[3] A total of 314 were United Kingdom graduates; 155 others had EEA status and had qualified in other European countries (131) or elsewhere (24)—their medical schools had been mainly in Germany (57) and Spain (35). There were 213 senior house officers without EEA status (referred to here as overseas doctors); among these, the largest number by far (93) had graduated in India. The ratio of United Kingdom graduates to other EEA graduates to overseas doctors in the region ranged from 70:13:17 at the teaching hospital to 18:40:42 at one district general hospital. The average ratio at the nine district hospitals in the deanery was 41:25:34. Differences between specialties were seen, with United Kingdom doctors being in the majority in medicine (54:20:26) and in a minority in obstetrics and gynaecology (31:34:34).

Time since qualification showed large differences between United Kingdom doctors (average 3.9 years), other EEA doctors (5.5 years), and overseas doctors (7.6 years). Many senior house officers had qualified more than 10 years previously (12 (4%) United Kingdom doctors, 13 (8%) other EEA doctors, and 43 (20%) overseas doctors). Thirty doctors in the grade had qualified more than 15 years previously, and some up to 28 years previously.

These figures are from only one deanery, but there must be doubt about whether recruiting more than half of senior house officers from countries other than the United Kingdom is sustainable. Is it appropriate for so many doctors still to be in the senior house officer grade—the general professional training grade—more than 10 years after qualification, and should a major revision of the grade be undertaken?

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UK encourages unrealistic expectations among overseas applicants for training

EDITOR—The current situation regarding overseas graduates and training posts in the United Kingdom is unsatisfactory. I recently went through 147 applications for four senior house officer posts in medicine at the district general hospital where I work. Of these, four were from British nationals (two of whom were graduates of British universities). Most applicants were graduates from India (77), with the others being from African countries (16), Germany (9), Greece (8), the Middle East (6), Myanmar (3), Pakistan (3), and Sri Lanka (3).

Most of the overseas graduates had not worked in the United Kingdom; of the few who had done, most had worked in accident and emergency, care of the elderly, or psychiatry departments. These doctors had, however, stated in their curriculum vitae that they intended to pursue training in general medicine and various medical specialties. Clearly, their choice of jobs had been dictated not by their training needs or intentions but by the service needs of the NHS. I have since found that the wide gulf between supply and demand for training posts is not restricted to medicine.

Far more overseas graduates are seeking higher professional training in the United Kingdom than can be trained satisfactorily. It thus seems inappropriate, if not callous, to continue to permit large numbers of candidates to sit the Professional and Linguistic Assessment Board (PLAB) test; and even more so to start holding examinations in the candidates' home countries, encouraging more to take them. If the United Kingdom is sincere about its commitment to postgraduate medical training it must institute measures to reduce the number of overseas graduates sitting the PLAB test and coming to the United Kingdom via overseas doctors training schemes. Institutions responsible for examination and training should, in their communications with overseas doctors, state clearly the dearth of training posts in certain specialties.

The more knowing among the overseas doctors here, particularly the sizeable numbers with higher qualifications in medicine and surgery who now work as general practitioners, believe that the United Kingdom has always used overseas graduates and the PLAB test to recruit doctors for the less sought after specialties.[1] Inaction about the current unsatisfactory situation will only serve to confirm this view.

Of equal cause for concern must be the paucity of home graduates seeking training posts.[2] An oversupply of overseas graduates and an undersupply of local ones implies that something is fundamentally wrong with manpower planning in the NHS. The sooner the issue is addressed seriously the better for all concerned.

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Adding methionine to every paracetamol tablet

Paracetamol overdose is so rare in India that adding methionine would be wrong

EDITOR—Krenzelok is perhaps right about *N*-acetylcysteine and methionine not being universally available in developing nations.[1] But we do not agree with his "ethical" suggestion that methionine should be added to paracetamol tablets in developing countries and its use encouraged. Paracetamol overdose is rare in India. Adding methionine would be medically inappropriate and the additional financial burden unjustified.

