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Quality of drinking water
Household interventions to improve microbiological quality of water reduce diarrhoea

People who drink water that is contaminated with human faeces are at risk of diarrhoea, a condition that results in 1.8 million deaths in children each year.¹ In this week’s *BMJ*, a systematic review and meta-analysis by Clasen and colleagues² finds that household interventions to improve the microbiological quality of drinking water reduce the occurrence of diarrhoea. Their results show that the quality of water has an impact on health. They also highlight the value to public health of achieving the targets outlined in the seventh millennium development goal—to reduce by half the proportion of people without sustainable access to safe drinking water.

Two articles published in 1985 and 1991 are the most cited reviews on the effectiveness of interventions to prevent diarrhoea.³ ⁴ These considered only improvements to the water source, however. They did not assess the microbiological quality of the water at the point of use, and they did not include any of the recent studies that evaluated microbiologically effective treatment of drinking water at the point of use. They concluded that improvements in the quality of drinking water at source reduced diarrhoea by 15–17%, in contrast to larger reductions as a result of increased water supply, promotion of hand washing, and improved sanitation.

During the past two years, two reviews with meta-analyses have included many new studies on water treatment at point of use and re-evaluated the effect of improved water quality on diarrhoea.⁵ ⁶ The first concluded that in high quality studies, water treatment at point of use reduced diarrhoea by 39% compared with 11% (not statistically significant) for interventions that improved the quality of water at source.⁵ The second reviewed interventions that used water treatment with sodium or calcium hypochlorite, it analysed only the youngest age group reported in each study, and it concluded that chlorine treatment at point of use reduced diarrhoea by 29%.⁶

The meta-analysis by Clasen and colleagues of 42 controlled trials and 56,000 participants is the most rigorous review to date.² Studies that met their criteria included those assessing all water disinfection techniques at point of use and improvements to the water source, and published and unpublished studies. Clasen and colleagues conclude that interventions to improve the microbiological quality of drinking water are generally effective in reducing diarrhoea in adults and children under 5 years, and that household interventions are more effective than water source interventions.

However, they caution that heterogeneity between trials means that effectiveness may vary according to the setting.

These promising results suggest that the measurement used to assess progress towards the millennium development goal should be changed to reflect the importance of microbiological water quality. Currently, the global standard for safe water is an assessment of the proportion of the population that has access to an “improved water supply.”⁷ ⁸ However, an improved water supply is an engineering definition. For example, piped water or a protected spring is an improved water supply compared with water from a tanker truck or an unprotected spring.⁹ Importantly, improved water supplies are often contaminated with human faecal organisms—that is, they are not microbiologically safe water supplies¹⁰ ¹¹ ¹² Thus, the reduction in diarrhoea shown by Clasen and colleagues resulting from microbiological treatment of water at point of use does not necessarily apply to improved water supplies.

For these findings to translate to improved health, water quality needs to be measured by the microbiological quality of the water that people actually drink, rather than the types of water sources. In 2006 the United Nations projected, using the outdated metric, that the world is on track to meet the millennium development target for safe water.¹³ The risk is that the United Nations will claim victory over unsafe water when, in fact, water supplies that are technically defined as “improved” will provide little health benefit to the population in need.

Populations with the lowest mortality rates from diarrhoeal disease have microbiologically safe water piped directly to point of use. Until such services can be provided in low income countries, point of use water treatment is a potential interim solution. However, experience of scaling up the implementation of treating household water to large populations is limited. Research is needed to evaluate whether the health gains demonstrated in the carefully controlled efficacy studies reviewed by Clasen and colleagues can be achieved in large populations at high risk for mortality from diarrhoeal disease when point of use water treatment is not provided free of cost, and when household visits to encourage use are limited.

² Clasen T, Schmidt-W P, Rabie T, Roberts I, Cairncross S. Interventions to improve water quality for preventing diarrhoea: systematic review and meta-analysis. BMJ 2007 doi: 10.1136/bmj.39118.489931.BE.
In this week’s BMJ, Ferreira-González and colleagues report that clinical trials may mislead if they use composite end points.1 For example, a statement that an intervention reduces a composite end point of cardiovascular mortality, myocardial infarction, and revascularisation procedures is misleading if revascularisation procedures were more common outcomes than death or infarction, or if the intervention had a large apparent treatment effect on revascularisation but not on death or infarction.1 It is not enough for people who use the research—doctors and patients—to be aware of such potential to mislead: pharmaceutical regulators should also examine their role.

Pharmaceutical regulation has provided benefit to society by harnessing the innovation of industry towards improving health. Pharmaceutical regulation helps to ensure that drugs are safe and achieve clinically relevant benefits for patients. Regulation also governs the manner in which drugs may be marketed to prescribers and to patients. It allows only claims that can be supported by trial evidence to be used as a basis for promotional activities. Ensuring the evidence base of information to prescribers is a laudable aim, but as Alfred North Whitehead said, “We think in generalities, but we live in detail.” The implementation of regulation has led to innovation in trial design, specifically in the choice of primary outcome measures, such as composite outcome or surrogate measures, which can lead to major challenges for people trying to interpret and use results of research, who may not be adequately served by the process.

A key aspect of drug regulation is embodied in the principles of α spending—that is, the allocation of type 1 error (the error of rejecting a null hypothesis when it is actually true) in a manner designed to avoid spurious positive conclusions.2 Because the likelihood of observing a statistically significant result by chance alone increases with the number of tests, it is important to restrict the number of tests undertaken and limit the type 1 error to preserve the overall error rate for the trial. To do this, the type 1 error is allocated to different outcomes, most simply through the specification of a primary and potential secondary outcome. Alternatively, the available type 1 error may be split between different primary outcomes, or indeed outcomes may be placed in a predefined hierarchal list, with type 1 error “spent” down the list until the conventional one sided 2.5% α level is reached (equivalent to a two sided 5% level—but no drug is ever licensed for being significantly worse than the comparator).

In terms of whether a trial has a positive or negative result, the choice of primary outcome may be of central importance. For example, the recent ADOPT trial3 compared time to failure of monotherapy (defined as a confirmed concentration of fasting plasma glucose of >180 mg/dl) in 4360 newly diagnosed patients with type 2 diabetes treated with rosiglitazone, metformin, or glyburide who were followed for a median of four years.

An additional challenge in the market authorisation for pharmaceutical products is the use of composite outcomes, which potentially provide an opportunity for sponsors to “game” their trials.4 Composite outcomes bring together two or more events that are considered as a single outcome.5,6 They have statistical advantages...
In this week’s BMJ, Adhikari and colleagues report a systematic review of the impact of inhaled nitric oxide on physiological outcomes, morbidity, and mortality in people with acute respiratory distress syndrome. They found that nitric oxide resulted in a limited improvement in oxygenation but did not reduce mortality (risk ratio 1.10; 95% confidence interval 0.94 to 1.30), the duration of ventilation, or the number of days free of ventilation.

Acute respiratory distress syndrome is an important public health problem. It is a catastrophic form of acute respiratory failure that arises after pulmonary (for example, pneumonia or aspiration of gastric contents) or extrapulmonary (for example, sepsis or polytrauma) insults. Not only does it have an incidence as high as 64 cases per 100 000 people per year, but it has a high mortality (30-60% in unselected populations) and risk of subsequent morbidity in survivors.

The many cellular and molecular actions of nitric oxide (the 1992 “molecule of the year”), also known as endothelial derived relaxing factor, are incompletely understood. However, intensive care physicians were quick to use inhaled nitric oxide to treat acute respiratory distress syndrome because of its immediately observable beneficial effects on oxygenation and pulmonary vascular pressures in these patients, and because of the lack of other effective treatments.

Inhaled nitric oxide acts as a selective vasodilator. It is inactivated by haemoglobin and so acts only on the pulmonary circulation, lowering pulmonary vascular resistance and improving cardiac output. As it is only delivered to lung units that are ventilated, it provides a valid and reliable measure of some clinically relevant and important treatment benefit in the patient population. As required in the regulators’ own guidance on the design and analysis of clinical trials. Secondly, while it is our opinion that composite outcome measures do have a useful role in the evaluation of health technologies, the difficult problem of the appropriate interpretation of composite outcome measures in regulatory policy should be dealt with.

This might be achieved by using a corollary (such as a health warning), which makes it clear that on their own the individual components of a composite have not been shown to be affected by the experimental treatment.

7 The DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 2006;368:1096-105.
preferentially increases blood flow to these units, improving ventilation-perfusion matching and oxygenation. Theoretically, these actions could improve oxygenation and oxygen delivery, allow for less injurious mechanical ventilation, and ultimately reduce the prevalence or severity of the multiorgan dysfunction that is the cause of death in most patients with acute respiratory distress syndrome. Unfortunately, randomised controlled trials of inhaled nitric oxide have not borne out this theory.

Adhikari and colleagues’ methodologically rigorous and clinically sound systematic review and meta-analysis of 12 randomised controlled trials provides evidence that nitric oxide can provide modest short term improvements in oxygenation. However, all but one of the nine relative risk point estimates for mortality favoured patients in control groups. This lack of concordance between physiological improvements and outcome for patients is a recurring theme in critical care,6,7 and it probably plays a part in our collective reluctance to abandon these interventions.

As Adhikari and colleagues’ study is a meta-analysis that includes several small underpowered randomised controlled trials, the results are best treated as hypothesis generating.8 The review suggests that nitric oxide has no significant effect on mortality. Alternatively, and in keeping with the post hoc finding that people receiving nitric oxide had an increased risk of developing renal dysfunction (1.50, 1.11 to 2.02), we could speculate that patients with acute respiratory distress syndrome receiving nitric oxide have slightly higher mortality. What this meta-analysis does not provide is any suggestion of benefit with inhaled nitric oxide.

Given these findings, routine use of inhaled nitric oxide in such patients cannot be recommended. Indeed given the costs and potential for harm, its routine use in acute respiratory distress syndrome should be actively discouraged. I suggest that it should be used in this syndrome only for rare cases of refractory hypoxaemia, after considering modalities such as high frequency oscillation or prone positioning.9

In the light of this new evidence should we persist with trying to show that nitric oxide improves outcomes in acute respiratory distress syndrome? Not finding a benefit is not proof of no benefit. However, the trend towards harm seen across these many trials makes it unlikely that we will eventually prove a benefit through persistence alone. This does not mean that nitric oxide is without merit; it is still useful in other diseases such as persistent pulmonary hypertension of the newborn.10

Even in acute respiratory distress syndrome, nitric oxide may yet have a role outside salvage therapy for severe hypoxaemia, but this work by Adhikari and colleagues indicates that we need to change radically the designs of randomised controlled trials of nitric oxide in these patients. For example, future trials could explore alternative dosing schedules for nitric oxide (such as titrated decremental dosing11), the application of nitric oxide to specific subgroups of patients, or combining nitric oxide with other treatments (such as mechanical ventilation strategies to reduce pressure, or early aggressive fluid resuscitation12).

Future trials should be grounded in sound observations from physiological animal and early phase human studies, along with observations from completed randomised trials. Making the successful leap from a solid mechanistic theory to a large randomised controlled trial is challenging,13 and trying to do so without this grounding seems destined for failure, regardless of persistence.

Cytochrome P450 genotyping and antidepressants

An imperfect measure of a modest predictor of response to antidepressants may not be ready for clinical application

Patients’ responses to treatment with antidepressants vary greatly. The largest study on the effectiveness of antidepressants to date suggested that roughly one third of patients will recover fully given a long enough trial, one third will improve substantially, and one third will not respond.¹ A subset in all three groups will have adverse effects such as sexual dysfunction, insomnia, nausea, and weight gain. Side effects are rarely dangerous, but they cause many patients to discontinue treatment, often after a single prescription.²

Similar concerns exist for many drugs, not just antidepressants. What makes antidepressants especially frustrating for clinicians and patients is the lack of factors to predict how individual patients will respond to a given treatment. We know that one third of patients will have minimal improvement, but we have few data to guide selection of alternative treatments. Indeed, while the psychiatric literature abounds with reports of clinical predictors, the findings are rarely replicated.³ One of the only replicated predictors, that atypical depression responds better to monoamine oxidase inhibitors than to tricyclics, does not seem to apply to newer antidepressants. Worse, many of the widely touted and taught predictors turn out to be invalid on closer inspection. For example, conventional wisdom holds that antidepressants with “activating” properties, such as bupropion, are less likely to be effective in patients with anxiety or insomnia. In a clinical trial, however, this was not the case.⁴ ⁵

Any predictive test, especially one with the shiny lustre of genetics and the promise of rapid and highly accurate results, therefore causes excitement among psychiatric clinicians. The marketing of a test that can define a person’s genetic profile in terms of two important P450 enzymes has generated just this sort of excitement. One journal devoted its cover to the headline, “New tool: genotyping makes prescribing safer, more effective!” However, a recent report by the US Agency for Healthcare Research and Quality⁶ found little evidence to support a role for cytochrome P450 genotyping when prescribing antidepressants.

The argument for P450 genotyping is straightforward. Selective serotonin reuptake inhibitors and other newer antidepressants are metabolised by enzymes in the cytochrome P450 system, so variation in the encoding genes would be expected to influence concentrations of these inhibitors in the blood. In theory, people who metabolise these inhibitors poorly might develop supratherapeutic concentrations and be more likely to have adverse effects; conversely, those who metabolise them rapidly might develop subtherapeutic concentrations and be less likely to respond well to treatment.

As the agency report highlights, both aspects of this argument are suspect. The 11 studies that examined the relation between P450 genotype and antidepressant concentrations found only the suggestion of an association. A key point here is that P450 genotype is just one of many factors that influence drug concentrations. Other factors include variables that can change over time, such as diet, smoking, and cotreatment with other P450 substrates or inhibitors.⁷ Furthermore, newer generations of antidepressants do not exhibit clear dose-response relations, and concentrations of antidepressants in the blood are rarely informative, except at the extremes. Measuring drug concentrations may be more useful in populations at higher risk; one study of depressed elderly patients did suggest that therapeutic drug monitoring led to changes in treatment about half the time.⁸

So P450 genotype is not an accurate predictor of drug concentration in the blood, which in turn is not a strong predictor of outcome. Still, even modestly accurate predictors might have benefit. Unfortunately, no adequately powered studies have investigated this question directly. The suggestion that people who metabolise antidepressants rapidly may have a worse response and that those who metabolise them slowly may have more side effects is encouraging but not convincing. Notably, the largest study to look at this question failed to find an effect on adverse effects.⁹

Therefore, before P450 genotyping can be recommended when prescribing antidepressants, we need to establish that this test can help improve outcomes, either in terms of tolerability or effectiveness. Studies that examine the effects of P450 in populations where the consequences of adverse effects might be greater (such as elderly patients) or suspicion of metabolic differences is high, or in patients who fail to respond to multiple antidepressant trials, would be particularly valuable. In the meantime, what should individual clinicians do? Where concern for drug interactions or toxicity is high, the simplest approach is to begin with antidepressants minimally metabolised by P450 isoforms CYP2D6, CYP3A, and CYP2C19. If this is not practical, the most direct and informative approach is to check concentrations of antidepressants in the blood.

How quickly we forget. In the mid-1980s, the dexamethasone suppression test was widely touted as a sensitive test for identifying major depressive disorder. Only later did it become clear that it is neither sensitive nor specific.¹⁰ In a specialty where biomarkers of disease are rare, any biomarker is welcome—provided it is truly clinically useful. Unfortunately, at least as far as antidepressant prescribing is concerned, insufficient evidence is available to support the routine use of P450 genotyping. Ultimately, as with any other diagnostic tool, the value of pharmacogenetic tests needs to be determined by well designed and adequately powered trials before they are used in practice.
Stockpiling smallpox virus

Other viruses pose greater public health threats, so isn’t it time to move on?

Emotions still run high over the stocks of smallpox virus placed into the P4 freezers of Atlanta and Novosibirsk more than 30 years ago by the World Health Organization. In this week’s BMJ, two articles present opposing views on whether the United States and Russia should destroy their stocks of smallpox virus (*Variola*).1 2

One argument for maintaining smallpox stocks is that they are needed to develop safer vaccines.3 Our current effective vaccine is safe when used judiciously—not for mass vaccination of populations, but for targeting those at risk after screening out people with a history of HIV, leukaemia, or eczema at higher risk of complications after vaccination.5 Moreover, new vaccines are based on *Vaccinia*, not smallpox.4 No new vaccine can be tested for efficacy until human cases of smallpox reappear.

Another argument is that smallpox stocks are needed to assess antiviral agents for the treatment of smallpox. Again, no agent can be properly tested until human cases reappear. Moreover, the production of an effective antiviral is unlikely to be profitable, given the likely number of cases, and the altruism of manufacturers will probably be limited. An antiviral agent might even be of limited use in practice. Many cases are identified late, after the appearance of irreversible sequelae. Others are identified at exposure, well before onset of symptoms, when vaccination provides substantial protection and reduces the mortality rate if not the occurrence. Immunoglobulin from vaccinated people and even from survivors of smallpox (the first available and the second theoretically available) could similarly modify outcomes.

A third argument is that stocks are needed to develop better diagnostic tests. We already have rapid and sensitive tests for orthopoxvirus.4 The need to distinguish between smallpox and zoonotic orthopoxviruses would not be an immediate priority in the context of potential terrorism, as the emergency test should emphasise sensitivity, not specificity. If the introduction of smallpox did produce multiple cases, the epidemiological pattern of severity would provide a fairly accurate diagnosis. In fact, the unique appearance of a patient with early severe smallpox would quickly be disseminated via the media, and subsequent cases would be recognised by lay people. Control would proceed whether or not every diagnosis had been confirmed. Even the classic differential diagnostic alternative of *Varicella* poses few problems in an unvaccinated population, as confusion in the past was created largely by smallpox modified by past vaccination.

So what then are the arguments for destroying smallpox stocks? The major benefit of destroying the stocks is a reduction in the probability that smallpox cases will reappear.2 The virus originally stored in one of these facilities may be the only source available, because as time goes by with no indication to the contrary it becomes less likely that other clandestine stocks exist. The danger of escape is increased by dissemination to investigators and other laboratories.

However, even if smallpox were to be introduced into the population, it would not attain the proportions that it did in medieval times. Under current Western social circumstances of small family size and highly efficient communication, the number of cases is unlikely to be large.3 Most cases of smallpox are acquired at the bedside, whether in urban hospitals6 or in rural villages,4 and transmission between houses occurs through social relationships. If a large outbreak did occur, it would probably be the result of simultaneous exposures to the same (hospital) bedside rather than extended transmission.3 If a chain of transmission does not die out on its own, it would quickly be contained by the standard control techniques of public health and hospital epidemiologists.2 The unique appearance of an infectious case; the interval of roughly two weeks between exposure and symptoms; and the triad of surveillance, isolation, and effective vaccination would act together to ensure that control is established within a few case generations. Neither a widespread nor a long term epidemic is probable, whether judged from past history,6 from extrapolation of the experience with severe acute respiratory syndrome,2 or from any of the recent mathematical models.8 9 11 The net impact of an introduction would be comparable to a large common source outbreak of a severe disease caused by an agent such as hantavirus or encephalitis virus, although that impact might be substantially augmented by complications if mass vaccination were to be initiated.3

Thus, a case can be made for destroying the stocks, given the absence of compelling contrary arguments, although the stocks do not pose a great threat. Destroying the stocks would have two added benefits—it would fulfil the commitment made by the US in 1990 to destroy stocks after the genome had been identified and it would circumvent any pressures to return stocks to their countries of origin.2

Another real benefit would be the permanent elimination of this question as a distraction. More important problems need to be dealt with. Even more dangerous viruses may be found in P4 and lesser facilities. Release of the highly virulent recombinant 1918 influenza virus would be a real catastrophe,12 yet retention and distribution of recombinant strains for study is enthusiastically justified on the basis of the need for effective prevention, diagnosis, and treatment.
INSTITUTIONAL RACISM

Editorial is unduly provocative

As black psychiatrists working in the NHS, we find McKenzie and Bhu’s editorial unhelpful and unduly provocative.1 For example, although it is possible that racism has a role in increasing detention rates among black patients, the editorial ignores other well established and, in our view, more important factors.