We studied the records of 68 adults and children admitted to three major hospitals with poisoning or drug overdoses over six months in 1996 in Pune. Pune is a city in western India of about 4 million people. We did not come across a single case of paracetamol overdose. We also interviewed 27 physicians and paediatricians working in acute care in five major hospitals. None had seen a case of paracetamol overdose in the previous year. One physician recalled seeing two cases, and another recalled seeing six over 12 years. According to the paediatricians, kerosene poisoning was the commonest poisoning in children. Organophosphorus poisoning due to a bed bug killer was the commonest in adults. These data suggest that paracetamol overdose is rare in Pune.

We do not believe that our city is different from the rest of India. Unfortunately, we do not have a registry of overdoses in Pune and are unable to provide more data.

Krenzelok's suggestion that methionine should be added to paracetamol for the entire developing world is based on his personal "experience in developing nations." We believe that it is an unacceptable generalisation, especially in the present era of evidence based medicine.

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1 Jones AL, Hayes PC, Proudfoot AT, Vale JA, Prescott LF, Krenzelok EP. Should methionine be added to every paracetamol tablet? *BMJ* 1997;315:301-4. (2 August.)

Methionine is important in treatment of chronic pancreatitis

EDITOR—Jones et al present a cogent argument against the routine inclusion of methionine in paracetamol formulations.[1] They highlight documented sequelae of ingestion of high doses of methionine (8-20 g daily), which include folate deficiency, electrolyte disturbances, schizophrenia, and, experimentally, potential carcinogenesis. Emphasising the theoretical link between ingestion of methionine and raised plasma homocysteine concentrations, they further warn of an association with various cardiovascular diseases.

It should be reiterated that association does not confirm cause and effect. Furthermore, the rat dose of methionine, which was followed by angiotoxic effects, corresponds to 14 g daily in an average human—a large dose by any measure. We agree that needless long term ingestion of methionine, paracetamol, or, indeed, any drug is best avoided. We are equally concerned that unwarranted extrapolation of the authors' article might severely hinder the treatment of patients with chronic pancreatitis. Published clinical studies carried out by the Pancreato-Biliary Service, summarised in a recent overview,[2] show that an antioxidant cocktail including selenium, vitamin C, and methionine is extremely effective in this disease, relieving symptoms and the need for surgery. The basis for this approach has also been reviewed.[3] Such treatment, typically with a daily dose of 2 g methionine, has been intensely monitored both clinically and biochemically; no evidence of serious side effects has been seen during follow up of up to 14 years. Empirically, methionine treatment is avoided in any patient with suspicion of neoplastic disease. We would be pleased to provide further data on request.

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1 Jones AL, Hayes PC, Proudfoot AT, Vale JA, Prescott LF, Krenzelok EP. Should methionine be added to every paracetamol tablet? *BMJ* 1997;315:301-4. (2 August.)
2 Leach FN, Braganza JM. Treatment of recurrent pancreatitis with antioxidants. *Hosp Pharmacist* 1997;4:169-71.
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Drugs as important as paracetamol in developing countries should not be tainted

EDITOR—Krenzelok's assertion that methionine should be added to paracetamol preparations in the developing world indicates a fundamental misunderstanding of both the health economics and the epidemiology of the situation.[1] The analgesic and antipyretic properties of paracetamol, which is both cheap and effective, have alleviated incalculable morbidity and mortality in developing countries. Even a slight increase in its cost could deter many potential users of the drug, with serious effects.

Paracetamol poisoning is not common in developing countries. A recent study of poisoning in Sri Lanka found that the most common agents involved were pesticides and acids, with drugs of any kind responsible for under 1% of cases.[2] There are many health problems in developing countries that require urgent international action. I do not consider paracetamol poisoning to be one of them. The suggestion that a drug of the public health importance of paracetamol should be tainted for dubious benefit is irresponsible.

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1 Jones AL, Hayes PC, Proudfoot AT, Vale JA, Prescott LF, Krenzelok EP. Should methionine be added to every paracetamol tablet? *BMJ* 1997;315:301-4. (2 August.)
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Plan is needed for way in which paracetamol and other analgesics are sold

EDITOR—Paracetamol is immensely useful, partly because it allows self determination about treatment for patients.[1] The problem is its cost in terms of life, hospital stay, and expense. What we need to do is consider the best ways of managing self treatment with analgesics. Limiting the numbers of tablets sold should reduce "sudden impulse" overdoses, but there are still many people at special risk, for whom paracetamol-methionine should be promoted—for example, people in prisons, psychiatric wards, or homes where one person has already taken an overdose or there is a visiting teenager of uncertain habit.

We do not have enough information about the long term effects of use of paracetamol-methionine; no data exist on plasma homocysteine concentrations, but 800 mg DL-methionine spread through the day is unlikely to have an appreciable effect,[2] especially in the presence of a demand for cysteine from paracetamol metabolism. This is also likely to increase the conversion of D-methionine to L-cysteine. The long term effects of substituting ibuprofen for paracetamol and aspirin are not yet clear, but more cases of gastrointestinal ulceration, perforation, and haemorrhage might be expected.[3]

Paracetamol manufacturers claim that taking an overdose must always be deliberate, but this evades the question of intention. Taking five tablets may be a deliberate action but clearly does not imply an intention of major self harm. Considerable numbers of overdoses probably come into this category, including some in which the individual, for nutritional or pharmacokinetic reasons, is exceedingly sensitive and may come to death and liver failure "accidentally" through having taken too large a dose.

We need action by manufacturers, poisons centres, regulators, and users to produce a plan for the way in which paracetamol and other analgesics are sold. The plan should also cover the information given with medicines and the way in which alternatives are marketed to try to maintain the benefits of these relatively safe drugs while reducing the adverse effects. A strategy to encourage proper use of paracetamol would include new labelling, perhaps with a statement such as "Some sensitive individuals may suffer severe and unpleasant illness with liver damage from as few as 20 tablets taken at one time." Attention needs to be paid to marketing; packaging; and information for patients, doctors, and coroners. Lastly, manufacturers should undertake research into the use and misuse of all analgesics since these are major causes of morbidity. Perhaps we need a consensus conference on the regulation and use of analgesics.

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1 Jones AL, Hayes PC, Proudfoot AT, Vale JA, Prescott LF, Krenzelok EP. Should methionine be added to every paracetamol tablet? *BMJ* 1997;315:301-4. (2 August.)
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British trial of transmyocardial revascularisation is continuing

EDITOR—Josefson reported the decision by the US Food and Drug Administration's advisory committee not to support approval of the transmyocardial revascularisation heart laser system (PLC Systems).[1 2] We are writing to reinforce the need to support the British randomised controlled trial of this and similar technologies. Unlike the American study, the British trial, funded by the Medical Research Council, does not allow crossover from medical to surgical treatment. The trial is being conducted with meticulous attention to good scientific practice, and an independent data monitoring committee reviews the results of interim analyses. In the most recent review the committee considered evidence for stopping the trial, including reports from the American studies, and recommended completion as planned with follow up of 190 patients to one year.

Our experience in conducting this trial, in the face of some scepticism and opposition from mostly non-British clinicians providing a transmyocardial revascu-

larisation service, supports the following observations. There is an increasing problem in the United States when randomised controlled trials are timed to follow on from lengthy uncontrolled non-randomised studies, often in the same centres. The reluctance of American doctors and patients to take part in a randomised controlled trial of transmyocardial revascularisation led to the crossover design and short term follow up, both features that were criticised by the Food and Drug Administration.[1 2]

To avoid such problems in Britain the health technology assessment process needs to be sufficiently responsive to ensure that randomised controlled trials of new technologies are conducted in a timely manner. There may also be a case for more cooperation between centres, a proposition arising from our second observation, which concerns recruitment to the British trial of transmyocardial revascularisation. We should have reported definitive results last autumn, but, because recruitment was slower than expected, a one year extension was agreed with the Medical Research Council, at additional cost. Although efforts have been made to publicise the trial widely, the uneven pattern of referral, with higher numbers from local regions, does not reflect the geographical distribution of coronary artery disease. Maybe an additional trial centre located in the north of the country would have resulted in more rapid recruitment. The NHS research and development health technology assessment programme, the Medical Research Council, and other major funders could play a part in encouraging grant applicants to work together to complete such trials as quickly and efficiently as possible. In the meantime, the jury in the trial of transmyocardial revascularisation is still out.