In our combined clinical experience, which includes acute adult, forensic, and child and adolescent psychiatry and many Mental Health Act assessments, one of the main reasons for increased detention rates for black patients is an inadequate community support network. Supportive intermediaries (such as family members) can increase treatment adherence, detect early relapse signs, and enable early non-coercive intervention.2 In our experience, compared to other ethnic minorities, the relative inadequacies of support networks predispose black patients to adverse care pathways resulting in crisis and police intervention and disproportionate use of the Mental Health Act. This experience is supported by the AESOP study, which found that black patients were more likely to live alone.3

We are neither blaming the victim nor shooting the messenger, but blanket invoking of racism is too simplistic and fails to acknowledge other difficulties in black communities, some of which we can tackle better by reflectively looking inward rather than outward.

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Competing interests: None declared.


Article too strong? I think not

Although I understand the results of AESOP and the logic of Ani and Ani’s argument (previous letter),1 I fail to see how a lack of community supports can be allowed to justify restraint or the ill-informed ethnocentric misbehaviours of the NHS (or any institution that claims to care).

Unless and until every potential confounder to providing a healthy intervention is rooted out, then nothing will change. After all, if hospitals, in Ani and Ani’s view, continue to support lack of community or family cohesion by admitting people because of inadequate support, what will ever happen to change those very communities and families in a more positive direction? Perhaps they are in the state they are in precisely because these folk feel so systematically enfeebled.

And, surely, this is how we help to “make mental health everyone’s business”?2

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Competing interests: None declared.


GLOBAL PARTNERSHIP

NHS chief must direct that time overseas is an asset

Rapid responses on 30 March to the editorial on global health partnerships produced something special: a letter from the chief executive of the Medical Research Council and president of the Academy of Medical Sciences, followed by three letters from coalface workers showing the disastrous effects of Modernising Medical Careers (MMC) as they are experiencing it.2 3 This cluster follows letters from the major UK overseas research institutions,3 all the tropical medicine schools, and Médecins sans Frontières (MSF UK).2

Blakemore and Bell call for mobility between Britain and the rest of the world for clinicians while maintaining their career


NEW MENTAL HEALTH BILL

Bill aims to protect people at times of high risk

Crichton and Darjee claim that the new mental health bill is insufficiently concerned with care and treatment.1 The bill’s aim is to ensure that people with mental disorder receive the treatment they need at times of high risk. This will benefit patient and public safety—14% of the 1300 patient suicides that occur annually in England and Wales and 25% of the 52 patient homicides are preceded by refusal to take medication—but the starting point will be better care.

The bill introduces supervised community treatment. A similar power exists in many countries, including Scotland (where the authors work). Patients will be eligible for this treatment only if they are already detained in hospital for treatment—a safeguard that goes beyond what is in the Scottish legislation. The bill also removes the “treatability test” that currently acts as an impediment to care for some people with personality disorder.

Crichton and Darjee claim, without evidence, that an overemphasis on public safety will be counterproductive. But whose overemphasis are they referring to? The House of Lords has amended the bill so that supervised community treatment cannot be used for the suicidal patient, and the Mental Health Alliance, described by the authors as a “remarkable coalition,” has asked the government not to reverse this change.

Protection for the violent patient but not the suicidal patient? Remarkable indeed.

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Competing interests: LA advises the government on mental health policy.

security, and they cite calls for the same thing from others. But in a giant organisation like the NHS “calling for” counts for nothing, even if the call comes from the prime minister or the chief medical officer. Middle managers spend their days trying to discover what they are being directed to do and then trying to do it, usually with sufficient general awareness to know that this contradicts something else that they are being directed to do.

MMC has arisen from a “call for,” or consultation document, published in 2000. That call has now been translated, doubtless via almost uncountable directives through chains of middle managers, into the horror of MMC 2007. The flexibility of the original call is now a depressing rigidity, and mediocrity is the ruling standard throughout. The chief executive of the NHS will just have to follow the call of his predecessor, Lord Crisp, and direct that time spent overseas is always to be counted as a strong asset in promotion or entry to further training, and that any NHS trust that has not made an effort to link with an institution overseas is going to have to explain itself to him.

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Competing interests: None declared.

2 Electronic responses. Global health partnerships. www.bmj.com/cgi/eletters/334/7594/7595

DE-PROFESSIONALISING DOCTORS

Academy of Royal Colleges spoke out in 2002

Drife writes: “So when they set up new bodies to replace key functions of the royal colleges, who resisted? Not the colleges or faculties, all 27 of them with their 28 opinions.1

The facts are different. The Academy of Medical Royal Colleges unanimously approved an article for publication, which the BMJ published in 2002, under my name as chairman of the academy at the time, with the title “De-professionalising doctors.” So all the colleges and faculties could and did agree a single opinion and publicly issued a warning with this striking title.

Simultaneously, the academy gave written advice to the Department of Health, important parts of which were rejected.

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Competing interests: DPG was chairman, Academy of Medical Royal Colleges, 2000-2.


PERINATAL DEATH IN TWINS

Author’s reply on absolute risk

In response to Cheetham,1 as stated, our study was able only to address the relative risk to the second twin given the nature of the data.2 We previously addressed both absolute risk and the effect of caesarean section using record linkage of the Scottish Morbidity Record and the Scottish Stillbirth and Infant Death Enquiry. This linkage provides both the numerator and denominator required for the comparisons proposed.

The absolute risk of perinatal death for second twins born at term was 1 in 270 for all causes, 1 in 350 for death due to intrapartum anoxia, and 1 in 500 for anoxic death due to a mechanical cause.3 Planned caesarean section is associated with a lower risk of perinatal death and, if causality is assumed, the number needed to treat is 264 caesarean deliveries to prevent each death.4 These numbers reflect higher absolute risks than calculated by Cheetham. This may reflect flaws in the assumptions of his calculations. It may also reflect the observation that, although the second twin was at increased risk of death at term in both populations, the relative risk was higher in Scotland. We cannot address whether this reflects a greater absolute risk to the second twin in Scotland or to the first twin in England, Northern Ireland, and Wales.

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Competing interests: None declared.

1 Cheetham C. Absolute risk: better basis for decision making. BMJ 2007;334:561-2. (31 March.)

HISTORY OF MEDICINE

Understanding the history of medicine

Ravichandran says that Andrew Cunningham, in his BBC Radio series The Making of Modern Medicine, tries to make sense of the past in its own terms.1 If we try to understand the past in its own terms we will never make sense of it.

For example,2 in 1868 (the year after Lister published on antisepic surgery) John Hughes Bennett, a professor of medicine in Edinburgh, published an article showing that the whole approach of Pasteur and Lister was misconceived: he reported experiments that “proved” that germs generate spontaneously, so one could never create a germ free environment. In his own understanding, Hughes Bennett (who discovered leukaemia) had disproved the germ theory of disease. In our understanding, Hughes Bennett had failed adequately to sterilise his experimental apparatus. If we want to know what really happened we need to use our own science. Proponents of the “make sense of the past in its own terms” school advocate “charitable interpretation,” but there are limits to charity in a case like this: no amount of charitable interpretation will make Hughes Bennett right and Pasteur and Lister wrong.

Historians of medicine thus have a simple choice: on the one hand, you can understand the past in its own terms (in which case Hippocrates and Galen saved lives), or, on the other, you can understand the past in the light of modern science (in which case they killed much more often than they cured).

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Competing interests: None declared.

1 Ravichandran B. Celebrating the medical past, again. BMJ 2007;333:587. (17 March.)
Doctors facing some types of misconduct allegation by the UK regulatory body, the General Medical Council, will be able to escape full disciplinary hearings by agreeing to have conditions attached to their registration.

“Consensual disposal” will be available for the less serious conduct cases, allowing a doctor to agree, for example, not to practise single handedly, not to perform minor surgery in a GP setting, or to undergo a period of retraining.

Cases relating to problems with a doctor’s health or performance can already be resolved by undertakings about future action, but the power to dispose of a case at the investigation stage by agreement with the doctor is to be extended to cases of conduct, although the date of the extension is still to be decided.

Graeme Catto, the GMC’s president, said that complainants would be asked if they were happy for the case to be resolved without a hearing, and undertakings by doctors would be publicly disclosed.

The most serious cases—those where a doctor might be suspended or removed from the medical register and those where there was a public interest in a hearing—would still go before a fitness to practise panel of the GMC.

It would be open to the Council for Regulatory Healthcare Excellence to challenge a consensual disposal in the high court as unduly lenient, Professor Catto said.

He was speaking at a press briefing after last week’s GMC council meeting, where the council agreed to press ahead with plans to collect data about the ethnicity of all licensed doctors.

A pilot study last year that collected data on ethnicity and on scope of practice was considered a success, with a response rate of 73%.

Professor Catto said, “For a long time we’ve seen the need to have greater access to ethnicity data.”

Act now to stop babies being born with HIV

Oona Mashta LONDON

The UK government should financially support the health services of developing countries to provide the drugs and care that pregnant, HIV positive women need to stop them passing the infection to their babies, a new Unicef report urges.

More than 90% of pregnant, infected women in poor countries miss out on services that could prevent their babies being born with the disease, the report says.

Every minute a baby is born with HIV, most of whom are destined to die before their second birthday, yet the risk of mothers passing HIV to their babies can be reduced simply and cheaply, claims the children’s organisation.

The new report marks the launch of Unicef UK’s campaign to raise £1.5m (€2.2m; $3m) over the next 18 months to ensure that more babies in poor countries are born free of HIV.

It is specifically urging the UK government to provide long term funding to expand the health systems of developing countries. Pregnant women need to be offered HIV testing and specific doses of antiretroviral drugs during pregnancy and birth to prevent their babies being born with HIV, says Unicef. It contributes to many such schemes, as part of its attempt to reduce mother to child transmission. Olga, an HIV positive mother from the Ukraine (pictured), took part in one such scheme, and her daughter, Anna, aged 5, has been confirmed free of HIV.

Developing countries currently have a shortage of about four million health workers.

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Born Free from HIV is accessible at www.unicef.org/uk/bornfree.

GMC to introduce “plea bargaining” for less serious misconduct cases

Clare Dyer BMJ

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MPs back creation of hybrid embryos

Adrian O’Dowd LONDON

Government proposals to prevent the creation of part human, part animal embryos for research purposes have been condemned by an influential group of MPs.

MPs on the House of Commons Select Committee on Science and Technology said that the Department of Health’s stance was out of line with scientists, funders of research, the regulator, patients’ groups, other government departments, and even the prime minister.

The committee this week published the findings of its inquiry into government proposals for the regulation of human-animal chimeras or hybrid embryos.

The issue arose after two teams of scientists at Newcastle University and King’s College London submitted applications last year to the Human Fertilisation and Embryology Authority (HFEA) to create animal-human embryos known as “cybrids” for stem cell research (BMJ 2007;334:495, 10 Mar). Such cybrids would be 99.9% human and 0.1% animal and would produce embryonic stem cells to help efforts in understanding diseases such as Parkinson’s disease, Alzheimer’s disease, and cystic fibrosis.

But licences will not be granted until the HFEA completes its own consultation in September.

The government proposed banning such research in a white paper published in December last year. It is currently agreeing its draft bill (due out in May) that will form the basis of new laws on fertility treatment and embryo research.

The science and technology committee, in its newly published inquiry, said that the government’s proposals were unacceptable and too prohibitive.

It has urged the authority to consider the current research applications by King’s College London and Newcastle University promptly.

The report says: “Research, by its very nature, is aimed at enhancing knowledge. Whilst we recognise scientific debate about the potential usefulness of cytoplasmic hybrid embryos in research, we do not believe that the existence of differing views of whether a methodology is workable before it has been sufficiently tested is reason enough to prohibit such research from taking place.”

The committee called for legislation to allow regulation of research using animal-human hybrid embryos through licensing.

It strongly criticised the HFEA for delaying the research applications in question, which had held up the start of important research.

The chairman of the committee, Phil Willis, the Liberal Democrat MP for Harrogate and Knaresborough, said, “This is a test of the government’s commitment to science. Scientists, funders, the regulator and patient interest groups, even the DTI [Department of Trade and Industry] and the Prime Minister, have spoken out against the Department of Health’s proposals.

“We very much hope the department will listen and reflect the committee’s conclusions when the draft Tissue and Embryos Bill is published next month.

“We fully appreciate the concerns of those who oppose research into hybrid and chimera embryos—or indeed any human embryos—on moral and ethical grounds, but we feel that it is in the interests of science, the public, and the UK that the current applications should be considered by the HFEA promptly.”

The report can be seen at http://www.parliament.uk/parliamentary_committees/science_and_technology_committee.cfm.

UK ranks among lowest in Europe on cervical cancer survival

Roger Dobson ABERGAVENNY

Rates of survival for cervical cancer in the United Kingdom are among the lowest in Europe, a new study shows.

The study, which was published in Gynecologic Oncology on 30 March (www.sciencedirect.com; doi: 10.1016/j.gyno.2007.01.048) and was based on data from more than 70 000 women in 18 countries, shows that survival in Europe overall has improved slowly but steadily. But it also shows that the trend is not geographically uniform, with central European countries and the UK seeing little or no improvement.

Some of the biggest differences between countries were among women aged over 75. The five year survival rate in this group was below 30% in Scotland, Denmark, and four eastern European countries—Estonia, Slovakia, Slovenia, and Poland—whereas in the Netherlands the rate was 56%.

“This finding is distressing, because it suggests different standards of treatments for elderly women in different countries,” write the authors, from the Eurocare Working Group. The Eurocare project is an international collaborative study on the survival of cancer patients in Europe.

The study looked at relative survival and the relative excess risk of death within five years of diagnosis among 73 022 women in the 18 European countries in the Eurocare study aged 15-99 years whose cancer was diagnosed during 1983 to 1994 and who were followed up to 1999. Data came from 34 population based cancer registries.

The results show that relative survival at five years dropped markedly with age at diagnosis in most countries—overall from 78% in women aged 15-44 to 33% in women aged 75-99.

Age standardised relative survival at five years ranged from around 70% in several northern and western European countries (Iceland, Norway, Sweden, France, and the Netherlands) to 50-60% in eastern European countries (Estonia, Poland, Slovakia, and Slovenia). Survival in England, Scotland, and Wales was around 60%.

The results also show that the five year survival rate for localised disease was in the range of 78-88% in most countries, with relatively little variability.

AGE STANDARDISED SURVIVAL AT FIVE YEARS IN EUROPEAN WOMEN AGED 15-99 WITH CERVICAL CANCER*
Australia lags behind in attempts to improve health of indigenous people

Stephen Pincock SYDNEY

Australia’s efforts to improve the health of its indigenous peoples lag behind those of similar wealthy countries, concludes a new report from Oxfam Australia and the National Aboriginal Community Controlled Health Organisation.

The report compares the situation of Australian Aboriginal and Torres Strait Islanders still die at an age nearly 20 years younger than most other Australians.

It shows that those three countries have narrowed the gap in life expectancy between non-indigenous and indigenous people to approximately seven years. In contrast, Australia’s Aboriginals and Torres Strait Islanders still die at an age nearly 20 years younger than most other Australians.

Specifically, the report shows that life expectancy was 69 years for New Zealand’s Māori people and 68.9 years for the first nation peoples of Canada. In contrast, Australian Aboriginal and Torres Strait Islander men have a life expectancy of just 56 years.

“I find it embarrassing, I find it scandalous,” said Andrew Hewett, executive director of Oxfam Australia, “but I think it’s time we moved beyond embarrassment to doing something about it. We’re a rich country and we have the resources to do it.”

Other key health indicators in the report, such as infant mortality, also indicate that Australia could be doing better. Close the Gap: Solutions to the Indigenous Health Crisis facing Australia is at www.oxfam.org.au/media/files/CTG.pdf.

Jonathan Gornall LONDON

A group of doctors who last week accused the UK General Medical Council of failing children are forming an action group to counter what they say is the “intimidation” of child protection professionals.

In a paper published in *Pediatrics* on 2 April, more than 50 UK paediatricians and other professionals accused the GMC of deterring doctors from raising concerns about children’s safety and increasing the risk of serious child abuse. The GMC’s actions against the paediatricians Roy Meadow and David Southall, they said, “conflict with current child protection laws and guidance for professionals” (*Pediatrics* 2007;119:800-2).

Many believe that the combined efforts of the GMC, campaigning groups, and the media are seriously disrupting the safeguarding of children. A large number of paediatricians and allied professionals are now organising themselves into a lobby group with the aim of correcting misleading propaganda about child protection issues.

“Neither the government nor, thanks to the media, the public appear to realise just how serious the situation has become,” said one doctor, who asked not to be named.

“Such is the extent of the intimidation that fewer and fewer paediatricians are prepared to engage with child protection, and that can result in only one thing: deficiencies in the care of vulnerable children.”

The GMC defended its decisions to take action against Professor Meadow and Dr Southall. “We have sought only to act to protect the public interest from doctors who fall significantly short of accepted standards,” a spokesperson said. “After careful and separate consideration, we decided that both [cases] justified fair and scrupulous enquiry before a panel.”

Many paediatricians, however, resent what they regard as the GMC’s persecution of Dr Southall, a consultant paediatrician at the University Hospital of North Staffordshire. They point out that he is now in the middle of a second hearing of a professional conduct committee, adjourned last November for an entire year, and that if he survives this he faces a record third set of charges.

Furthermore, they say that the conduct of the first hearing was far from fair. In 2004 a professional conduct committee found Dr Southall guilty of serious professional misconduct for having reported his concern that it was Stephen Clark, and not Sally Clark, who had killed the couple’s children. Dr Southall was banned from child protection for three years (*BMJ* 2004;329:366).

The *Pediatrics* article echoes widespread disquiet about the GMC’s decision to instruct as its sole expert witness a doctor who had already been intimately involved in the Clark case.

That witness was Tim David of Manchester University. Professor David became involved in 1999 when he was instructed as a joint expert by all four parties to the care proceedings initiated by Cheshire County Council in respect of the Clarks’ surviving child: the local authority as the applicant, the child’s guardian, and the two parents, each of whom had separate legal representation.

Subsequently, in October 1999, Professor David was ordered to give evidence as an expert witness at the trial of the criminal case against Sally Clark, following an application by Mrs Clark’s lawyers.

When Dr Southall raised his concerns about Stephen Clark in 2000, the Family Court instructed Professor David to examine them. Then it was the turn of the GMC. As Dr Southall’s lawyer observed at the 2004 GMC hearing, “Professor David is, first of all, a witness of fact . . . Secondly, he is an expert in the family proceedings . . . Thirdly, and this is the unusual and somewhat unique set of circumstances, he has then been converted by the GMC . . . into an expert in these proceedings.”

This, say critics, created a potential conflict of interest, which the GMC could and should have avoided.

Professor David is also the GMC’s witness in Dr Southall’s latest professional conduct committee hearing.

Asked about the use of Professor David as a witness, a spokesman for the GMC said: “We considered the position of Professor David carefully and took legal advice which we acted upon. We are not in a position to comment on our use of expert witnesses in upcoming hearings.”