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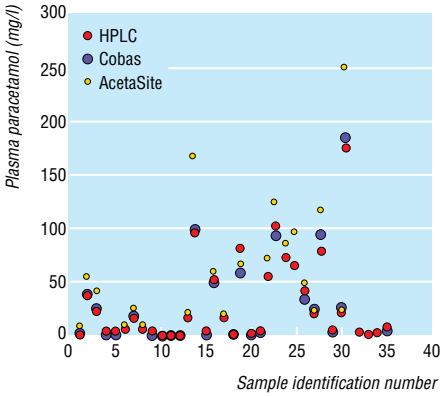
Comparison of assays for measuring plasma paracetamol

Possibility of calibration error needs evaluation

Editor—Egleston et al report a significant difference in plasma paracetamol concentrations assayed with the AcetaSite bench assay and a standard laboratory assay.[1] Rapid and accurate determinations of plasma paracetamol concentrations are crucial in the expeditious and appropriate administration of antidotal treatment, which prevents severe liver damage if given sufficiently early in the course of poisoning.[2]

We compared two methods for estimating plasma paracetamol (Cobas paracetamol assay kit (Cambridge Life Sciences, Ely) and AcetaSite blood acetaminophen (paracetamol) test (Cambridge Life Sciences)) with a standard high performance liquid chromatographic method.[3] We used the methods on 35 samples from 23 patients presenting between 5 and 50 hours after a paracetamol overdose who claimed to have taken a mean of 22.0 g (range 5-50 (SD 13.1) g) of paracetamol alone. Samples were taken and stored at −40°C, and all assays were performed in our laboratory.



Plasma paracetamol concentrations assayed by AcetaSite, Cobas, and standard high performance liquid chromatographic (HPLC) methods in 35 samples from 23 patients who admitted having taken paracetamol overdose

The figure shows the results obtained with the three methods. Compared with high performance liquid chromatography, the AcetaSite assay overestimated plasma paracetamol concentration in a considerable number of cases; the difference was significant ($P=0.002$, paired t test). There was no significant difference between the results obtained with the Cobas assay and high performance liquid chromatography ($P=0.81$, paired t test. The Pearson correlation coefficients of the AcetaSite and Cobas assays with standard high performance liquid chromatography were 0.97 and 0.97 respectively.

We believe that the most likely source of the discrepancy between the AcetaSite assay and the other methods in our study was a calibration error within the AcetaSite method. All assays were carried out in our laboratory by an experienced clinical chemist (by contrast, some of the assays in Egleston et al's study were done by emergency doctors). We therefore believe that operator error is an unlikely explanation for the results of our study or those of the study reported by Egleston et al. The possibility of a calibration error in the AcetaSite system requires further evaluation; external calibration is not possible with this assay.

Egleston et al do not make clear what results they obtained in the 100 patients who had apparently not taken paracetamol but from whom blood was taken for assay. These results should have been negative by both methods; this is an important point for exclusion of false positive results. In patients who admit to having taken paracetamol, interference in the assay by other drugs taken concurrently is a potential source of error.

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1 Egleston CV, Browning C, Hamdi I, Campbell-Hewson G, Robinson SM. Comparison of two assays for measuring plasma concentrations of paracetamol. *BMJ* 1997; 315:991-2. (18 October.)
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Training and education in use of assay are important

Editor—Egleston et al compared the accuracy of a standard laboratory paracetamol assay with that of a rapid bedside test (AcetaSite).[1] Egelston et al used a statistical method developed by Bland and Altman[2] to assess agreement between the two methods of clinical measurements. The limits of agreement were calculated to be 0.16 and 5.04. This translates into poor agreement between the two assays, with 95% of values obtained with AcetaSite being between 0.16 and 5.04 times the values obtained with the laboratory assay. The authors concluded that the AcetaSite test should not replace the established laboratory method.

We have also evaluated the AcetaSite test, recruiting 58 patients to our study. Four sets of results were excluded from the analysis because the Stat-Site meter recorded a maximum of >250 mg/l (by contrast, the laboratory gave a specific reading). At the lower end of the range (<20 mg/l) 15 sets were excluded for similar reasons. On the remaining 39 samples, using Bland and Altman's test, we found our limits of agreement to be 0.79 and 1.1. Our results therefore suggest good agreement between the two assays. The performance ($r=0.974$) matches closely that shown in the datasheet for AcetaSite compared with standard reagents ($r=0.97$ and $r=0.983$).

When evaluating a new technology, such a contrast between studies merits careful analysis. Egleston et al make some suggestions for the reason for the poor agreement between the two assays in their study. Although there may be other reasons, the most likely is training and education. Our study was carried out by the six middle grade doctors in the accident and emergency department and a small number of senior house officers after a one to one training programme. An algorithm card was used from the outset (modified after piloting). Particular attention should be paid to this much overlooked aspect of study design if accurate results are to be attained and valid conclusions drawn.

We believe that the AcetaSite test does provide a rapid and accurate bedside assay of paracetamol concentrations. Further analysis in our study, however, indicates that

in economic terms and in accelerating care pathways to referral it should not replace the standard, cheaper, laboratory method in most cases.

The AcetaSite kit was supplied by Cambridge Life Sciences but is not available in Britain at present.

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Prescription Medicines Code of Practice Authority investigates criticisms of advertisements

EDITOR—Several letters recently have criticised the advertising of prescription medicines.[1] Two points should be borne in mind. Firstly, a marketing authorisation for a medicine cannot be obtained unless the quality, safety, and efficacy of the medicine have been shown to the satisfaction of the United Kingdom Medicines Control Agency or the European Medicines Evaluation Agency. Secondly, all claims made for a product have to be consistent with the summary of product characteristics, which is approved as part of the authorisation procedure.

Both European and British law require the provision of references in advertisements only when published work is referred to, and that is also the case with the Association of the British Pharmaceutical Industry's code of practice for the pharmaceutical industry, which the Code of Practice Authority administers. The code nevertheless has stringent requirements regarding evidence to support promotional material. It requires that any information, claim, or comparison must be capable of substantiation and that substantiation must be provided without delay at the request of a health professional. If a pharmaceutical company is unable or unwilling to provide substantiation for a claim then the company should not make it in the first place. Any health professional who has not had satisfaction in this regard should complain to us.

The code also requires that promotional material must be certified by two people on behalf of the company. One of the signatories must be a registered medical practitioner and the other an appropriately qualified person such as a pharmacist. The signatories certify that the material complies with the code.

It is our longstanding practice to take up as complaints under the code any specific criticisms of the promotion of medicines that appear in the media. Accordingly we have taken up the criticism of an advertisement for nifedipine (Adalat) with Bayer.[1] We considered the advertisement for donepezil (Aricept) issued by Eisai and Pfizer in response to an earlier letter in the *BMJ* on 24 May. That advertisement has been found not to breach the code but we are nevertheless looking at the matter again.

Anybody who doubts the rigour with which we deal with such matters is invited to ask for a copy of our quarterly "Code of Practice Review," in which every case is reported in detail. Perusal of the review will dispel any idea that the code is a soft touch.

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1 Evidence based advertising? [Letters.] *BMJ* 1997;315: 1621-3. (13 December.)
2 Advertisements for donepezil (Aricept) in the BMJ [letters]. *BMJ* 1997;314:1555-6. (24 May.)

Psychotropic drug treatment

Some antidepressants are more effective than others

EDITOR—I challenge Pathare and Paton's statement that "All antidepressants are equally effective in treating depression."[1] There is growing evidence that antidepressants that block the reuptake of both serotonin and noradrenaline have greater clinical efficacy than those that act on just one neurotransmitter.

Patients with mild depression often show a high rate of response to placebo, and differences between drugs can be hard to detect. Differences will (usually) be shown only when patients with moderate to severe depression are studied. Another way to look for differences between drugs, or classes of drugs, is to combine trials to gain statistical power in a meta-analysis.