A spokesperson for Manchester University said, “Professor David is emphatically giving no comment about this article.”
IN BRIEF

Woman loses fight to use frozen embryos: Natalie Evans, from Trowbridge, Wiltshire, who was left infertile after cancer treatment, has lost her fight in the European Court to use her frozen embryos, which were fertilised by her former partner Howard Johnston. The couple began in vitro fertilisation treatment in 2001, before Ms Evans underwent chemotherapy, but Mr Johnston withdrew consent for the embryos to be used after they split up. See bmj.com.

Man is jailed for infecting partner with HIV: A man who infected his lover with HIV and hepatitis C has been jailed for nine years by Glasgow High Court. The 38 year old man refused to wear condoms after beginning a sexual relationship with a woman in Edinburgh in 2003. The National Aids Trust said that it was concerned at the severity of the sentence and that prosecutions should occur only in the most extreme and exceptional circumstances.

GMC to look into prescribing errors: The General Medical Council is offering £100 000 (€150 000; $200 000) in funding for research into what causes prescribing errors. It says that understanding the reasons for such errors will help it target its regulatory activities. Interested researchers should submit a tender proposal to the GMC by 9 May.

Dutch to review safety of magic mushrooms: Dutch health minister Ab Klink has ordered the Netherlands Public Health Institute to reassess the dangers of hallucinogenic mushrooms, after they were linked to the possible suicide of a French teenager in Amsterdam. The dried mushrooms, which are stronger than fresh ones, are banned as a hard drug, but fresh varieties can still be bought in so called “smart shops.” A majority of MPs are now demanding a total ban.

Mediterranean diet may reduce children’s asthma: A diet that is high in fresh fruit and vegetables and in nuts seems to reduce the incidence of childhood asthma, concludes research published by the BMJ group journal Thorax (doi: 10.1136/thrx.2006.069419). Although the diet seems to reduce asthma, it does not reduce skin allergies.

Private ultrasound tests to be repeated on NHS: Health managers in the north west of England are arranging for some 900 ultrasound tests to be repeated. The tests had been handled by a private company, Atos, but an audit of the work done during February led to concerns about the quality of patients’ records and of scan results.

HFEA wants greater use of single embryo transfers in IVF

Robert Short LONDON

The United Kingdom’s Human Fertilisation and Embryology Authority (HFEA) has launched a consultation to examine four options to reduce multiple births after in vitro fertilisation (IVF).

Each year in the UK 126 babies born after IVF die as a consequence of multiple birth, and the risk of death in mothers, although low, is doubled in women who are expecting twins. Currently 24% of women who have had IVF have a multiple birth.

The HFEA wants to encourage the use of single embryo transfers in each treatment cycle in patients who are most likely to conceive (such as those who are relatively young and who have not had many failed IVF attempts). At the moment many of these women receive two embryos in a treatment cycle.

The HFEA has previously limited women aged under 40 to two embryos per treatment cycle, but this has failed to reduce the high percentage of births of twins.

It believes that the current rate of twin births of about 23% of all births after IVF needs to be brought down to below 10%. In its consultation paper it argues: “This [rate] has been shown internationally to be achievable without damaging patients’ chances to conceive.”

The HFEA proposes to:

• Set a maximum rate of twin births of no more than 10% that each clinic must not exceed (which could be phased in over a number of years)
• Develop code of practice guidance that defines the cases in which only one embryo should be replaced, which would be based on, for example, age, number of previous treatment cycles, medical history, and, possibly, embryo quality
• Combine the second and third options—that is, clinics could initially be given an overall maximum rate of twin births; clinics that fail to achieve this target could have single embryo transfer criteria imposed on them by the HFEA

Consultation will be for three months from April, and a report is due in autumn 2007.

The HFEA stresses that it has no remit to make IVF treatment funded on the NHS more widely available, which it acknowledges is the biggest obstacle to the acceptance of policy change.

Evan Harris MP, the Liberal Democrats’ science spokesman and member of the House of Commons Science and Technology Select committee, agrees that access to NHS IVF services is the main issue in the UK.

He said: “Couples forced to pay for their own treatment may resent being told they are now not allowed to choose multiple embryo transfer after having the risk explained to them, even if their doctor thinks it will improve their chances of conception.”

The Best Possible Start to Life is at www.hfea.gov.uk/en/483.htm.
BMA public health doctor is accused of stigmatising sex workers

Michael Day LONDON
A senior BMA figure has come under fire for claiming that rates of infection of sexually transmitted diseases in the United Kingdom would fall by 50% if the sex trade were legalised and rigorously regulated.

Chris Spencer Jones, chairman of the BMA’s public health committee, told the association’s annual public health conference last week that focusing on prostitutes, particularly immigrant and drug addicted sex workers, would also save the NHS £330m (£485m; €670 000) a year.

Sexual health specialists immediately accused Dr Spencer Jones of making unsubstantiated claims that might further stigmatise sex workers.

Dr Spencer Jones told the conference: “In Birmingham it has been reported that 70% or more of STIs [sexually transmitted infections] are circulated in a pool of prostitutes and their clients.

“STIs are a bit rough and ready, to be honest.” But he added: “As chairman of the BMA public health committee I have a duty to ensure that important public health issues that are not being talked about are actually discussed. What I’ve said is not really disputed.”

He said that regulation of the sex trade would probably require mandatory health checks and that this would “clean up” and even destigmatise the industry. He added that, in turn, more prostitutes would be encouraged to become registered.

However, Helen Ward, an epidemiologist at Imperial College London and a leading authority on the sexual health of prostitutes, described Dr Spencer Jones’s comments as “scurrilous.”

She said, “He is suggesting that sex workers are responsible for much of the STIs and HIV in Birmingham and possibly the rest of the country. He does not appear to have cited any of the research on sex work—hardly the dizzy heights of evidence based practice that we should be aspiring to in public health and the BMA.

“The problem with what he said was that it increases stigma against sex workers—and foreigners while he was at it—and argues for mandatory testing, which is an extreme abuse of human rights.”

Investigators to review conflicts of interest at NIH

Janice Hopkins Tanne NEW YORK

Daniel Levinson, inspector general of the US Department of Health and Human Services, has said that his office will reopen 103 cases of conflicts of interest among scientists at the US National Institutes of Health (NIH).

The investigation will be carried out by the inspector general’s Special Investigations Unit, staffed by five criminal investigators.

Mr Levinson’s office was active in prosecuting Lester Crawford, the former head of the Food and Drug Administration, who was fined nearly $90 000 (£46 000; €67 000) for falsely reporting he had sold stock in companies regulated by the FDA while he still owned the shares (BMJ 2007;334:492).

The special unit will also investigate conflicts of interest among about 40 000 scientific teams at about 2000 universities, medical centres, and non-profit institutions that receive research grants from NIH, potentially a much bigger problem. The NIH’s rules on conflicts of interest do not apply to outside researchers, who are supposed to be regulated by their institutions.

Although the NIH requires institutions to adopt similar policies, “the agency conducts virtually no oversight and has no rules regulating the behavior of government grant recipients who double dip on industry payrolls,” says the Integrity in Science project of the non-profit Center for Science in the Public Interest.

“It’s a situation ripe for investigation,” Merrill Gozner, director of the integrity project, said. He questioned how thoroughly universities monitored conflicts of interest among their researchers and how well NIH reviewed university monitoring.

Mr Levinson described his office’s investigation in a letter to the representative John Dingell (Democrat, Michigan), chairman of the House of Representatives Committee on Energy and Commerce, which oversees biomedical research.

Mr Dingell said, “Even if only a few of these [reopened] cases result in criminal prosecution, it is clear that the NIH bungled the investigation the first time around.”
Swapping scrubbing brushes for stethoscopes

Zosia Kmietowicz LONDON

Refugee doctors face a struggle trying to secure a job in the NHS, but with the help of Dr Sheila Cheeroth some have achieved their goal.

A newspaper advertisement for Save the Children currently appearing in the national press says “I will be a refugee forever—teacher one day,” together with the adage “Rewrite the future for children around the world.” Substituting “doctor again” for the word “teacher”—“I will be a refugee forever—doctor again one day”—aptly describes what Sheila Cheeroth does one day a week, and which she says has taken over her life.

A GP in the east end of London, Dr Cheeroth is also director of the refugee and overseas qualified doctors’ programme, which runs courses for refugee doctors who qualified outside the European Union and who have managed to get permanent resident status in the United Kingdom.

To many of the doctors, finding themselves unemployed and short of money comes as a terrible shock. “They come here from a middle class background and have been in a position with some status in their own country, and when they come here they become nothing,” says Dr Cheeroth.

She has taken it upon herself to try to rebuild that self respect by helping doctors overcome the obstacles to securing posts in the NHS. The process is often emotionally fraught, and it involves long days preparing for the Professional and Linguistic Assessment Board (PLAB) tests, a rigorous assessment of medical knowledge and its application in the UK set by the General Medical Council. It does not always end in success.

Dr Cheeroth recounts the case of one Somali refugee who trained in medicine in Russia, became professor of obstetrics and gynaecology in St Petersburg, led the Red Crescent’s relief effort when he returned to Somalia, and later held posts in Geneva working for the World Health Organization. He spoke five languages but couldn’t get a job in the NHS.

“He was not acceptable to work at a senior level because he didn’t know the NHS systems of working. But he wouldn’t be accepted at a junior post either because he was deemed too experienced,” says Dr Cheeroth.

She can’t recall a case where a refugee doctor entered the NHS at the level to which they practised back home. Most doctors have to switch specialty, because the one in which they trained is often too competitive here. They have to start from scratch, competing with year two foundation trainees for specialist training or GP training posts. For some, the flexibility demanded is just too great.

“Sometimes people find they can’t make it in the climate of the NHS. They may not be able to adapt their skills or change direction so that they are able to find a job in the sector that will accept them,” says Dr Cheeroth.

Her students come from every war torn corner of the globe. When she set up the course 10 years ago, many of the refugee doctors came from Iraq, several from the former Yugoslavia, and a few from Pakistan, Somalia, Sudan, and Sierra Leone. They continue to flow in from Iraq, with more also coming from Afghanistan.

Dr Cheeroth points out that the programme takes only those refugees and overseas doctors who have permanent residence rights and full employment rights, so that they do not need work permits.

Her students learn about the programme, which is based at Queen Mary’s School of Medicine and Dentistry, largely through word of mouth, often after many months looking for a path back to medicine while being advised to take up cleaning jobs by their local job centre.

The programme provides what financial support it can to students in the form of book grants, travel and childcare expenses, and PLAB exam fee subsidies. Between 2002 and 2005, 103 students enrolled on the programme, at a cost of £400 000 (€590 000; £790 000) over three years. Eighty five (83%) passed their PLAB exams and became “job ready,” with 73 (71%) securing NHS posts.

When it was set up in 1997 the programme survived largely on charity donations. But a £300 000 grant from the Mercers’ Company of the City of London for 2002-5 gave it long term prospects and allowed Dr Cheeroth to develop a formal and comprehensive syllabus over the next three years.

When the Mercers’ money came to an end, the North East London Strategic Health Authority continued funding in 2005-6, and it seemed the programme would become mainstream. However, grants in the cash strapped NHS of 2007 are more difficult to come by, says Dr Cheeroth. The course is currently funded till the end of June 2007. After that the future is uncertain.

At a cost of £5500 per working doctor—compared with the £250 000 it takes to train a doctor from a school leaver in the UK—her programme produces doctors at a cheaper rate than anybody, says Dr Cheeroth.

But what the programme does is much more than that. “What we are doing is giving people who are not using their potential and who have been doing low income jobs and often drawing benefits back their pride. We are turning them into fully contributing members of society who will pay quite a lot of taxes and give to the community,” says Dr Cheeroth. Everybody wins.

Dr Cheeroth does not underestimate the value that refugee doctors bring to the NHS.

“The accusation always levelled at the medical profession is that they are out of touch, that they have been privileged, and that they do not reflect the people they serve and therefore do not understand patients’ positions and are less able to help them.

“Refugee doctors are people who have often been homeless, who have had to sit in housing offices, live in council flats, and send their children to sink schools—and who have had to help their community members facing difficulty to access health care because of language and other barriers.

“They have often seen UK health and social care from the other side.”

To learn more see www.ihse.qmul.ac.uk/chs/nhs/refugeedoctors/index.htm
Incretin mimetics are a new class of glucoregulatory drugs that stimulate glucose dependent insulin secretion, inhibit glucagon secretion, slow gastric emptying, and reduce food intake. Exenatide, the first drug registered in this class, was previously found to improve glycaemic control in people with type 2 diabetes if added to treatment with metformin or sulfonylurea. A recent trial sponsored by the manufacturers explored the effects of adding exenatide to thiazolidinediones, with or without metformin.

The placebo controlled randomised trial comprised 233 people with suboptimally controlled type 2 diabetes treated in 49 clinics in Canada, Spain, and the United States. After 16 weeks, people receiving subcutaneous injections of exenatide twice daily had lower glycated haemoglobin, serum fasting glucose, and body weight than controls. Fewer than three quarters of the participants finished the trial, mostly because of nausea and vomiting with exenatide. On the basis of these results, the US Food and Drug Administration approved the new indication for exenatide.

The linked editorial (pp 527-8) critically examines the pitfalls of the trial: none of the participants received lifestyle and dietary advice; more than a fifth of them weren’t receiving metformin even though it is the first line drug for type 2 diabetes; and we don’t know how many participants received maximum recommended dosages of thiazolidinediones or metformin. All this lessens the generalisability of the trial results to practice settings. With short follow-up and too few participants to conduct helpful subgroup analyses, clinicians seem to be left with more questions than answers.

Ann Intern Med 2007;146:527-8

Sumatriptan-naproxen works well for migraine

The complex pathophysiology of migraine contributes to the continuous challenge of developing optimal treatments. Two classes of drugs—triptans and non-steroidal anti-inflammatory drugs—have been shown to help people with migraine, but their success is limited and many patients are dissatisfied with treatment.

Two recent randomised double blind trials of more than 3000 people compared the efficacy and safety of a new drug—a tablet containing 85 mg of sumatriptan succinate and 500 mg of naproxen sodium—with monotherapy for 85 mg sumatriptan, 500 mg naproxen, or placebo. At two hours after dosing, sumatriptan-naproxen was more effective than placebo for headache relief and reducing sensitivity to light and sound. The combination drug was also more effective than either monotherapy or placebo in sustaining relief from pain for 24 hours after dosing. The adverse event profile of the combination drug was comparable to that of monotherapy with sumatriptan.

Combining these two drugs with different antimigraine mechanisms seems to confer added benefits to monotherapy alone. The authors warn, however, that the benefits and safety profile reported in the trials cannot be extrapolated to concurrent use of the two drugs separately, especially at the different dosages available on the market.

JAMA 2007;297:1443-54

When should routine screening for breast cancer start?

While the benefits of routine screening for breast cancer seem to outweigh harms in women aged 50 years and older, this may not be so for women in their 40s. A systematic review of randomised trials and observational studies examined the evidence on benefits and risks of mammography screening for women aged 40-49.

Although a meta-analysis showed that screening in this age group reduced mortality from breast cancer by 7-23%, risks were considerable. The linked editorial (pp 529-31) simplifies the numbers—for every 10 000 women who have yearly routine mammography from age 40, only six women might benefit through reduced risk of dying of breast cancer. Most women will not have breast cancer, and some will have it detected too late for a cure.

On the other hand, after 10 routine mammograms, up to half of the women will have one false positive test result. This will usually be followed by further diagnostic procedures, and about 2000 women will undergo biopsy. Apart from associated anxiety and costs, other risks include exposure to radiation, overdiagnosis, and false reassurance. Linked clinical guidelines suggest that decisions on whether to screen women in their 40s need to be made individually (pp 511-5).


False positive mammography may have long term effects

We know that women’s psychological well-being is negatively affected when they receive a false positive mammography test result, but reports of long term consequences have until now been scattered through the literature. A systematic review of observational studies looked into how such false positive results influence women’s behaviour, wellbeing, and beliefs in the long term.

The review, which was restricted to studies published in English, found 23 longitudinal studies that included more than 300 000 women aged at least 40. Compared with women who had a normal result, women with a false positive result had higher, although not pathologically raised, levels of distress and anxiety several months after receiving the results. They also thought more about breast cancer pathology several months after receiving the results.

In the United States, women who once received a false positive result were more likely to return for routine screening, while the opposite was true for Canada. Among European women, false positive results did not affect the likelihood of returning for the next routine mammography.

Ann Intern Med 2007;146:502-10

WHAT’S NEW IN THE OTHER GENERAL JOURNALS
Kristina Fister, associate editor, BMJ kfister@bmj.com

Addition exenatide to thiazolidinediones in type 2 diabetes: who will it help?

**EXENATIDE AND BODY WEIGHT IN TYPE 2 DIABETES**

Adapted from Ann Intern Med 2007;146:477-85

[Diagram of body weight change (kg) over 16 weeks for Exenatide and Placebo]
European legislation on working time and the maximum 48 hour working week is currently languishing in a no man’s land. The battle between supporters of the opt-out from its provisions, led by the United Kingdom, and opponents to such a move, championed by France, has resulted in a stalemate in efforts to update measures that were first introduced in 1998.

At the same time, national governments are having to take into account rulings from the Luxembourg based European Court of Justice, which interprets the legislation. The two most important are SIMAP (Sindicato de Médicos de Asistencia Pública) (2000) and Jaeger (2003). These held that on-call duty performed by a doctor when required to be physically present in the hospital must be regarded as working time.

These rulings are having a direct effect on countries such as France, Austria, Poland, Slovenia, and Hungary, which traditionally did not calculate all periods of on-call time towards the working week. The court has also ruled on the compensatory rest that employers must give their staff when they work longer hours than usual.

The European Commission has written to the governments of all 27 countries in the European Union, asking them what provisions they have put in place to comply with the Luxembourg judgments and the financial costs of doing this. In particular, it has highlighted four issues: the reference period (used to calculate the average 48 hour work week), resting period, on-call time, and multiple contracts.

**Deadline**
The deadline for replies was the end of March, but few will be surprised if this slips. On the basis of the information, the commission will have to decide whether national procedures are now in line with the judges’ rulings. If it considers they are not, it would be under pressure to open legal proceedings against the offending countries.

One difficulty will lie in establishing which sectors the commission will investigate. Health services are obviously affected; so too are other emergency services such as fire, ambulance, and police. But the conditions also apply to residential establishments, as France discovered at the end of 2005 when judges ruled that the hours worked by a special needs teacher on night duty had to be counted in their entirety as working time.

**Amending the rulings**
In a bid to make it easier to implement the rulings and to give politicians, rather than judges, responsibility for shaping the legislation, the European Commission had proposed amendments to the original text. These were enthusiastically taken up by Finland, which, as EU president, tried to secure a breakthrough among employment ministers last November. The proposed amendments emphasised the need to ensure greater flexibility in organising working time, “particularly with regard to on-call time and, more specifically, inactive periods during on-call time,” and to strike a new balance “between reconciling work and family life on the one hand and a more flexible organisation of working time on the other.”

The commission proposed inserting a new article to confirm that the inactive part of on-call time would not be considered working time “unless national law or, in accordance with national law and/or practice, a collective agreement between the social partners decides otherwise.”

The inactive part of on-call time would be calculated as a percentage of on-call time, taking account of the practice of the sector concerned, collective agreements, and national legislation. It would not be taken into account when calculating daily or weekly rest periods, unless national collective agreements or legislation deemed otherwise.

When it came to compensatory rest, the proposal suggested that the current wording of “equivalent periods of compensatory rest” should be replaced by “equivalent periods of compensatory rest within a reasonable period, to be determined by national legislation or a collective agreement.” This was designed to give countries a degree of flexibility in contrast to the European Court of Justice’s view that this should take place immediately.