It is important to look at the different classes of drug that block the reuptake of serotonin and noradrenaline. Such drugs comprise the older tricyclic antidepressants, which can be subdivided into those that have their main action on noradrenaline (for example, desipramine) and those that have their action on both serotonin and noradrenaline (for example, clomipramine); the selective serotonin reuptake inhibitors (for example, paroxetine and fluoxetine), which block the reuptake of serotonin only; and the newer class of serotonin and noradrenaline reuptake inhibitors, which block the reuptake of both serotonin and noradrenaline.

Early suggestions that drugs with dual action had advantages over those that increased just one neurotransmitter came from the Danish University Antidepressant Group,[2] which looked at the efficacy of clomipramine compared with that of paroxetine. The group found that from the second week the tricyclic antidepressant had greater efficacy than the selective serotonin reuptake inhibitor.

More recently, a meta-analysis was carried out of 25 studies in which tricyclic antidepressants and selective serotonin reuptake inhibitors were compared in 1377 patients in total; it showed that overall efficacy was significantly greater ($P < 0.02$) for the tricyclic antidepressants (data presented at satellite symposium at 6th world congress of biological psychiatry, 22-27 June 1997). A second meta-analysis, which included venlafaxine (a serotonin and noradrenaline reuptake inhibitor) as well as tricyclic antidepressants and selective serotonin reuptake inhibitors, has confirmed that the efficacy of venlafaxine is superior to that of the selective serotonin reuptake inhibitors.[3] Individual double blind trials with venlafaxine (for example, that by Dierick et al[4]) have also shown that it has greater efficacy than fluoxetine.

Many of the doctors who read the *BMJ* do not have specialist knowledge of depression and rely on review articles to keep up to date. It is important that this debate is at least mentioned in any review on the effectiveness of antidepressants.

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1 Pathare S, Paton C. ABC of mental health: psychotropic drug treatment. *BMJ* 1997;315:661-4. (13 September.)
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Repeated prescription charges for weekly treatment may be deterrent to patients

EDITOR—Pathare and Paton clearly reviewed the use of antidepressant drugs in the treatment of depression and provided helpful guidelines for preventing suicide.[1] But general practitioners in England and Wales often find practical difficulties in implementing one of their suggestions: that of giving small supplies to patients at risk, possibly a week's prescription at a time. There is no problem in giving weekly prescriptions to patients who are exempt from paying prescription charges. For patients who are not exempt but are not on a high income, however, the £5.65 prescription charge for seven days' treatment can be a deterrent, particularly at a time when they may be experiencing side effects and deriving little benefit from the drug.

One way around this problem would be to prescribe a month's supply of the drug but to ask the pharmacist to dispense it weekly. Under the current system in England and Wales this is problematic for pharmacists to implement because they are only paid one dispensing fee per prescription and would be reluctant to take on the extra work without recompense. A second option might be to entrust the drug to another person, but this is often not possible or may cause conflict between the parties. The Scottish instalment dispensing scheme seems ideal; in this, the patient pays one prescription charge while the pharmacist receives a payment for each time he or she dispenses. With the recent

high profile Defeat Depression campaign and its emphasis on better recognition and treatment of depression by general practitioners,[2] introduction of this scheme in England and Wales should be given serious consideration.

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1 Pathare SR, Paton C. ABC of mental health: psychotropic drug treatment. *BMJ* 1997;315:661-4. (13 September.)
2 Baldwin DS, Priest RG. The defeat depression campaign. *Primary Care Psychiatry* 1995;1:71-6.

Authors' reply

EDITOR—Lennox-Smith uses our review article, which was aimed at general practitioners and non-specialists in psychiatry, to present a biased view of the literature. The clear aim of our article was to present the basic knowledge that non-psychiatric specialists require to prescribe effectively for the most common psychiatric illnesses. However, we wish to reply to the points he raises.

While it is true that some studies show tricyclic antidepressants to be more effective than selective serotonin reuptake inhibitors in the treatment of depression, others show selective serotonin reuptake inhibitors to be more effective. These differences are probably due to a combination of study design, characteristics of the patients, and chance. A meta-analysis by Song et al concluded that there was no difference in overall efficacy between tricyclics and selective serotonin reuptake inhibitors.[1]

The Danish study cited by Lennox-Smith, which suggested that clomipramine was more effective than paroxetine, was designed to favour the tricyclic antidepressant.[2] Patients who dropped out early because of side effects (mostly patients treated with the tricyclic antidepressant) were not included in the final analysis. The rating scale used to measured change has an excess of sleep items (three), which are likely to show an early response to a sedating tricyclic. Furthermore, patients who had not responded at four weeks were classified as non-responders; four weeks is too early to assess response. It is therefore wrong to extrapolate from this study and suggest that tricyclic antidepressants in general are more effective than selective serotonin reuptake inhibitors. A review of the literature in respect of severe depression has shown this not to be the case (S Montgomery, 6th world congress of biological psychiatry, 22-27 June 1997). Furthermore, the study by Einarson et al was not a meta-analysis as stated by Lennox-Smith but a cost effectiveness analysis which used an unpublished meta-analysis and expert panel to construct a decision tree.[3]

Though there may be a suggestion in the literature that dual action antidepressants offer small advantages in some clinical situations, it is no more than a suggestion. This potential advantage is greatly outweighed by the fact that as many as 88% of prescriptions for tricyclic antidepressants written in primary care are for subtherapeutic doses.[4]

The greatest contribution to the treatment of depression would be made by increasing detection and prescribing a therapeutic dose of any antidepressant for an adequate period. These are the goals that all non-specialists should aim for.

Harris and Smith highlight an important practical issue; we agree with their suggestions and hope that they are widely implemented.

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Media are too eager to link silicone to disease

See pp 403, 417

EDITOR—Legal aid has been granted to a woman who alleges that her child's stomach cramps, skin problems, and food allergies are due to a silicone breast implant. The controversy surrounding silicone breast implants continues despite epidemiological studies finding no connection with neurological and connective tissue diseases.

Use of silicone is common. Some teats of infant bottles are made of silicone (box), and all are lubricated with silicone oil; baby milk formulas contain silicone. Silicone in breast milk is independent of the presence of silicone implants. Ten million bottles of dimethicone (for colic and griping pain) are sold each year.

"Second generation silicone disease" is promoted by a small group of American scientists. Levine et al suggested that a scleroderma-like oesophageal disease resulted from breast feeding by women with implants.[1] Their scientific methodology led to many rebuttals.[2]

Shanklin and Smalley developed a T lymphocyte stimulation test for silicone sensitivity,[3] believing that reaction to crystalline silica was equivalent to reaction to silicone. Crystalline silica, a known immunostimulant, is not a component of breast implants. The implant envelope contains amorphous silica; conversion to crystalline silica requires high temperatures and catalysts. They believe, controversially, that silica arises in vivo from degradation of silicone. There is no valid assay for silicone itself

The legitimacy of the test has been refuted in the United States. Shanklin et al have reported that 2000 lymphocyte tests had been performed at $350 per test,[4] and their work has been given wide exposure in the media. The media seem eager to seize on any negative information about silicone implants or proponents of it, often allowing little time for an objective scientific response.

In a recent letter to the lord chancellor, four professors (including the chairpersons of the 1992 United States Food and Drug Administration panel and 1992 Canadian government investigation) expressed their dismay that the British legal process may fall prey to unreliable scientific evidence. They reminded him that the United Kingdom Medical Devices Agency's review panel on breast implants has twice concluded that there is no evidence of a connection between breast implants and systemic disease. They warn of the "price paid in North America as a direct result of such … litigation."

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Non-medical and medical sources of silicone

Non-medical	Medical	
Infant bottle teats	Drugs	Intraocular lens implants
Baby milk formulas	Hypodermic needles	Testicular prostheses
Deodorants	Intravenous tubing	Penile implants
Hair sprays	Syringes	Digital joint arthroplasty prostheses
Cosmetics	Cerebrospinal fluid shunt tubing	Breast implants
Food additives	Slow release hormone implants	
Food processing	Cardiac valves	
Drinking water		
Polishes		