**Opt-out causes talks to flounder**
On both key issues, there was a large degree of consensus among government ministers, but the talks eventually floundered on use of the opt-out. The proposal had tried to bridge the gap between the two camps by emphasising that the opt-out was an exception to
the general principle of a maximum 48-hour working week and that its use would have to be “subject to appropriate safeguards, to protect the safety and health of workers and the voluntary nature of this option.” It would also have to be laid down by collective agreement or national legislation.

Finland tried to insert tougher individual guarantees. The amendments stated that no employee should be required to work more than 60 hours over a seven day period, calculated as an average over three months; that an employee’s agreement to do so should be renewed every year; and that any consent they might have given when signing an individual employment contract or during the first four weeks of employment would be invalid.

Another refinement was that use of the opt-out should be monitored by the European Commission, which would liaise with trade union and employers’ organisations and report its observations to national governments.

Talks collapse
But the talks collapsed when five countries—Italy, Spain, Greece, Cyprus, and France—insisted that the amended legislation had to contain a date by which the opt-out would no longer be possible, while the remaining 22 were content to leave its future open ended. Afterwards, Alistair Darling, the UK’s trade and industry secretary, said: “We always made clear that our bottom line was to preserve the opt-out and we have done that.”

Faced with the implacable blocking minority, the Finnish chairman brought the meeting to an early conclusion, admitting: “Even if we sat here till the early hours of the morning, we would not find a solution.” Despite the deadlock, the outcome was a tactical success for the UK. Previously it had been in a minority in defending the opt-out; now the minority consisted only of those insisting it be phased out.

Are amendments possible?
The prospect of amendments to the original legislation being agreed by EU governments is now highly unlikely. Germany, as current EU president, has made clear it does not intend to consider the matter during its six month tenure. Its successor, Portugal, is unlikely to invest time and political capital in a venture that another small country, Finland, could not complete. The only possible gleam of light is a change of government in some of the five blocking countries (France is one possibility).

Some quarters have suggested that it should be possible to take out issues of importance to the health sector and emergency services, such as on-call time and rest periods, and treat them in a separate piece of legislation, but these suggestions have been quickly rejected. Vladimir Spidla, the employment commissioner, has said: “It is absolutely clear there is no particular interest on the part of member states for such an approach.”

Other avenues
With the legislative route currently blocked, other avenues are being examined to comply with the European Court of Justice’s rulings while keeping as low as possible the extra costs involved from the recruitment of more doctors and nurses. Some countries have amended their national legislation. This is the case of Germany, where the inactive period of on-call time had previously been classified as a rest period. The change was made in 2004. However, because of fears that 15,000 extra doctors would be required, a transitional clause allowed for exemptions, and it is only since January that German legislation has been in complete conformity.

The Czech Republic, which updated its legislation in January, estimates it will need a further 2000 doctors, and Poland has indicated it would require 15,000 more employees for the health and fire brigade sectors. Sweden changed its legislation last year to ensure that any collective agreement that gave staff less than the European court stipulated would be invalid. The Netherlands introduced rules in 2005 providing for on-call time in the workplace to be considered as working time.

The rulings have led to changes in working patterns, notably in the UK, where rotas and on-call time have given way to shifts and a major reorganisation has taken place in the NHS. This has come at a cost of some £200m-300m (€295m-445m; $395m-590m). Despite some suggestions otherwise, the UK government is confident that the changes in working fully implement the court judgments.

EU-wide snapshot
An analysis carried out for the European Parliament’s employment and social affairs committee, based largely on earlier work by the European Commission, gives a general snapshot of the situation across the EU. This indicates that 18 countries do not comply with the provisions on on-call time and 21 contravene compensatory rest requirements. Four countries—Germany, Lithuania, Malta, and Poland—do not respect the reference period, and another four—Spain, France, Hungary, and the UK—contravene the individual opt-out. The analysis, which some experts insist should be treated with caution, suggests that only Italy and Luxembourg seem to be entirely in conformity, while France and Slovakia are in the process of amending their legislation.

The way ahead is unclear. Politically, it would be almost unthinkable for the European Commission to start court action against almost every EU country. “If Jose Manuel Barroso wants to be reappointed as commission president for another five years, then he would not want to upset so many governments,” suggests one Brussels official.

Although legislation might be in place, whether it is implemented on the ground is another question. The likelihood is that the commission will play a long game while national authorities gradually bring their practices into line—and allocate the necessary resources—with the way the European court has interpreted the legislation.

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A new private venture is offering NHS patients the chance to inspect their complete medical record, in electronic form, on any personal computer. Health eCard, being piloted in north London, is the latest of several initiatives that aim to give patients access to their medical records by using IT (information technology). Although the concept of electronic “patient held records” is not new, the technology seems to be coming of age—kindling debate on safety, confidentiality, the amount of information to which patients should routinely have access, and the potential impact on NHS resources.

Allowing patients to view their own records is one goal of the £12.4bn (€18bn; $24bn) national programme for IT in the National Health Service in England. However, initiatives led by general practitioners and commercial suppliers are moving more swiftly and allowing more comprehensive access than has been promised by the “official” system for access to records, which is due to go live later this year.

**Practical matters**

Although all parties agree that using IT to give patients access to their records is a good thing, there is fierce debate over several practical matters.

One is whether records should be accessible over an online network (usually the internet) or stored in a portable medium in a form that can be displayed via personal computers. Health eCard takes the second option. Participating patients buy a smartcard that is similar to a credit card but is equipped with an adapter allowing it to be plugged into the USB (universal serial bus) socket found in most current models of personal computers.

Copies of records are downloaded from the general practice’s system via a one-way connection box that the company provides free to GPs. The card stores the record in a structured form, with important information such as recent test results grouped together, says Health eCard’s managing director, Jul Kornbluth. The record also contains images such as x rays. Kornbluth says the system is compatible with 80% of GP practice computers and the card can be read on virtually any personal computer by plugging it in and entering a password. Holders can also make a summary of emergency information, such as current medication and allergies, available without a password.

Smartcard records are in use in several countries and have already been tried by the NHS. In 1989, some 8000 patients living in the Exmouth area were issued with “Care Cards” containing records of care encounters and decisions, including prescriptions. Although the Exmouth scheme was a technical success, the NHS did not take the idea further.

When the NHS national programme for IT was conceived in 2002, policy makers almost immediately ruled out patient held cards in favour of online access for both NHS staff and patients. Later this year, if all goes well, some patients will be given access to summaries of their records as part of the process begun this spring of loading summaries of clinical information onto the central care records computer. Consenting patients at a hand

Consenting patients at a hand

**Different technologies**

Both approaches have advantages. Online records can be kept continuously up to date, can be integrated easily into NHS clinical systems, and do not depend on patients remembering to carry their cards. For portable records, the advantages are security—anyone gaining unauthorised access would need to have the card itself as well as the password—and the ability to store images as well as text.

Despite the differences in technology, the Record Access Collaborative and Health eCard teams agree on several key points. One is that patients should have access to the entire record and not just a summary. “It’s all or nothing,” Kornbluth says. Another is the need for educating patients in such matters as picking a non-guessable password (Kornbluth says the biggest threat to the Health eCard may come from members of the patient’s family, who might have almost unlimited opportunity to attempt to access the card by trial and error). Dr Hannan requires patients to watch an hour-long training video and fill in a four-page questionnaire to ensure they understand the issues at stake, including that of security.

Security measures for Healthspace have yet to be finalised, but they will probably involve patients enrolling at their GP surgery and receiving an electronic token to use in tandem with a password.

**Complementing the NHS programme**

In the charged political climate surrounding NHS IT, both the Health eCard and the Records Access Collaborative emphasise that they see their roles as complementing the national programme, not competing with it.
The biggest unknown is whether electronic personal health records improve patients’ outcomes

NHS Connecting for Health, the agency running the national programme, is watching the initiatives with enthusiasm tinged with apprehension. The feeling is that although success at the grass roots may help build public support for electronic records, it would give ammunition to critics questioning the need for a national system, especially the central electronic care records’ “spine.” Failure, such as a high profile breach of confidentiality, could damage the credibility of all electronic records.

Uncertainties
A report published in March by the Nuffield Trust points to several things that need to be understood before electronic personal health records become a mainstream part of NHS care.4 Electronic personal health records (ePHRs) “have the potential to impact positively on the delivery of care [but] this will require careful attention to technical, organisational and human barriers, supported by further research to demonstrate objective benefits and contextual influences,” it concludes. Most patients will welcome access to ePHRs, but few patients are likely to consult them regularly: “The most frequent users are likely to be patients with long term conditions (or their carers), who have the greatest need to track their illness and treatments and manage interactions with the health service, and those experiencing episodic periods of care that generate new information needs.”

Challenges identified by the report include how to integrate the patient held record into the process of care and how to manage the transfer of responsibility to patients. Another uncertainty is over the funding of records access. Health eCard relies on patients being willing to spend £39.50 on the card (of which £10 goes to their GP: this is the usual fee charged for a copy of paper records). Membership of the Record Access Pilot is free, though the scheme is funded by a private company. If the scheme were to be extended nationally, funding would have to be found for educating and supporting patients. Another issue is equitable access—thanks to the “digital divide,” people with most need of NHS services might not have access to the internet, the Nuffield report says that records might be made available via mobile phone and digital TV as well as personal computer.

More research is also needed into the impact on doctors’ time—patients “empowered” by access to information may be healthier and more compliant, needing fewer appointments. On the other hand, empowered patients may need longer with their GPs.

The Nuffield report also points out that much of the evidence on such matters has been gathered in small scale pilots run by enthusiasts: “Although the lessons learned have been valuable and echo those of larger implementations in the US, the feasibility and benefits of widespread ePHR have yet to be demonstrated.” The biggest unknown is whether electronic personal health records improve patients’ outcomes. On this, the Nuffield report cites “a lack of hard evidence . . . although formative research suggests improved perceptions of patient-centred care, empowerment for health self-management and the potential for improved data quality and medication compliance.”

Despite these reservations, there is a sense that, nearly 20 years after the 1990 Access to Health Records Act, the idea that patients should use their records is becoming the norm. Dr Hannan says he has so far judged only one patient unsuited to viewing his record—and that decision was reached jointly with the individual, who was receiving psychiatric care in the community.

On the technological mechanism, and key questions such as security, the jury is still out. Professor Mike Pringle, joint clinical lead for the NHS National Programme for IT, says that the ideal technology for patient access has yet to be developed. Both the Record Access Collaborative’s approach and the Health eCard may be too demanding for most patients, he says, while the Healthspace summary record may not be comprehensive enough for the long term. “My best guess is we evolve somewhere halfway between the two. For those who want it, we should be enabling access to the whole record. But that may be wanted by relatively few patients, we don’t know. The whole point is to try to find out.”

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3 Cross M. NHS starts uploading clinical data to central computer. BMJ 2007;334:604. doi:10.1136/ bmj.39160.586829.BD
I have been surprised by the extensive and continuing media coverage of the announcement that Elizabeth Edwards, wife of the US presidential candidate John Edwards, has recurrent breast cancer. It was front page news here when it was announced. The Edwards’s decision to continue his campaign despite the cancer was then analysed and discussed endlessly, with multiple follow-up stories and interviews in the newspapers, on the network news programmes, and in the blogosphere. Why all the fuss?

First, a bit of background. John Edwards, a former US senator, ran for president in 2004 and was beaten by John Kerry, who then picked him as his vice presidential running mate. On election day 2004 Mrs Edwards found out that she had breast cancer. She subsequently had surgery and radiation therapy and was pronounced cured. John Edwards is running again for president in the 2008 election and generally has been third in public opinion polls, after Hillary Rodham Clinton and Barack Obama.

Further relevant background. The Edwards’s had two teenage children. Their 16 year old son died in 1996 in a car crash. In her late 40s Elizabeth Edwards then had two more children, who are now aged 6 and 8.

On 22 March, Elizabeth and John Edwards held a press conference to announce that her breast cancer had returned. It has metastasised to her bones and possibly to internal organs as well. Although the cancer is stage IV and incurable, her cancer burden is small, and her doctors told her that it is “completely treatable.”

She said that she feels well, is planning to undergo unspecified treatments to control her cancer, and that she and her husband had jointly decided to press on with his campaign.

The pundits are having a field day with this one. Elizabeth and John Edwards were immediately called courageous and forthright by many, but others have criticised their decision to carry on with the campaign under such uncertain circumstances. Some thought it callous to focus on his career instead of her health. Others say that they are short changing their young children by not spending every possible minute with them. Katie Couric, a television network news anchor who famously lost her own husband to colon cancer, interviewed them and asked whether they were in denial and being unrealistic in their expectations. Many wondered how candidate (let alone president) Edwards could focus on the affairs of the world while his wife’s health is so precarious. Others saw this as a plea for a sympathy vote.

Mrs Edwards responded by saying that all of us are dying; her only difference is that she now knows what she will die from. She wants to be seen as living with cancer rather than dying from it, and to her the only choice is whether to “push forward or start dying.” She and her husband have spoken about their young children and how they told them the news. John Edwards says that he wants no one to vote for him out of sympathy but that voters may learn something important about him from this. He feels that he has shown his ability to continue to function in his job during periods of family stress because he has done it twice before: when their elder son died and at the time of his wife’s first cancer diagnosis.

So why all the press furore in America over this news? I think there are three reasons. Firstly, Americans are obsessed with the domestic affairs of their political leaders. Nothing that Hillary Rodham Clinton does as a candidate for president engenders greater interest and attention than her role as wronged wife during her husband’s presidency. Similarly, the Republican candidate Rudy Giuliani, former mayor of New York, gets more press for the ongoing saga of his wives and their previous husbands than for his policy statements. John Edwards only made it onto the network news shows when his wife’s cancer recurrence was revealed.

Secondly, this was a recurrence of cancer, not a primary diagnosis. As one of my friends, herself a cancer survivor, said, “Everyone’s got breast cancer—it’s no big deal.” It is commonplace to hear about a celebrity with breast cancer who undergoes treatment and announces that she is cured. Recurrence, however, is not part of the public drill. It is scarier, and terms such as “stage IV,” “metastases,” and “incurable” upset the press and the public. In a world full of media consultants and carefully scripted appearances, everyone understands that the future for this couple is not predictable. It is going to play out in real time in front of the country.

Finally, and related to that, there is clearly something very special about Elizabeth Edwards. Her direct, no-nonsense approach is genuine and appealing. Her intelligence, thoughtfulness, and toughness come through clearly. She is a woman who has been given much but has also been put through much. We all wonder how we would deal with such unhappy news in private and in public. At least some of us, myself included, would hope for her strength and grace. It is as much about us as them.

As the actor Tim Robbins’s character Andy Dufresne said in the film *Shawshank Redemption*, “It usually comes down to a simple choice, really—get busy living or get busy dying.”

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Implications of shift work for junior doctors

Yasmin Ahmed-Little provides evidence that junior doctors’ dislike of shift working is more than a stubborn reaction and discusses how to make shifts more tolerable

Junior doctors in the UK have seen their working hours cut through implementation of the European Working Time Directive and the Department of Health’s new deal to improve working conditions. However, the resulting increase in shift working has caused great dissatisfaction. Juniors report fatigue and poor performance on the night shift, and evidence from outside medicine suggests there may be long term health effects. Concerns have been raised about future recruitment and retention, particularly in the acute 24 hour specialties. Shift working is likely to increase further as junior doctors’ working hours are reduced to a maximum of 48 hours per week by 2009. Without an evidence based approach to the implementation of such large scale changes, there is a real danger of adding new, unknown risks and perhaps even worsening the status quo.

Shift working patterns in the UK
Traditionally junior doctors worked long hours in a resident, on-call capacity with continuous shifts of up to 56 hours, and an average working week of up to 72 hours of duty. The performance implications of these working patterns are now widely recognised, and increases in the UK medical workforce have allowed sensible reductions to working hours and the introduction of full shift working.

Full shift working for UK junior doctors usually means a fixed normal working day plus rotating long day shifts and regular weeks of night shifts. Although overall working hours have reduced, the proportion of out of hours working has increased. This affects training because established international evidence shows that people’s capacity to learn overnight is significantly impaired and sleep is required to consolidate new learning. Most full shift rotae currently require junior doctors to work seven consecutive, 13 hour night shifts. The Royal College of Physicians recently recommended avoiding such rostering. It suggests limiting consecutive night shifts to a maximum of four and reducing the duration of shifts in order to decrease the risk to patients and staff. Single night shifts are safest, but more doctors would be required to support such rotae, which is unlikely to be affordable.

Health effects
Plenty of evidence supports the negative effect on health and performance of working long hours. Some studies specifically support the European limit of a maximum 48 hour working week. Many of these lessons come from industry and may not be directly transferable to medicine. However, young doctors would benefit from better awareness of the potential dangers of shift working in general.

Epidemiological studies suggest shift working increases the risks of peptic ulcers, diabetes, and coronary heart disease. Researchers in Denmark hypothesised that up to 20% of cardiovascular disease in the country could be prevented if psychosocial risk factors such as stressful working conditions, passive smoking, and shift work were not present.

Few studies have considered the effects on women, but it seems they may be affected more than men. For example, a population based case-controlled study from Denmark found a 50% increase in the risk of breast cancer in women working regular night shifts. A cohort study of American female nurses showed a dose dependent response, with the risk of coronary heart disease rising as the number of years of shift work increased, and suggested that working night shifts for six or more years significantly increases cardiovascular risk.

Rates of miscarriages, low birthweight babies, and premature births are also more prevalent among shift workers, with some researchers recommending that women are relieved of shift working duties during pregnancy on the strength of current evidence alone.

These findings have repercussions for planning the future workforce given the rapidly increasing proportion of women in medicine. Many women may also wish to work part time at some point, so lengthening the years they will spend working night shifts. Societal costs of treating the adverse outcomes of shift work, especially among women, may outweigh the benefits gained. It is unclear whether knowledge of the potential health effects would deter women from agreeing to shift work or whether junior doctors need to give informed consent.

Similarly it may not be possible to ask senior doctors to work resident shifts without compromising their health. Tolerance and adaptation to shift work seems to decrease with age, with researchers recommending that those aged above 40-45 years should work fewer night shifts, if they work them at all. The more experienced junior doctors are already unhappy about working shifts.
Making shifts work

Tolerance to shift working can be increased through improved rostering (box).\textsuperscript{1,15,16} The design of rotas must be evidence based to minimise the potential detrimental effects on employees’ health and performance. One solution is to reduce the frequency of night shifts for individual doctors, either by increasing the pool of doctors providing overnight cover or initiatives such as Hospital at Night, which uses competency based multidisciplinary teams to provide out of hours cover.\textsuperscript{17} Minimising the number of consecutive night shifts worked would also help. Accumulated sleep deprivation from consecutive night shifts worsens daily, leading to poorer health and performance. One study recommends a minimum of 16 hours off duty between shifts to allow workers to get at least seven hours’ sleep.\textsuperscript{4,7}

When these options are not feasible, a range of compensatory measures can minimise the effect of shift work on individuals’ health and performance. These include the strategic use of caffeine or bright lights through the night shift,\textsuperscript{18,19} although strong evidence is lacking for any one approach. Many of the adverse outcomes from shift working are mediated through sleep deprivation. Structured naps during the night shift supported with appropriate rest facilities can optimise rest, compensating for sleep loss. Access to private rooms where employees can sleep after a night shift can alleviate fatigue before driving home. Better provision of extended NHS childcare facilities should help women tolerate shift working, as many struggle to rest between night shifts because of domestic and childcare responsibilities.\textsuperscript{15}

Longer term there is evidence that regular exercise can improve tolerance to shift working, as well as moderate physical exercise a few hours before the main sleep when working nights.\textsuperscript{14,15} Trusts should be given more support to provide exercise facilities for NHS staff. Occupational health departments could also have a proactive role in education and surveillance, supporting health promotion around shift working, discussing the range of compensatory measures, and advising staff with sleep disorders.

Future challenges

If the problems of shift working are not taken into consideration now, there may not be enough trained junior doctors available to staff junior medical rotas when the 48 hour working week becomes a legal requirement.\textsuperscript{10} Changes to postgraduate medical training may mean junior doctors no longer have the appropriate skills to deliver service. Skill mix and new ways of working will provide solutions only at the most junior grades and are unlikely to replace the level of competence at which general medicine or general surgery specialist registrars currently operate, for example. The Department of Health’s aspiration of a future NHS led and delivered by consultants\textsuperscript{13} could fail, owing to a lack of staff over the age of 40 prepared to work the shifts required to provide this, and few appropriately skilled juniors remaining to make up the shortfall.

Knowledge is the key. The NHS has a responsibility to improve rostering to reduce adverse effects and to provide education about the dangers of and coping with shift working through appropriately resourced occupational health departments. Research is also essential to improve our knowledge of the effects on doctors specifically and to determine whether reduced working hours affects the ability to cope with night shifts. Most studies have examined groups of workers doing long hours and night work, as most shift workers do both. The advice given here applies to other health systems and other professions.

Contributors and sources: YA-L is a part time trainee. She has led work on issues related to junior doctors’ hours, including the European Working Time Directive, in Greater Manchester since 2003. This article arose from a secondary review of existing literature conducted as part of her masters dissertation in health services management at Manchester Centre for Healthcare Management.

Competing interests: None declared.

Provenance: Non-commissioned, externally peer reviewed.

EVIDENCE BASED ROSTERING

- Consecutive night shifts should be minimised and the maximum number of weekends possible kept freew\textsuperscript{6}
- Shifts are better tolerated when they rapidly rotate in a clockwise manner that is, they change every few days in a morning, afternoon, then night pattern (phase delay)
- Individual shifts should last no longer than 10-12 hours
- Employees are more likely to accept a specific shift working pattern positively if they have participated in its construction\textsuperscript{15}

Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis

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ABSTRACT
Objective To review the literature on the use of inhaled nitric oxide to treat acute lung injury/acute respiratory distress syndrome (ALI/ARDS) and to summarise the effects of nitric oxide, compared with placebo or usual care without nitric oxide, in adults and children with ALI or ARDS.

Design Systematic review and meta-analysis.

Data sources Medline, CINAHL, Embase, and CENTRAL (to October 2006), proceedings from four conferences, and additional information from authors of 10 trials.

Review methods Two reviewers independently selected parallel group randomised controlled trials comparing nitric oxide with control and extracted data related to study methods, clinical and physiological outcomes, and adverse events.

Main outcome measures Mortality, duration of ventilation, oxygenation, pulmonary arterial pressure, adverse events.

Results 12 trials randomly assigning 1237 patients met inclusion criteria. Overall methodological quality was good. Using random effects models, we found no significant effect of nitric oxide on hospital mortality (risk ratio 1.10, 95% confidence interval 0.94 to 1.30), duration of ventilation, or ventilator-free days. On day one of treatment, nitric oxide increased the ratio of partial pressure of oxygen to fraction of inspired oxygen (PaO₂/ FiO₂ ratio) (13%, 4% to 23%) and decreased the oxygenation index (14%, 2% to 25%). Some evidence suggested that improvements in oxygenation persisted until day four. There was no effect on mean pulmonary arterial pressure. Patients receiving nitric oxide had an increased risk of developing renal dysfunction (1.50, 1.11 to 2.02).

Conclusions Nitric oxide is associated with limited improvement in oxygenation in patients with ALI or ARDS but confers no mortality benefit and may cause harm. We do not recommend its routine use in these severely ill patients.

INTRODUCTION
Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), defined by acute hypoxaemia and bilateral lung infiltrates on radiography without left atrial hypertension,¹ are characterised by inflammation of the alveolar-capillary membrane triggered by various insults.² Because the pathophysiology involves mismatching of ventilation and perfusion and pulmonary hypertension, the possibility of using inhaled nitric oxide (NO) generated considerable interest.³ Nitric oxide is a selective pulmonary vasodilator and has anti-inflammatory properties.⁴⁵ Based on limited data on efficacy, clinicians rapidly adopted this therapy; 63% of European intensive care specialists surveyed in 1997 reported using it, primarily for ALI or ARDS.⁶ A more recent survey of specialists in Ontario, Canada, found that a substantial proportion (39%) reported using nitric oxide at least sometimes in selected patients with ARDS.⁷

A systematic review and meta-analysis of nitric oxide published in 2003⁸⁹ that included five randomised controlled trials w⁴ w⁷ found no effect on mortality or ventilator-free days; one trial showed improved oxygenation.⁶³ Because confidence intervals were wide, the authors concluded that the effects of nitric oxide on morbidity and mortality were uncertain. We have incorporated data from new randomised controlled trials to evaluate the effects of nitric oxide on pulmonary physiology (oxygenation and pulmonary arterial pressure) and important clinical outcomes.
(mortality, duration of ventilation, and adverse effects) in patients with established ALI or ARDS.

**METHODS**

**Search strategy**

We electronically searched Medline, CINAHL, Embase, and CENTRAL (to October 2006), limiting citations to randomised controlled trials. We also searched proceedings of four conferences (1994-2006), screened bibliographies of retrieved studies and recent review articles,10-18 and contacted content experts to identify additional trials. There were no language restrictions. Further details of the search strategy and other aspects of study methods are on bmj.com.

**Study selection**

Two reviewers independently screened studies for inclusion, retrieved potentially relevant studies, and decided on study eligibility. We selected parallel group trials that enrolled adults or children (excluding neonates), with ≥80% of patients or a separately reported subgroup having ALI or ARDS (using

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**Table 1 | Details of randomised trials of inhaled nitric oxide (NO) in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)**

<table>
<thead>
<tr>
<th>Author (funding*)</th>
<th>Population</th>
<th>Details of NO administration</th>
<th>Control group and crossovers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day,*6 1997 (not for profit)</td>
<td>24 children, 1 centre. Acute bilateral CXR infiltrates, PEEP ≥ 0.5 cm H2O, FiO2 ≥ 0.5 for &gt; 12 hours. Enrollment for ≥ 84 h after meeting study criteria</td>
<td>10 ppm until oxygenation and PEEP criteria met</td>
<td>Usual care. All patients randomised to control received NO 10 ppm after 24 hours; no crossovers before 24 hours</td>
</tr>
<tr>
<td>Schwebel,*2 1997 (not for profit; industry supplied gas)</td>
<td>19 adults, 17 centres. Any CXR infiltrates, P/F &lt; 200 mm Hg, 10×PAP/18 mm Hg, 6×PEEP≥10 cm H2O. Duration of ARDS ≥ 24 hours</td>
<td>10 ppm for 17 hours, then at clinician’s discretion; mean 4.6 days (range 1.25 to 11)</td>
<td>Placebo gas (nitrogen). Crossovers mandated before 17 hours if P/F ≤ 100 mm Hg and permitted thereafter (at least 5/10 patients randomised to control received NO)</td>
</tr>
<tr>
<td>Dobyns,*6 1999 (not for profit)</td>
<td>108 children (1 month of age, median age 2.5 years), 7 centres. Any CXR infiltrates, O2 ≥ 15 on 2 arterial blood gases within 6 hours (mean duration of ventilation before randomisation 3.5 days in NO group, 3.7 days in control group)</td>
<td>1.25, 5, 20, 40 or 80 ppm until 28 days or oxygenation and PEEP criteria met. Protocol for weaning NO</td>
<td>Placebo gas (nitrogen). No crossovers</td>
</tr>
<tr>
<td>Mehta,*9 2001 (not for profit and industry supplied gas)</td>
<td>203 adults, 23 centres. ACEC criteria for ARDS, lung injury score ≥ 2 after 24 hours of “therapeutic optimisation” (mean duration of ventilation before randomisation: 5.3 days in NO group, 5.9 days in control group)</td>
<td>1-40 ppm (lowest effective dose); mean dose 9 (SD 8) ppm, until end point met (reversal of AR or severe respiratory failure), up to 30 days; mean 9 (SD 6) days</td>
<td>Usual care. Patients meeting severe respiratory failure criteria could receive NO (6/87 patients randomised to control received NO)</td>
</tr>
<tr>
<td>Lundin,*7 1999 (not for profit and industry supplied gas)</td>
<td>180 adults, 43 centres. Any CXR infiltrates, P/F ≤ 1 65 mm Hg, PEEP ≥ 25 cm H2O, mean airway pressure ≥ 10 cm H2O. Duration of ventilation 0.7-5 days. NO responder*</td>
<td>10 ppm for 72 hours, then weaned if failure criteria not met</td>
<td>Usual care. Patients meeting failure criteria could receive NO (27/55 patients randomised to control met failure criteria and 2 other patients withdrawn from control group; 29 patients likely received NO)</td>
</tr>
<tr>
<td>Payen,*8 1999 (not for profit; industry supplied gas)</td>
<td>203 adults, 23 centres. ACEC criteria for ARDS, lung injury score ≥ 2 after 24 hours of “therapeutic optimisation” (mean duration of ventilation before randomisation: 5.3 days in NO group, 5.9 days in control group)</td>
<td>10 ppm, until oxygenation and PEEP criteria met; median 5 days</td>
<td>Placebo gas (nitrogen). Patients meeting failure criteria crossed to other group (19/105 patients randomised to control and 12/98 patients randomised to NO crossed over)</td>
</tr>
<tr>
<td>Mehta,*9 2001 (not for profit and industry supplied gas)</td>
<td>14 adults, 1 centre. Bilateral CXR infiltrates, P/F ≤ 200 mm Hg, PEEP ≥ 8 cm H2O, PaO2 ≥ 18 mm Hg. Duration of ARDS ≤ 5 days</td>
<td>Dailytitrations (5, 10, 20 ppm every 30 min) for 4 days. Most received 5-10 ppm on day 2-4; continued until oxygenation criteria met; mean 8 (SD 9) days</td>
<td>Usual care. No crossovers</td>
</tr>
<tr>
<td>Gerlach,*10 2003 (not for profit)</td>
<td>40 adults, 1 centre. Bilateral CXR infiltrates, P/F ≤ 210 mm Hg, PEEP ≥ 10 cm H2O, PaO2 ≥ 18 mm Hg. Duration of ventilation ≥ 48 hours with FiO2 ≥ 0.6 (median duration of ventilation before randomisation: 14 days in NO group, 11.5 days in control group)</td>
<td>10 ppm (with daily dose response analysis) until weaning initiated</td>
<td>Usual care. No crossovers</td>
</tr>
<tr>
<td>Park,*11 2003 (not reported)</td>
<td>17 adults, 1 centre. ACEC criteria for ARDS. Duration of ARDS ≤ 2 days</td>
<td>5 ppm for mean 3.5 (SD 1.5) days (stopping criteria not reported). Patients also received one lung recruitment manoeuvre (same as control group). Third group (n=6) received NO 5 ppm alone for 8.2 (SD 4.7) days</td>
<td>One lung recruitment manoeuvre (inflation pressure of 30-35 cm H2O for 30 seconds). No crossovers</td>
</tr>
<tr>
<td>Taylor,*12 2004 (industry)</td>
<td>385 adults, 46 centres. ACEC criteria for ALI except P/F ≤ 250 mm Hg, 0.5×FiO2≥0.95 on PEEP ≥ 8 cm H2O. Duration of ALI ≤ 3 days</td>
<td>5 ppm for 28 days or until oxygenation and PEEP criteria met</td>
<td>Placebo gas (nitrogen). No crossovers</td>
</tr>
</tbody>
</table>

**Notes:**

ACEC = American-European Consensus Conference.†CXR = chest radiograph. LIS = lung injury score.‡Oxygenation index (100×mean airway pressure/[PaO2/FiO2]). PAOP = pulmonary artery occlusion pressure. PeEP = positive end expiratory pressure. P/F = partial pressure of inspired oxygen/PaO2/FiO2. OI = lung injury score.30

Funding refers to data collection and analysis and supply of study gas (where information available).

*Patients given NO 0, 2, 10, 40 ppm every 10 min and response defined as relative increase in PaO2 of 25% (n=140) or 20% (n=40). Responders were randomised.
authors’ definitions). Included trials compared nitric oxide with placebo or usual treatment (not prevention) for ALI or ARDS and reported mortality (at any time), duration of ventilation, ventilator-free days, or pulmonary physiological parameters on days one to four of treatment (\(\frac{\text{PaO}_2}{\text{FiO}_2}\) [partial pressure of oxygen]/[fraction of inspired oxygen]; oxygenation index, defined as 100 × mean airway pressure/\(\frac{\text{PaO}_2}{\text{FiO}_2}\)); mean pulmonary arterial pressure). We included trials with cointerventions applied equally in both groups. We assessed agreement between reviewers for trial eligibility using Cohen’s \(k\).

Data abstraction and validity assessment
Two reviewers independently abstracted data and methods from included trials. We resolved by consensus any disagreements that remained after contacting trial authors. From included studies we abstracted method of randomisation and allocation concealment, blinding of caregivers and outcomes assessors, and number of withdrawals after randomisation and determined whether mechanical ventilation, weaning, and sedation were standardised or applied equally in treatment groups.

We attempted to contact authors of all included trials to request additional data and clarify data and methods if necessary.

Quantitative data synthesis
Our primary outcome was mortality in hospital (or, if not available, mortality in the intensive care unit or at 28 or 30 days). We decided a priori to combine trials with less than half of patients crossing over from control to nitric oxide arms in analyses of clinical outcomes. Our analyses adhered to the intention to treat principle. In studies with two or more nitric oxide groups receiving different doses, we combined data to determine an overall effect for the nitric oxide group.

Secondary outcomes included duration of ventilation, ventilator-free days to 28 or 30 days, and pulmonary physiology. We decided post hoc to combine data on renal dysfunction after obtaining outcomes for most randomised patients, but we describe other adverse events qualitatively.

### Table 2 Scientific quality of trials of inhaled nitric oxide (NO) in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)*

<table>
<thead>
<tr>
<th>Author</th>
<th>Allocation concealment</th>
<th>Blinding</th>
<th>Ventilation</th>
<th>Other cointerventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day, 1997</td>
<td>Blinded draw of 1 lot per eligible patient</td>
<td>None</td>
<td>Clinician discretion</td>
<td>Not described</td>
</tr>
<tr>
<td>Schwebel, 1997</td>
<td>Table of gas cylinder codes (revealed in sequence)</td>
<td>Clinicians, outcomes assessors</td>
<td>Protocol (no details) for 17 hours; clinician’s discretion thereafter</td>
<td>Not described</td>
</tr>
<tr>
<td>Dellinger, 1998</td>
<td>Sealed, opaque envelopes</td>
<td>Clinicians, outcomes assessors</td>
<td>Guideline (Pplat35 cm H2O; PEEP to optimise compliance; FiO2 minimised)</td>
<td>More patients in NO group received corticosteroids after day 6 (20/112 v 6/57)</td>
</tr>
<tr>
<td>Michael, 1998</td>
<td>Not reported</td>
<td>None</td>
<td>Clinician discretion</td>
<td>Mode unchanged for 72 hours; mean PEEP similar between groups for 72 hours</td>
</tr>
<tr>
<td>Troncy, 1998</td>
<td>Envelopes‡</td>
<td>None</td>
<td>Protocol ((V_t) 10 ml/kg and goal PaCO2 35-45 mm Hg; maximum PEEP 15 cm H2O and goal PaO2 65 mm Hg)</td>
<td>Sedation, blood transfusion, and nutrition protocols. No prone ventilation in any patient</td>
</tr>
<tr>
<td>Dobyns, 1999</td>
<td>Envelopes‡</td>
<td>Clinicians, outcomes assessors</td>
<td>Guideline (‘open lung approach’ with Ppk ≤ 40 cm H2O, (V_t) limitation, titrated PEEP; HFOV by clinician discretion)</td>
<td>Not described</td>
</tr>
<tr>
<td>Lundin, 1999</td>
<td>Central</td>
<td>None</td>
<td>Clinician discretion</td>
<td>Not described</td>
</tr>
<tr>
<td>Payen, 1999</td>
<td>Central</td>
<td>Clinicians, outcomes assessors</td>
<td>Guideline before randomisation; unclear if applied afterwards ((V_t), Pplat, Ppk limitation; various recruitment strategies)</td>
<td>Not described</td>
</tr>
<tr>
<td>Mehta, 2001</td>
<td>No§</td>
<td>None</td>
<td>Clinician discretion</td>
<td>No prone ventilation in any patient</td>
</tr>
<tr>
<td>Gellach, 2003</td>
<td>Envelopes‡</td>
<td>None</td>
<td>Protocol (no details)</td>
<td>Protocol for prone ventilation and extracorporeal membrane oxygenation</td>
</tr>
<tr>
<td>Park, 2003</td>
<td>One random number generated when patient eligible</td>
<td>None</td>
<td>Protocol ((V_t) 6 ml/kg; Pplat ≤ 30 cm H2O; PEEP to optimise PaO2; FiO2 minimised)</td>
<td>Weaning protocol. No prone ventilation in any patient</td>
</tr>
<tr>
<td>Taylor, 2004</td>
<td>Central</td>
<td>Clinicians, outcomes assessors</td>
<td>Guideline (Pplat ≤ 35 cm H2O; PEEP to optimise compliance; FiO2 minimised)</td>
<td>Prone ventilation similar (NO: 10/192 and control: 14/193), weaning protocol</td>
</tr>
</tbody>
</table>

\(\text{FiO}_2\)=fraction of inspired oxygen; \(\text{HFOV}\)=high frequency oscillatory ventilation; \(\text{PaO}_2\)=partial pressure of arterial oxygen; \(\text{PaCO}_2\)=partial pressure of arterial carbon dioxide, \(\text{Pplat}\)=plateau airway pressure; \(\text{Ppk}\)=peak airway pressure; \(\text{PEEP}\)=positive end expiratory pressure; \(\text{V}_{\text{r}}\)=tidal volume.

\(\text{‡Unblinded investigator at each site.}
\text{‡Envelopes sealed, sequentially numbered, and opaque.}
\text{§Computer generated random numbers. Investigator had access to entire randomisation list at time of randomisation.}

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We used random effects models\(^{20}\) implemented in Review Manager 4.2.7 (Cochrane Collaboration, Oxford) for all analyses and considered P≤0.05 (two sided) as significant. We report binary outcomes as risk ratios and continuous outcomes as weighted mean differences (measure of absolute change) and ratios of means (measure of relative change).\(^{21}\) Summary effect estimates are presented with 95% confidence intervals.

We assessed homogeneity between studies for each outcome using the Cochrane Q statistic,\(^{22}\) with P≤0.10 indicating significant heterogeneity,\(^{23}\) and I\(^2\)=0\(^{24}\)\(^{25}\) with suggested thresholds for low (25%-49%), moderate (50%-74%), and high (>75%) values. We developed several a priori hypotheses to explain significant heterogeneity (excluding duration of ventilation and ventilator-free days), including dose and duration of nitric oxide therapy and whether therapy was restricted to patients whose oxygenation improved acutely (“nitric oxide responders”) or to those with ARDS (the more hypoxaemic subset of ALI).

**RESULTS**

**Trial flow**

Electronic database searches yielded 1262 citations. After evaluating these citations, conference abstracts, review articles, and bibliographies of included trials, we included 12 parallel group randomised controlled trials\(^{1-12}\) (fig 1). The two reviewers completely agreed (k=1) on the selection of included studies. We obtained additional information from 10 authors (new clinical\(^{1,2,4,7-9,11,12}\) or physiological data\(^{1,2,4,7-9,11,12}\), clarifications of data\(^{6,9}\) or methods\(^{1,4,7-9,11,12}\)).

**Study characteristics and methodological quality**

Table 1 describes the included studies, two of which were published as abstracts only.\(^{4,7-9,12}\) Data from one trial were distributed in two abstracts\(^{4,7,12}\) and data from another trial were distributed in two articles.\(^{10,11}\) Trials randomised 1237 patients (median 40; range 14-385) with ALI or ARDS. Two trials enrolled only children,\(^{1,4}\) one trial included a few children,\(^{10}\) and the remaining trials enrolled only adults. All patients met American-European Consensus Conference oxygenation criteria for ARDS except for one trial that included some patients with ALI.\(^{12}\) Seven trials used a fixed dose of nitric oxide (median 10 ppm; range 5-10 ppm),\(^{1,2,4,7,8,10,12}\) and five used the lowest dose to achieve an oxygenation response\(^{4,7,8,10}\) or randomised patients to different doses.\(^{8,12}\) One trial enrolled only patients whose oxygenation improved after a nitric oxide challenge (“nitric oxide responders”),\(^{9}\) and one used a cointervention (a recruitment manoeuvre) in both groups.\(^{11}\) Trials continued nitric oxide until prespecified gas exchange end points,\(^{4,7,8,10,12}\) or for a fixed period of time after which nitric oxide was tapered by using gas exchange criteria\(^{4,7,8,10}\) or managed at clinicians’ discretion.\(^{8}\) One trial did not report on criteria for stopping nitric oxide.\(^{11}\) The median duration of administration was 6.5 days (range 3.5-9.0 days; data available from five trials\(^{4,7-9,11}\)). One trial randomised patients to nitric oxide or control for 24 hours, after which all patients received nitric oxide.\(^{11}\) In five other trials, control patients received nitric oxide as rescue therapy after randomisation if they met prespecified criteria (<50% of controls in three trials\(^{4,7,8}\) and ≥50% in two trials\(^{8,10}\)). Not for profit agencies funded five trials\(^{1,4,7,8,10}\) industry funded two trials\(^{8,12}\) both sources funded or supported four trials\(^{7,8,10,11}\) and one trial did not report this information.\(^{11}\)

The 12 trials had good scientific quality (table 2). Ten concealed randomisation\(^{1,4,7-10,12}\) Mechanical ventilation was delivered according to protocol in three unblinded trials\(^{5,7,10}\) and one blinded trial\(^{12}\) and according to guidelines in three blinded trials\(^{7,8,12}\). Six trials described or standardised at least one other cointervention, such as corticosteroids,\(^{7}\) sedation,\(^{7}\) prone ventilation,\(^{7,8,10,12}\) and ventilator weaning.\(^{7,8,12}\) All trials had complete follow-up, analysed patients by assigned group, and withdrew no one from clinical outcomes analyses. One trial stopped early because of slow enrolment (achieving 45% of the planned sample size\(^7\)), and another trial enrolled 75% of the planned sample, for unclear reasons.\(^{12}\)

---

**Table 1**

<table>
<thead>
<tr>
<th>Study</th>
<th>Nitrates</th>
<th>Controls</th>
<th>Risk ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dellinger(^5)</td>
<td>35/120</td>
<td>17/57</td>
<td>11.2 (0.98 to 1.59)</td>
<td>6.8</td>
<td>1.22 (0.65 to 2.29)</td>
</tr>
<tr>
<td>Michael(^6)</td>
<td>12/30</td>
<td>3/9</td>
<td>6.8</td>
<td>6.7</td>
<td>1.13 (0.60 to 2.11)</td>
</tr>
<tr>
<td>Troncy(^7)</td>
<td>9/15</td>
<td>8/15</td>
<td>22.5 (1.10 to 1.55)</td>
<td>30.3</td>
<td>1.12 (0.83 to 1.50)</td>
</tr>
<tr>
<td>Lundin(^8)</td>
<td>41/93</td>
<td>35/87</td>
<td>1.5 (0.40 to 5.65)</td>
<td>1.4</td>
<td>0.75 (0.19 to 2.93)</td>
</tr>
<tr>
<td>Payen(^9)</td>
<td>4/8</td>
<td>2/6</td>
<td>1.4</td>
<td>1.4</td>
<td>1.09 (0.28 to 4.32)</td>
</tr>
<tr>
<td>Mehta(^10)</td>
<td>3/20</td>
<td>4/20</td>
<td>18.2 (0.77 to 1.66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gerlach(^11)</td>
<td>4/11</td>
<td>2/6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taylor(^12)</td>
<td>4/410</td>
<td>39/192</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>577/509</td>
<td>39/193</td>
<td></td>
<td>100.0</td>
<td>1.10 (0.94 to 1.30)</td>
</tr>
</tbody>
</table>

---

**Fig 2** Effect of nitric oxide on mortality. Weight is the relative contribution of each study to the overall estimate of treatment effect on a log scale assuming a random effects model. Two trials with ≥50% of control patients crossing over to nitric oxide also reported mortality data.\(^4,6\) Inclusion of these trials did not alter summary mortality estimate (risk ratio 1.09, 0.94 to 1.27).
Table 3 | Effects of inhaled nitric oxide (NO) on clinical and physiological outcomes in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No of trials (patients)</th>
<th>Treatment effect (95% CI); P value</th>
<th>P value for homogeneity; I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality*</td>
<td>9 (1086)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Duration of ventilation (days)</td>
<td>3 (237)</td>
<td>1.17 (0.80 to 1.70); 0.41</td>
<td>3.6 (~4.0 to 11.1); 0.36</td>
</tr>
<tr>
<td>Ventilator-free days†</td>
<td>5 (804)</td>
<td>0.94 (0.84 to 1.06); 0.33</td>
<td>-0.6 (~1.8 to 0.7); 0.37</td>
</tr>
<tr>
<td>PaO2/FiO2 (mm Hg);</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>5 (416)</td>
<td>1.05 (0.98 to 1.13); 0.17</td>
<td>7 (~4 to 18); 0.21</td>
</tr>
<tr>
<td>Day 3</td>
<td>5 (450)</td>
<td>1.07 (1.02 to 1.12); 0.01</td>
<td>15 (4 to 25); 0.009</td>
</tr>
<tr>
<td>Day 4</td>
<td>4 (334)</td>
<td>0.85 (0.76 to 0.96); 0.02</td>
<td>—</td>
</tr>
<tr>
<td>Oxygenation index (100)*mean airway pressure/(PaO2/FiO2) (cm H2O/mm Hg);</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>3 (296)</td>
<td>0.86 (0.75 to 0.98); 0.02</td>
<td>-3 (~5 to ~0.5); 0.02</td>
</tr>
<tr>
<td>Day 2</td>
<td>1 (164)</td>
<td>0.81 (0.67 to 0.98); 0.03</td>
<td>-3 (~6 to ~0.04); 0.05*</td>
</tr>
<tr>
<td>Day 3</td>
<td>2 (245)</td>
<td>0.82 (0.64 to 1.06); 0.13</td>
<td>-3 (~7 to ~0.2); 0.04</td>
</tr>
<tr>
<td>Day 4</td>
<td>1 (134)</td>
<td>0.78 (0.63 to 0.96); 0.02</td>
<td>-4 (~8 to ~0.3); 0.03*</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mm Hg);</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>4 (165)</td>
<td>0.95 (0.88 to 1.03); 0.24</td>
<td>-2 (~4 to 1); 0.22</td>
</tr>
<tr>
<td>Day 2</td>
<td>3 (167)</td>
<td>0.96 (0.89 to 1.02); 0.19</td>
<td>-1 (~3 to 0.6); 0.18</td>
</tr>
<tr>
<td>Day 3</td>
<td>2 (111)</td>
<td>0.94 (0.87 to 1.02); 0.12</td>
<td>-2 (~4 to 0.5); 0.12</td>
</tr>
<tr>
<td>Day 4</td>
<td>3 (130)</td>
<td>0.94 (0.88 to 1.01); 0.08</td>
<td>-2 (~4 to 0.3); 0.10</td>
</tr>
<tr>
<td>Renal dysfunction§</td>
<td>4 (895)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

PaO2/FiO2, partial pressure of arterial oxygen/fraction of inspired oxygen, ratio of means; nitric oxide relative to control. We used random effects models for all analyses and assessed heterogeneity using Cochran’s Q test.19 (P value for homogeneity shown) and I².20

*P value for homogeneity shown. Two trials with ≥50% of control patients crossing over to NO also reported mortality data.21-24 Inclusion of these trials did not alter summary mortality estimate (risk ratio 1.09, 0.94 to 1.27).

†Combined trials reporting ventilator-free days to day 28 and day 30.

‡Mean difference because only one trial contributed data.

§Risk ratio 1.10 (0.94 to 1.30); P=0.23; homogeneity P=1.00, I²=0%. Two trials with ≥50% of control patients crossing over to NO also reported mortality data.21-24 Inclusion of these trials did not alter summary mortality estimate (risk ratio 1.09, 0.94 to 1.27).

Data synthesis
Effect of nitric oxide on clinical outcomes
We combined nine trials3-5,7-12 in the mortality analysis (three were placebo controlled3-5,7,12; five used “usual care” controls3-5,7,9-11; one used recruitment manoeuvres in both arms11). We combined three trials that reported duration of ventilation (including all patients11 or only survivors7) and five trials reporting ventilator-free days.

Meta-analyses (table 3) showed that nitric oxide did not affect mortality (risk ratio 1.10; 95% confidence interval 0.94 to 1.30; fig 2), duration of ventilation (17% increase, −20% to 70%; 3.6 additional days, −4.0 to 11.1 days), or ventilator-free days (0% decrease, −16% to 6%; 0.6 fewer days, −1.8 to 0.7 days). There was moderate to high heterogeneity between studies for duration of ventilation only.

A funnel plot of standard error versus risk ratio for mortality did not suggest publication bias (fig 3).

Effect of nitric oxide on physiological outcomes
On the first day of therapy, NO was associated with small improvements in the PaO2/FiO2 ratio (nine trials; 13% higher, 4% to 23%; 16 mm Hg higher, 4 mm Hg to 27 mm Hg; fig 4) and oxygenation index (three trials; 14% lower, 2% to 25%; 3 cm H2O/mm Hg lower, 0.5 cm H2O/mm Hg to 5 cm H2O/mm Hg; fig 5). Some evidence suggested that improvements in oxyhemoglobin in the nitric oxide group persisted beyond day one. The PaO2/FiO2 ratio was higher on day two and four (but not on day three, and only in the ratio of means analysis on day two). The oxygenation index remained lower on days two, three, and four (only in the weighted mean difference analysis on day three), but only one trial3 (days two and four) or two trials5,12 (day three) trials contributed data. Differences in mean pulmonary arterial pressure were not significant on any day.

There was no evidence of important statistical heterogeneity in the physiological outcomes.

Adverse effects
Table 4 gives details of adverse effects. All 12 trials gave information about methaemoglobin concentrations. Four nitric oxide patients (of 651 randomised) and three control patients (of 586 randomised) developed >5% methaemoglobinemia.5,7,12 One trial reported three patients developing raised nitrogen dioxide concentrations; all had received 80 ppm nitric oxide.22 Nitric oxide increased the risk of renal dysfunction in one unblinded5,12 and three blinded5,7,12 trials that enrolled 72% of patients in all included trials (risk ratio 1.50, 1.11 to 2.02; fig 6). Other adverse events were variably reported, and we did not combine these data.
**DISCUSSION**

The routine use of inhaled nitric oxide is not beneficial for patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Our meta-analysis included 12 trials that randomly assigned 1237 patients and investigated the effects of inhaled nitric oxide in such patients. We found no benefit of nitric oxide on survival and an increased risk of renal dysfunction. Oxygenation improved over the first 24 hours (13% relative increase in PaO2/FiO2 ratio; 14% decrease in oxygenation index), with some data suggesting improvements to 96 hours. Given the limited physiological improvements and possible harm, we cannot recommend routine use of nitric oxide in these patients.

The trend towards increased mortality in patients receiving nitric oxide was highly consistent across trials, with no trial dominating the meta-analysis. Given the strength and magnitude of this trend, consistency across trials, biological plausibility, and the finding of other potential adverse effects of nitric oxide (for example, renal failure), our analysis raises concerns about its nitric oxide in this setting.

**Adverse events**

Descriptive analyses suggest that methemoglobinemia and raised nitrogen dioxide concentration are not common or clinically important consequences, except possibly in patients receiving high doses (at least 80 ppm) of nitric oxide for several days. Data from four large trials representing nearly three quarters of all randomised patients showed an increased risk of renal dysfunction in patients receiving nitric oxide. Cautious interpretation is warranted, however, as this result was a post hoc analysis and is potentially subject to publication bias (we were unable to obtain explicit data on renal outcomes in eight of 12 smaller trials, in which this relation may not have been measured or observed). In addition, the potential physiological mechanisms linking administration of inhaled nitric oxide to acute renal dysfunction—inhbition of mitochondrial and enzymatic function and damage to deoxyribonucleic acid and membranes—are controversial because of its simultaneous protective effects on renal blood flow and leukocyte adhesion.

**Why nitric oxide may not be beneficial**

There are several possible explanations for the lack of benefit of routine administration of nitric oxide in patients with ALI/ARDS. Firstly, short term physiological improvements in oxygenation seem to have no impact on patients’ survival, possibly because oxygenation is not necessarily related to severity of lung injury. Secondly, as most patients with ARDS die of multiple organ failure rather than refractory hypoxaemia, small changes in oxygenation might not lead to improvements in outcome. Thirdly, the prolonged fixed dosing regimen in most trials may have attenuated benefit over time because of increased sensitisation, dampening the oxygenation benefit while continuing to expose patients to toxic effects such as oxidative damage. Fourthly, the benefits of nitric oxide may have been overwhelmed by a harmful mechanical ventilation strategy, which perpetuated multiple organ failure. This, however, would not account for our finding of potential harm. Finally, trials restricting enrolment to patients with an acute oxygenation response to nitric oxide may have found a positive effect on mortality, although this hypothesis was not supported in one trial.

**Strengths and limitations**

We used several methods to reduce bias (comprehensive literature search, duplicate data abstraction, pre-specified criteria for methodological assessment and analysis) and analysed a comprehensive set of clinical and physiological outcomes. We were unable to obtain any additional information from three trials. Considering secondary clinical outcomes, we expected to find variation between trials in duration of ventilation and ventilator-free days related to different populations of patients. We analysed these outcomes, while acknowledging the limited interpretability of this analysis. Finally, given the small number of trials contributing to analyses of
Table 4 | Adverse effects of inhaled nitric oxide

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Methaemoglobin and nitrogen dioxide concentrations</th>
<th>Other adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day, 1997</td>
<td>No known raised concentrations</td>
<td>None</td>
</tr>
<tr>
<td>Schwefel, 1997</td>
<td>No methaemoglobinemia</td>
<td>None</td>
</tr>
<tr>
<td>Dellinger, 1998</td>
<td>Methaemoglobin concentration ≥5% (none ≥7%): NO 2.5% (3/120; 40 ppm, n=1; 80 ppm, n=2); control 2% (1/57); nitrogen dioxide level &gt;3 ppm: NO 2.5% (3/120; all received 80 ppm); control: none</td>
<td>Renal function (&quot;defined by adverse events&quot;): NO 11% (13/120), control 9% (5/57); creatinine ≥177 µmol/l: NO 17% (20/120), control 13% (7/57); Adverse events &quot;possibly&quot; related to study gas: NO 3% (4/120: myopathy; agitation; abnormal liver enzymes; apnoea, lung haemorrhage, coagulopathy; renal dysfunction), control 2% (1/57; hypertension). All adverse events: no significant differences</td>
</tr>
<tr>
<td>Michael, 1998</td>
<td>No methaemoglobinemia</td>
<td>None</td>
</tr>
<tr>
<td>Troncy, 1998</td>
<td>No methaemoglobinemia</td>
<td>None</td>
</tr>
<tr>
<td>Dobyns, 1999</td>
<td>Methaemoglobin concentration ≤5%: none; nitrogen dioxide concentration ≥2 ppm: none</td>
<td>No difference in &quot;intensive care unit-dependent therapies&quot;</td>
</tr>
<tr>
<td>Lundin, 1999</td>
<td>Methaemoglobin concentration ≥5%: NO 1% (1/93), control 1% (1/87); median methaemoglobin concentrations over 30 days: NO 0.5%-1.2%, control 0.2%-1.0% (&quot;overall lower&quot; than in NO group)</td>
<td>Adverse events related to study gas: NO 1% (1/93; gastrointestinal bleeding), control 2% (2/87; coagulopathy, intracranial bleed). Renal function (&quot;abnormal&quot;): NO 13% (12/93), control 5% (4/87). Renal replacement (incident cases): NO 27% (23/84), control 13% (10/79); risk ratio 2.16, 1.10 to 4.25. Creatinine ≥309 µmol/l without renal replacement (incident cases): NO 6% (5/80), control 3% (2/74). Other serious adverse events more common in NO group: circulatory failure: NO 31% (29/93), control 20% (17/87); encephalopathy: NO 3% (3/93), control none; sepsis: NO 8% (7/93), control, 3% (3/87). Other adverse events: no difference in incidence of raised total bilirubin, pneumothorax, or platelet, bleeding or clotting disorders or haemodynamic failure (definitions of haemodynamic v circulatory failure not given)</td>
</tr>
<tr>
<td>Payen, 1999</td>
<td>Methaemoglobin concentrations reported as always acceptable and not different between groups</td>
<td>Renal replacement (incident cases): NO 37% (33/89), control 29% (26/90); risk ratio 1.28, 0.84 to 1.96. Bleeding: NO 6% (6/105), control 3% (3/98)</td>
</tr>
<tr>
<td>Mehta, 2001</td>
<td>Methaemoglobin concentration ≥5%: none (concentration in 1/8 NO patients was 3.8% before therapy); nitrogen dioxide concentration ≥2 ppm: none</td>
<td>None</td>
</tr>
<tr>
<td>Gerlach, 2003</td>
<td>No methaemoglobinemia; no patients with increased nitrogen dioxide concentrations</td>
<td>None</td>
</tr>
<tr>
<td>Park, 2003</td>
<td>No methaemoglobinemia</td>
<td>None</td>
</tr>
<tr>
<td>Taylor, 2004</td>
<td>Methaemoglobin concentration ≥5%: NO 0/192, control 0.005% (1/193); nitrogen dioxide concentration ≥2 ppm: none</td>
<td>All adverse events: no difference (NO, 630 events; control, 666 events). No difference in cardiovascular, gastrointestinal, endocrine, haematological, metabolic and nutritional, and neurological adverse events. Adverse events with different frequencies. Infections: NO 66 infections, control 41 infections. Respiratory: NO 51% (98/192), control 61% (118/193); pneumonia, pneumothorax, apnoea more common in control group. Renal function: creatinine ≥265 µmol/l: NO 6% (12/192), control 4% (8/193); creatinine ≥309 µmol/l: NO 5% (10/192), control 3% (6/193)</td>
</tr>
</tbody>
</table>

Fig 6 | Effect of nitric oxide on renal dysfunction (defined as new renal replacement therapy, new renal replacement therapy or new raised creatinine concentration ≥300 µmol/l), or raised creatinine concentration ≥177 µmol/l or ≥265 µmol/l). The denominator includes only patients without baseline renal dysfunction; except possibly for one trial." Use of a different definition of renal dysfunction ("adverse event") in one trial did not alter the summary estimate (risk ratio 1.49, 1.10 to 2.03). Weight is the relative contribution of each study to overall estimate of treatment effect on log scale assuming a random effects model trials mitigates this possibility. The included trials did not specifically study the issue of nitric oxide as rescue therapy for patients with critically low oxygenation. With nitric oxide, short term improved oxygenation in these patients may create a window for other strategies to improve lung function, such as treatment of the underlying cause of ARDS.

Previous research

A previous systematic review and meta-analysis of inhaled nitric oxide for acute hypoxaemic respiratory failure included fewer randomised controlled trials and found no effect on mortality (risk ratio 0.98, 95% confidence interval 0.66 to 1.44; two trials, 204 patients). Our report is consistent with this work and extends it by including more trials, thus narrowing the confidence limits around the estimate of mortality. We also provide new estimates of the impact of nitric oxide on other clinical and physiological end points and raise the possibility of harm induced by nitric oxide.

In conclusion, our systematic review and meta-analysis found that inhaled nitric oxide improved oxygenation in patients with ALI and ARDS at 24 hours of
WHAT IS ALREADY KNOWN ON THIS TOPIC

Inhaled nitric oxide continues to be used to improve oxygenation in patients with acute lung injury, despite no clear supporting evidence

A previous meta-analysis in 2003 included five randomised trials of nitric oxide; there are now 12 trials

WHAT THIS STUDY ADDS

Nitric oxide improves oxygenation temporarily but does not improve survival and may cause harm

We do not recommend routine use of nitric oxide in patients with acute lung injury
Interventions to improve water quality for preventing diarrhoea: systematic review and meta-analysis

Thomas Clasen, lecturer,1 Wolf-Peter Schmidt, clinical research fellow,1 Tamer Rabie, public health specialist,3 Ian Roberts, professor of epidemiology,2 Sandy Cairncross, professor of environmental health1

ABSTRACT
Objective To assess the effectiveness of interventions to improve the microbial quality of drinking water for preventing diarrhoea.
Design Systematic review.
Data sources Cochrane Infectious Diseases Group’s trials register, CENTRAL, Medline, Embase, LILACS; hand searching; and correspondence with experts and relevant organisations.
Study selection Randomised and quasirandomised controlled trials of interventions to improve the microbial quality of drinking water for preventing diarrhoea in adults and in children in settings with endemic disease.
Data extraction Allocation concealment, blinding, losses to follow-up, type of intervention, outcome measures, and measures of effect. Pooled effect estimates were calculated within the appropriate subgroups.
Data synthesis 33 reports from 21 countries documenting 42 comparisons were included. Variations in design, setting, and type and point of intervention, and variations in defining, assessing, calculating, and reporting outcomes limited the comparability of study results and pooling of results by meta-analysis. In general, interventions to improve the microbial quality of drinking water are effective in preventing diarrhoea. Effectiveness did not depend on the presence of improved water supplies or sanitation in the study setting and was not enhanced by combining the intervention with instructions on basic hygiene, a water storage vessel, or improved sanitation or water supplies—other common environmental interventions intended to prevent diarrhoea.
Conclusion Interventions to improve water quality are generally effective for preventing diarrhoea in all ages and in under 5s. Significant heterogeneity among the trials suggests that the level of effectiveness may depend on a variety of conditions that research to date cannot fully explain.

INTRODUCTION
Diarrhoeal diseases kill an estimated 1.8 million people each year.1 In developing countries diarrhoea accounts for 17% of deaths among under 5s.2 For the 1.1 billion people who lack access to improved water supplies,3 and many more with contaminated water, diarrhoeal disease is highly endemic. Nevertheless, the effectiveness of interventions aimed at improving the quality of drinking water has been questioned.4-6 Because people can become infected with organisms that cause diarrhoea through multiple pathways, water quality alone may not interrupt transmission.7 Even in developed countries with improved water supplies, diarrhoea is often endemic.8,9

Previous reviews of environmental interventions to prevent diarrhoeal disease reported a 15% to 17% median reduction in diarrhoea from water quality interventions.10-11 All included studies concerned improvements at the water source or collection point (protected wells, boreholes, communal tap stands) and none at the household level or other points of use. Recent studies have drawn attention to the potential role of interventions at the household level to reduce the occurrence of diarrhoea.12-14 Such interventions might minimise recontamination in the home, a well known cause of water quality degradation.15

We report updated results of a systematic review undertaken with the Cochrane Collaboration on the effectiveness of interventions to improve the microbial quality of drinking water for preventing endemic diarrhoea.16

METHODS
We searched for all randomised and quasirandomised controlled trials of interventions to improve water quality for the prevention of diarrhoeal disease, regardless of language, publication status, or date of study. Participants were adults or children in settings with endemic diarrhoeal disease—that is, regularly present in the population. We excluded interventions in response to epidemic diarrhoea. Interventions included any measure to improve the microbial quality of drinking water. The primary outcome was diarrhoea related morbidity.

We searched the specialised register of the Cochrane Infectious Diseases Group, CENTRAL, Medline, Embase, and LILACS to December 2005. We hand searched conference proceedings, contacted researchers and organisations working in the specialty, and checked the references of identified studies. Two reviewers independently examined the electronic records for potentially eligible studies and examined
the full text of potentially eligible reports. Disagreements were resolved by a third reviewer.

Data extraction: measure of effect and methodological quality
Two reviewers independently extracted data. Measures of effects reported were risk ratios, rate ratios, odds ratios, and longitudinal prevalence ratios (number of days or weeks with diarrhea divided by number of days or weeks under observation in a person). As many of the trials were cluster randomised and had data taken into account in the data analysis (sometimes adjusting for covariates) we could not use the reported data to recalculate a common measure and yet preserve such adjustments. We therefore present the results separately according to the reported measures of effect.

For randomised controlled trials we extracted data on the methods used to generate the allocation sequence, allocation concealment, blinding of outcome assessment, and inclusion or losses to follow-up on the basis of criteria developed by Juni.17 For quasi-randomised controlled trials we assessed the comparability of intervention and control groups at baseline for water quality, diarrhoeal morbidity, age, socioeconomic status, access to water, hygiene practices, and sanitation facilities, and whether data collection for intervention and control groups was contemporaneous.

Data analysis and synthesis
We used a random effects inverse variance method on the log scale to calculate pooled estimates,18 and displayed the results graphically using forest plots and statistically by using the χ2 test with a 10% level of statistical significance19 and the I2 test for heterogeneity.20 Factors specified a priori in the study protocol as potential explanations for observed heterogeneity were age (all ages ≥5 years), point of intervention (water source or household), type of intervention (water quality only or compound interventions: including hygiene messages, improved sanitation, improved supply), compliance (<50% or ≥50%), and effectiveness under various conditions for water supply, sanitation, and water access (using global assessment definitions from the joint World Health Organization and United Nations Children’s Fund).3 We included all intervention arms in the meta-analysis even for trials in which two or more intervention arms were compared against one control, but identify this as a potential methodological flaw in the pooled estimates of effect.

RESULTS
The combined search strategies identified 976 potentially relevant studies of interventions to improve water quality for preventing diarrhoea. The full text of 68 potentially eligible reports was obtained for further assessment after screening of titles and abstracts. Of these 68 reports, 33 with 42 controlled comparisons met the inclusion criteria (fig 1).6-11,25 The meta-analysis includes three new studies not in the original review.6-8,29 Six studies included two or more intervention arms.

The 33 studies (22 randomised controlled trials, 11 quasi-randomised controlled trials) included about 55 650 participants (table 1). Eighteen studies presented results for participants of all ages, 10 included only under 5 years or a subgroup thereof, and the remainder reported on both age groups. In most trials the household was the unit of randomisation, although some randomised neighbourhoods, clusters of households, or villages. Trials of interventions at the water source (mainly the quasi-randomised controlled trials) were generally longer (median 36 months, range 12 to 60 months) than those of household interventions (median 7 months, range 9.5 weeks to 12 months). All but two trials from the United States8-9 were carried out in developing countries. Two trials took place in urban settings, two in peri-urban settings, three in urban informal or squatter settlements, two in refugee camps, one in multiple settings, and the others in rural settings.

Interventions
The interventions to improve drinking water quality were undertaken at the level of either the water source (seven trials) or the household (35 trials). Water source interventions included protected wells, bore holes, or distribution to public tap stands; none included piped in (reticulated) household connections. Household interventions comprised improved water storage (one trial) or one of four approaches for treating water in the home: chlorination (16 trials), solar disinfection (three trials), filtration (eight trials), or combined flocculation and disinfection (seven trials). Apart from solar disinfection and flocculation-disinfection using a water purifying product (PUR sachet; Procter and Gamble), there were potentially important differences in the types of interventions. For example, filtration interventions varied by filter medium and pore size, and chlorination varied by chlorine source, dose, and contact time.

Improvements in water quality were often accompanied by other environmental interventions intended to
Table 1 | Details of included studies on interventions to improve microbial quality of drinking water for preventing diarrhoea

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and setting (duration)</th>
<th>No of participants (age)</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alam 1989&lt;sup&gt;1&lt;/sup&gt;</td>
<td>QRCT among five political subunits of a village in rural Bangladesh (3 years)</td>
<td>623 (6-23 months)</td>
<td>Improved water supply and hygiene education</td>
</tr>
<tr>
<td>Austin 1993&lt;sup&gt;2&lt;/sup&gt;</td>
<td>RCT among 22 rural villages (11 intervention, 11 control) in Gambia; unit of randomisation was village (20 weeks)</td>
<td>231 (18-35 years)</td>
<td>Sodium hypochlorite solution used at household level</td>
</tr>
<tr>
<td>Aziz 1990&lt;sup&gt;3&lt;/sup&gt;</td>
<td>QRCT among two villages in rural Bangladesh (3 years)</td>
<td>About 9600 (all ages)</td>
<td>Improved water supply, sanitation, and hygiene education</td>
</tr>
<tr>
<td>Chiller 2005&lt;sup&gt;4&lt;/sup&gt;</td>
<td>RCT in 42 neighbourhood clusters in 12 rural villages in Guatemala (13 weeks)</td>
<td>3401 (all ages)</td>
<td>Flocculant-disinfectant sachets used at household level and hygiene education</td>
</tr>
<tr>
<td>Clasen 2004&lt;sup&gt;5&lt;/sup&gt;</td>
<td>RCT in rural Bolivian community (6 months)</td>
<td>280 (all ages)</td>
<td>Household gravity water filter system using imported ceramic filter elements</td>
</tr>
<tr>
<td>Clasen 2006&lt;sup&gt;6&lt;/sup&gt;</td>
<td>RCT in rural Bolivian community (5 months)</td>
<td>324 (all ages)</td>
<td></td>
</tr>
<tr>
<td>Clasen 2005&lt;sup&gt;7&lt;/sup&gt;</td>
<td>RCT among three villages in conflict affected rural Colombia (6 months)</td>
<td>680 (all ages)</td>
<td></td>
</tr>
<tr>
<td>Colford 2005&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Crossover triple blinded RCT in urban USA (12 months)</td>
<td>1296 (all ages)</td>
<td>Household reverse osmosis filters</td>
</tr>
<tr>
<td>Conroy 1999&lt;sup&gt;w10&lt;/sup&gt;</td>
<td>RCT among Maasai in rural Kenya (12 weeks)</td>
<td>206 (5-16 years)</td>
<td>Solar disinfection in plastic bottles at household level</td>
</tr>
<tr>
<td>Conroy 1999&lt;sup&gt;9&lt;/sup&gt;</td>
<td>RCT among Maasai in rural Kenya (1 year)</td>
<td>349 (under 6s)</td>
<td>Solar disinfection in plastic bottles at household level</td>
</tr>
<tr>
<td>Crump 2005&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Cluster randomised, RCT among rural 49 villages in western Kenya (20 weeks)</td>
<td>6650 (all ages)</td>
<td>Intervention 1, hygiene education and sodium hypochlorite used at household level; intervention 2, hygiene and flocculant-disinfectant sachets used at household level</td>
</tr>
<tr>
<td>Doocy 2006&lt;sup&gt;13&lt;/sup&gt;</td>
<td>RCT in Liberian camp for displaced people (12 weeks)</td>
<td>2191 (all ages)</td>
<td>Flocculant-disinfectant sachets used at household level and water storage vessel</td>
</tr>
<tr>
<td>Du Preez 2004&lt;sup&gt;14&lt;/sup&gt;</td>
<td>RCT in rural South Africa and Zimbabwe (6 months)</td>
<td>115 (under 5s)</td>
<td>Household commercial ceramic filter using imported components</td>
</tr>
<tr>
<td>Garrett 2004&lt;sup&gt;15&lt;/sup&gt;</td>
<td>QRCT in rural Kenya (not stated)</td>
<td>960 (under 5s)</td>
<td>Household chlorination using sodium hypochlorite solution; improved water supply; sanitation; hygiene education; and improved storage</td>
</tr>
<tr>
<td>Gasana 2002&lt;sup&gt;16&lt;/sup&gt;</td>
<td>QRCT in rural Rwanda (1 year)</td>
<td>150 (under 5s)</td>
<td>Improved source (pipes to stand post, sedimentation tank, ceramic filter, storage tank, and communal tap)</td>
</tr>
<tr>
<td>Handzel 1998&lt;sup&gt;17&lt;/sup&gt;</td>
<td>RCT in informal settlement in urban Bangladesh (8 months)</td>
<td>447 (3 to 60 months)</td>
<td>Household chlorination using sodium hypochlorite solution, special storage vessel, and hygiene instruction</td>
</tr>
<tr>
<td>Jensen 2003&lt;sup&gt;18&lt;/sup&gt;</td>
<td>QRCT among two villages in Pakistan (6 months)</td>
<td>226 (under 5s)</td>
<td>Village level chlorination of water supply using calcium hypochlorite</td>
</tr>
<tr>
<td>Kirchhoff 1985&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Blinded crossover RCT in rural Brazil (18 weeks)</td>
<td>112 people from 20 families (all ages)</td>
<td>Household level chlorination with sodium hypochlorite</td>
</tr>
<tr>
<td>Luby 2004&lt;sup&gt;20&lt;/sup&gt;</td>
<td>QRCT among three neighbourhoods in squatter settlements in Karachi, Pakistan (6 months)</td>
<td>2365 (≤15 years)</td>
<td>Bleach and regular storage vessel</td>
</tr>
<tr>
<td>Luby 2006&lt;sup&gt;21&lt;/sup&gt;</td>
<td>RCT among 47 squatter settlements in Karachi, Pakistan (8 months)</td>
<td>8949 (all ages)</td>
<td>Dilute bleach and storage vessel</td>
</tr>
<tr>
<td>Lube 2005&lt;sup&gt;22&lt;/sup&gt;</td>
<td>RCT among households in rural Uganda, at least one person HIV positive (5 months)</td>
<td>2201 (all ages)</td>
<td>Flocculant-disinfectant and soap</td>
</tr>
<tr>
<td>Mahfouz 1995&lt;sup&gt;23&lt;/sup&gt;</td>
<td>QRCT among nine villages in rural Saudi Arabia (6 months)</td>
<td>311 (under 5s)</td>
<td>Flocculant-disinfectant and storage vessel</td>
</tr>
<tr>
<td>Messou 1997&lt;sup&gt;24&lt;/sup&gt;</td>
<td>QRCT among four villages in rural Ivory Coast; two underwent intervention, two were controls (5 years)</td>
<td>985-1260, depending on study year (under 5s)</td>
<td>Improved water supply, sanitation, hygiene education, and oral rehydration therapy for those with diarrhoea</td>
</tr>
<tr>
<td>Quick 1999&lt;sup&gt;25&lt;/sup&gt;</td>
<td>RCT among two peri-urban communities in Bolivia (5 months)</td>
<td>791 (all ages)</td>
<td>Household level chlorination, storage vessel, and hygiene education</td>
</tr>
<tr>
<td>Quick 2002&lt;sup&gt;26&lt;/sup&gt;</td>
<td>QRCT in two peri-urban communities in Zambia (3 months)</td>
<td>1584 (all ages)</td>
<td>Household level chlorination, storage vessel, and hygiene education</td>
</tr>
<tr>
<td>Reiter 2003&lt;sup&gt;27&lt;/sup&gt;</td>
<td>RCT among 12 villages in rural Guatemala (12 months)</td>
<td>2982 (all ages)</td>
<td>Intervention 1, flocculant-disinfectant; intervention 2, bleach only; intervention 3, bleach and storage vessel; intervention 4, flocculant-disinfectant and storage vessel</td>
</tr>
<tr>
<td>Roberts 2001&lt;sup&gt;28&lt;/sup&gt;</td>
<td>RCT in a Malawi refugee camp (4 months)</td>
<td>1160 (all ages)</td>
<td>Improved storage: bucket with spout and narrow opening to limit hand entry</td>
</tr>
<tr>
<td>Rose 2005&lt;sup&gt;29&lt;/sup&gt;</td>
<td>RCT in urban slum in south India (6 months)</td>
<td>200 (under 5s)</td>
<td>Solar disinfection in plastic bottles at household level</td>
</tr>
<tr>
<td>Semenza 1998&lt;sup&gt;30&lt;/sup&gt;</td>
<td>RCT in urban Uzbekistan among 240 households, half with and half without access to piped water (9.5 weeks)</td>
<td>1583 (all ages)</td>
<td>Household level chlorination, storage vessel, and hygiene education</td>
</tr>
<tr>
<td>Turon 1982&lt;sup&gt;31&lt;/sup&gt;</td>
<td>QRCT in two small villages in Guatemala (12 months)</td>
<td>2103 (all ages)</td>
<td>Source protection (spring), chlorination facilities, &quot;adequate storage,&quot; and water mains with faucets to yards</td>
</tr>
<tr>
<td>Universidad Rafael Landivar 1999&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Study from three demographic regions of Guatemala (12 months)</td>
<td>1120 (under 5s)</td>
<td>Intervention 1, locally fabricated ceramic filters; intervention 2, locally fabricated ceramic filters and hygiene education</td>
</tr>
<tr>
<td>Xiao 1997&lt;sup&gt;33&lt;/sup&gt;</td>
<td>QRCT among two villages in rural China (3 years)</td>
<td>4649 (all ages)</td>
<td>Improved water supply, sanitation, and hygiene education</td>
</tr>
</tbody>
</table>

QRCT: quasi-randomised controlled trial; RCT: randomised controlled trial.
prevent faecal-oral transmission, including improved sanitation and water supplies, improved water storage in the home, and instruction on basic hygiene regarding contaminated water and diarrhoeal disease (table 1). One study included the introduction of oral rehydration therapy.\(^1\) However, 14 trials consisted solely of water quality interventions, although ceramic filters and solar disinfection interventions may also improve storage.

### Compliance

Compliance (consumption of improved quality water) was not assessed directly. Trials of interventions at the home, and instruction on basic hygiene regarding sanitation and water supplies, improved water storage to determine the extent to which participants in the intervention group consumed treated water or avoided consuming untreated water.

### Outcome measures and effect estimates

Twenty one trials used the WHO definition of diarrhoea (three or more loose stools in the previous 24 hours); most others used local terms or mothers’ definitions. All were based on self report. In most trials participants were visited on a periodic basis, either weekly (14 trials), fortnightly (five trials), or more infrequently (five trials), and were asked to recall episodes of diarrhea during a

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**Table 2 | Summary of pooled estimates (random effects) for studies reporting rate ratios, risk ratios, longitudinal prevalence ratios, and odds ratios for all studies (source based and household based), by point of intervention (source or household), and by type of household water treatment (chlorination, filtration, solar disinfection, and flocculation-disinfection)**

<table>
<thead>
<tr>
<th>Measure of effect and intervention</th>
<th>All ages</th>
<th>Under 5s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of trials</td>
<td>Pooled estimate* (95% CI)</td>
</tr>
<tr>
<td>Rate ratios</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>12</td>
<td>0.75 (0.65 to 0.87)§</td>
</tr>
<tr>
<td>Source based</td>
<td>4</td>
<td>0.87 (0.74 to 1.02)</td>
</tr>
<tr>
<td>Household based:</td>
<td>8</td>
<td>0.62 (0.47 to 0.82)§</td>
</tr>
<tr>
<td>Chlorination</td>
<td>4</td>
<td>0.61 (0.46 to 0.81)§</td>
</tr>
<tr>
<td>Filtration</td>
<td>3</td>
<td>0.56 (0.25 to 1.27)</td>
</tr>
<tr>
<td>Solar disinfection</td>
<td>1</td>
<td>0.64 (0.41 to 1.00)</td>
</tr>
<tr>
<td>Risk ratios</td>
<td>8</td>
<td>0.50 (0.42 to 0.61)§</td>
</tr>
<tr>
<td>Source based</td>
<td>1</td>
<td>0.45 (0.43 to 0.47)</td>
</tr>
<tr>
<td>Household based:</td>
<td>7</td>
<td>0.49 (0.36 to 0.65)§</td>
</tr>
<tr>
<td>Chlorination</td>
<td>4</td>
<td>0.41 (0.26 to 0.65)</td>
</tr>
<tr>
<td>Filtration</td>
<td>2</td>
<td>0.41 (0.21 to 0.79)§</td>
</tr>
<tr>
<td>Improved storage</td>
<td>1</td>
<td>0.79 (0.61 to 1.03)</td>
</tr>
<tr>
<td>Longitudinal prevalence ratios</td>
<td>11</td>
<td>0.56 (0.27 to 1.16)§</td>
</tr>
<tr>
<td>Source based</td>
<td>1</td>
<td>0.56 (0.37 to 0.84)</td>
</tr>
<tr>
<td>Household based:</td>
<td>10</td>
<td>0.56 (0.25 to 1.23)§</td>
</tr>
<tr>
<td>Chlorination</td>
<td>5</td>
<td>0.82 (0.60 to 1.11)</td>
</tr>
<tr>
<td>Flocculation-disinfection</td>
<td>5</td>
<td>0.40 (0.14, 1.16)§</td>
</tr>
<tr>
<td>Odds ratios</td>
<td>10</td>
<td>0.65 (0.56 to 0.76)§</td>
</tr>
<tr>
<td>Household based:</td>
<td>10</td>
<td>0.65 (0.56 to 0.76)§</td>
</tr>
<tr>
<td>Chlorination</td>
<td>3</td>
<td>0.77 (0.58 to 1.02)§</td>
</tr>
<tr>
<td>Filtration</td>
<td>3</td>
<td>0.37 (0.27 to 0.49)</td>
</tr>
<tr>
<td>Solar disinfection</td>
<td>2</td>
<td>0.69 (0.63 to 0.74)</td>
</tr>
<tr>
<td>Flocculation-disinfection</td>
<td>2</td>
<td>0.77 (0.65 to 0.90)§</td>
</tr>
</tbody>
</table>

*Not applicable.

*For single studies, estimate is from that study only.

†Probability of heterogeneity.

‡Consistency.

§Includes studies with multiple intervention arms compared with a single control so that statistical significance of these analyses must be interpreted with caution.
previous period, usually seven days (18 trials) to 14 days (six trials). In some trials participants were asked to keep records of days with diarrhoea.

Effect estimates included rate ratios (12 trials), risk ratios (eight trials), longitudinal prevalence ratios (11 trials), and odds ratios (10 trials; table 2). One trial did not provide enough information to calculate the actual measure of effect and was excluded from the meta-analysis. Most studies adjusted for covariates. However, none of the source based interventions and four of the household based trials did not report adjusting for clustering and may thus receive excess weight in meta-analysis due to artificial precision.

Effectiveness

Figure 2 presents the forest plots for studies reporting effect estimates for all ages and for under 5s. Most trials recorded notable reductions in diarrhoea; none found the interventions to be associated with a statistically significant increase in diarrhoea related morbidity. The evidence from the pooled estimates of effect for all trials by each measure of effect suggests that interventions to improve the microbial quality of drinking water are effective in reducing the occurrence of diarrhoea both for all participants and for under 5s (table 2). Pooled estimates were, however, characterised by considerable heterogeneity (table 2).

A subgroup analysis was carried out on the criteria specified in the protocol to attempt to explain such heterogeneity.

Exploring heterogeneity

Water source versus household interventions

Table 2 shows the pooled estimates of interventions at the water source level and at the household level. Although individual trials of source based interventions reported the intervention to be effective, the pooled estimate for trials using rate ratios fell short of statistical significance, both among four trials reporting data for all ages (0.87, 95% confidence interval 0.74 to 1.02) and three trials reporting on under 5s (0.93, 0.82 to 1.05). The two studies on source based interventions reporting the highest level of effectiveness could not be pooled because they used different measures of effect. Moreover, the small number of clusters and the failure to take clustering into account in the analysis must raise doubts about the validity of such estimates. Household interventions, on the other hand, significantly reduced diarrhoea episodes among people of all ages and among under 5s, as measured with rate ratios, risk ratios, and odds ratios, but these pooled estimates were still heterogeneous. The pooled longitudinal prevalence ratio for household interventions was statistically significant when a possible outlier was excluded from the analysis for all age groups (0.70, 0.56 to 0.88; nine trials) and for under 5s (0.76, 0.66 to 0.88; nine trials).

Type of household intervention

Table 2 also shows the pooled estimates of effect by type of household intervention. Although such subgroups reduces heterogeneity among certain types of household interventions other pooled estimates were still characterised by considerable heterogeneity. Household chlorination was associated with a statistically significant reduction in diarrhoea among all age groups when measured using rate ratios and risk ratios, and in under 5s when using risk ratios. No statistically significant advantage was found for people of all ages when measured using longitudinal prevalence ratios or for under 5s when measured using rate ratios, longitudinal prevalence ratios, or odds ratios. Household filters were associated with a statistically significant and homogeneous reduction in diarrhoea among all ages and in under 5s for trials measuring risk ratios and odds ratios, but not among trials measuring rate ratios. Excluding the two studies carried out in the United States in settings with high ambient water quality, however, resulted in a single study reporting a statistically significant rate ratio in favour of the intervention (0.21, 95% confidence interval 0.07 to 0.61). Solar disinfection was associated with a reduction in diarrhoea among all ages in both trials measuring odds ratios. A single study that measured the effectiveness of the intervention among under 5s reported a rate ratio of 0.64 (0.41 to 1.00). For household based flocculation-disinfection, pooled estimates from the five trials reporting longitudinal prevalence ratios found no statistically significant difference in the number of diarrhoea episodes compared with the control, either for people of all ages or for under 5s. However, excluding one trial that found a substantial protective effect but which has been identified as a possible outlier rendered the pooled estimate statistically significant in favour of the intervention, both for all ages (0.60, 0.43 to 0.83) and for under 5s (0.66, 0.43 to 0.76). The two trials using odds ratios reported a statistically significant reduction in diarrhoea episodes for all ages from household based flocculation-disinfection but not for under 5s. The one trial that involved improved storage found a protective but, lacking power, not statistically significant difference in diarrhoea episodes measured with risk ratios, for people of all ages (0.79, 0.61 to 1.03) and for under 5s (0.69, 0.47 to 1.01).

Compliance

Among trials reporting odds ratios, the pooled estimate of effect was substantially higher in settings where compliance with the intervention was higher (≥50% compliance; four trials), odds ratio 0.39, 95% confidence interval 0.39 to 0.51; <50% compliance (four trials), 0.80, 0.71 to 0.89). These results must be interpreted with caution as the four trials comprising the less than 50% category are from one study and are compared with only one control group.

Water supply and sanitation

Subgroup analyses for each measure of effect were carried out according to whether the water supply or sanitation was “improved” or “unimproved” on the basis of established criteria. No statistically significant
differences were found between pooled estimates on the basis of these criteria. However, pooled estimates show a statistically significant effect in favour of intervention even in settings without improved water supply (seven trials reporting rate ratios, 0.74, 95% confidence interval 0.63 to 0.87; four trials reporting risk ratios, 0.46, 0.36 to 0.58; six trials reporting longitudinal prevalence ratios, 0.83, 0.68 to 1.01; and nine trials reporting odds ratios, 0.66, 0.57 to 0.77). Interventions were also effective in settings without
improved sanitation (four trials reporting rate ratios, 0.78, 0.64 to 0.95; two trials reporting risk ratios, 0.55, 0.47 to 0.65).

**Water quality only versus compound environmental interventions**

Pooled estimates showed that water quality interventions were significantly effective when introduced alone or in combination with other environmental interventions (hygiene instruction, improved water storage vessel, improved sanitation, or improved water supply). Notably, however, no evidence was found for water quality interventions being more effective when combined with other components than when implemented alone. Pooled estimates for water quality interventions alone (seven trials reporting odds ratios, 0.61, 95% confidence interval 0.50 to 0.73; five trials reporting rate ratios, 0.76, 0.52 to 1.02)

### Table 3 | Methodological quality of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomised controlled trials*</th>
<th>Quasirandomised controlled trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocation sequence†</td>
<td>Allocation concealment‡</td>
</tr>
<tr>
<td>Alam 1989*1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Austin 1993*2</td>
<td>Adequate</td>
<td>Adequate</td>
</tr>
<tr>
<td>Aziz 1990*3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Chiller 2005*4</td>
<td>Adequate</td>
<td>Adequate</td>
</tr>
<tr>
<td>Clasen 2004*5</td>
<td>Adequate</td>
<td>Adequate</td>
</tr>
<tr>
<td>Clasen 2006*6</td>
<td>Adequate</td>
<td>Adequate</td>
</tr>
<tr>
<td>Clasen 2005*7</td>
<td>Adequate</td>
<td>Adequate</td>
</tr>
<tr>
<td>Colford 2002*8</td>
<td>Adequate</td>
<td>Adequate</td>
</tr>
<tr>
<td>Colford 2005*9</td>
<td>Adequate</td>
<td>Adequate</td>
</tr>
<tr>
<td>Conroy 1996*10</td>
<td>Inadequate</td>
<td>Inadequate</td>
</tr>
<tr>
<td>Conroy 1999*11</td>
<td>Inadequate</td>
<td>Inadequate</td>
</tr>
<tr>
<td>Crump 2005*12</td>
<td>Unclear</td>
<td>Adequate</td>
</tr>
<tr>
<td>Doocy 2006*13</td>
<td>Adequate</td>
<td>Adequate</td>
</tr>
<tr>
<td>Du Preez 2004*14</td>
<td>Adequate</td>
<td>Adequate</td>
</tr>
<tr>
<td>Garrett 2004*15</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Gasana 2002*16</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Handzel 1998*17</td>
<td>Unclear</td>
<td>Adequate</td>
</tr>
<tr>
<td>Jensen 2003*18</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Kirchhoff 1985*19</td>
<td>Inadequate</td>
<td>Inadequate</td>
</tr>
<tr>
<td>Luby 2004*20</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
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<td>Adequate</td>
</tr>
<tr>
<td>Lule 2005*22</td>
<td>Unclear</td>
<td>Adequate</td>
</tr>
<tr>
<td>Mahfouz 1995*23</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Messou 1997*24</td>
<td>—</td>
<td>—</td>
</tr>
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<td>Quick 1999*25</td>
<td>Adequate</td>
<td>Adequate</td>
</tr>
<tr>
<td>Quick 2000*26</td>
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<td>—</td>
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<td>Reiler 2003*27</td>
<td>Adequate</td>
<td>Adequate</td>
</tr>
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<td>Roberts 2001*28</td>
<td>Inadequate</td>
<td>Inadequate</td>
</tr>
<tr>
<td>Rose 2005*29</td>
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<td>Adequate</td>
</tr>
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<td>Semenza 1998*30</td>
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<td>Adequate</td>
</tr>
<tr>
<td>Turon 1982*31</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Universidad Rafael Landivar 1995*32</td>
<td>Adequate</td>
<td>Adequate</td>
</tr>
<tr>
<td>Xiao 1997*33</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Criteria based on Juni.17
†Studies considered adequate if method is described and resulting sequences are unpredictable; unclear if trial stated as randomised but method not described; and inadequate if sequences could be related to outcomes.
‡Studies considered adequate if randomisation methods were used; unclear if no method was stated; and inadequate if randomisation methods were not described.
§Studies considered adequate if blinding was stated; unclear if not described or not stated; and inadequate if blinding was not used.
¶Studies considered adequate if losses to follow-up accounted for; unclear if no information was provided or if it was not clear how losses were handled; and inadequate if losses to follow-up were not accounted for.
**Comparability of characteristics between intervention and control groups such as water quality, diarrhoeal morbidity, age, socioeconomic status, access to water, hygiene practices, and sanitation facilities. Studies considered adequate if no substantial differences were present; unclear if not reported or not known whether substantial differences exist, and inadequate if one or more substantial differences exist.
††Studies considered adequate if data collected at similar time points; unclear if relative timing was not reported or not clear from trial; and inadequate if data not collected at similar time points.
were not statistically different from pooled estimates for trials combining water quality with instruction on basic hygiene (one trial reporting odds ratio, 0.52, 0.30 to 0.90; three trials reporting rate ratios, 0.85, 0.70 to 1.03), water quality with a storage vessel (three trials reporting odds ratios, 0.77, 0.58 to 0.84; four trials reporting rate ratios, 0.61, 0.46 to 0.81), water quality plus sanitation (three trials reporting odds ratios, 0.60, 0.43 to 0.84; one trial reporting rate ratio, 0.75, 0.70 to 0.80), or water quality with improved water supply (four trials reporting odds ratios, 0.70, 0.59 to 0.84; two trials reporting rate ratios, 0.77, 0.71 to 0.84).

**Study design; methodological quality**

Subgrouping trials on study design (randomised and quasi-randomised controlled trials) did not show a trend in favour of either design approach (table 3). Greater protective effects were generally reported among randomised controlled trials with high quality for sequence generation, allocation concealment, and inclusion or losses to follow-up. Only four studies, however, used double blinding (table 1) and none of these found a statistically significant protective effect from the water quality intervention. Similarly, among quasi-randomised controlled trials, effects in studies meeting the specified criteria for methodological quality were larger. Few trials, however, failed to meet these criteria, and subgroup analyses did not explain the heterogeneity.

**DISCUSSION**

This systematic review of 42 controlled trials among some 56 000 participants shows that interventions to improve the microbial quality of drinking water are effective in reducing the occurrence of diarrhoea in adults and children. Although substantial heterogeneity was found in the magnitude of the effects, the evidence for the effectiveness of water quality interventions was compelling.

Pooled estimates from 12 studies reporting rate ratios suggest that household based interventions are more effective at preventing diarrhoea than water source based interventions. Such estimates, however, exclude the results from the two studies of source based interventions that reported the highest level of effectiveness and that achieved results equivalent to the household based interventions using the same measure of effect. Evidence was also found for effectiveness being related to compliance with the intervention. Water quality interventions were effective in reducing diarrhoea even in the absence of improved water supplies and sanitation. Effectiveness did not seem to be enhanced by combining the intervention with other common strategies for preventing diarrhoea (instruction on basic hygiene, improved water storage, or improved water supplies and sanitation facilities). Although the evidence does not rule out additional benefit from combined interventions, it does raise questions about whether the additional cost of such integrated approaches as currently implemented is warranted on the basis of health gains alone.

**Methodological strengths and weaknesses**

The validity of the results of this systematic review depends on the validity of the included studies. Many of the trials were only quasi-randomised and failed to take all the steps necessary to avoid bias. In subgroup analyses, however, trials that were of higher methodological quality for allocation concealment showed a greater overall level of effectiveness. Only four of the 22 randomised controlled studies, however, were properly blinded, and in each no statistically significant protective effect was found. Two of the non-blinded trials were carried out in a developed country where drinking water already complied with US standards. One trial included only 112 people (the smallest of all the included trials) and was rated low on three other criteria for methodological quality, and one used dilute sodium hypochlorite in the control group, which may have improved water quality leading to an underestimate of the effectiveness of the study intervention. Thus other reasons apart from methodological concerns may exist for why these trials failed to show effectiveness. Nevertheless, in the light of the results from the non-blinded trials, some caution must be exercised in interpreting the strength of the evidence to date.

The design of the trials was not independent of the type of intervention. All seven trials concerning interventions at the water source were quasi-randomised, whereas 31 of the 35 studies of point of use interventions were randomised. Although this reflects the difficulty of randomising users of water source interventions, our inferences about the relative effectiveness of these two approaches may be biased by the study design. Subgrouping on study design and methodological quality did not suggest an association between effectiveness and method of randomisation. If the general observation that trials with weaker designs show more promising intervention effects applied to this population of studies, then the relative effectiveness of household and water source interventions may have been biased against household interventions.

Moreover, the context and length of follow-up in the trials was not independent of the intervention. Trials of household based interventions tended to be research driven investigations, whereas those of source based interventions were often evaluations of actual programmes. The duration of trials of source based interventions was nearly six times that of interventions at the household level. Four of the six trials on source based interventions lasted three or more years, whereas only four of the 35 household interventions lasted one year. Seasonality is important in assessing diarrhoea, and the failure to include data on diarrhoea for at least 12 months may have influenced the estimates of intervention of effect. Nevertheless, visual inspection of a scatter plot of trial duration against effectiveness showed no association.

The availability of water may be an important factor in the generalisability of these results. Interventions at the source are often designed primarily to improve
water quantity and availability rather than quality. However, such improvements in water supply may be a separate and possibly more significant contributor to health than improvements in water quality. In the case of the household based interventions, most trials were carried out in settings with sufficient water, which may mean that these results cannot be generalised to locations where water supplies are inadequate. Our conclusions about source based interventions should not be interpreted to extend to household connections, which observational studies have found to be more effective in reducing diarrhoea.²²

Results in relation to other studies
The most cited reviews of the effectiveness of interventions to prevent diarrhoea are by Esrey et al.⁸⁹ These reviews, however, used a limited search strategy that omitted many studies, combined observational studies and trials, had limited assessments of methodological quality, and reported intervention effects as median reductions. The reviews included only studies investigating improvements of water quality at the source and did not include interventions at the household level.⁸⁹ The 15% to 17% median reduction in occurrence of diarrhoea reported for source interventions is consistent with our results for source based interventions. Fewtrell et al¹⁴ reported significantly higher effectiveness from interventions at the household level (pooled estimates across different measures of effect of 35% from 12 household based interventions compared with a statistically insignificant 11% from three source based interventions), but did not include several unpublished studies and included interventions against epidemic diarrhoea in their analysis, which could skew results.

What the results mean
Interventions to improve the microbial quality of water are effective in reducing the occurrence of endemic diarrhoea. Some evidence was found that household based interventions are capable of significantly higher levels of effectiveness, roughly comparable to certain other environmental interventions to prevent diarrhoea, such as improved sanitation, hygiene (hand washing with soap), and improved water supply.¹⁴,²³ Moreover, contrary to previous conclusions,²⁴,²⁵ water quality interventions are effective even in the absence of improved sanitation and water supply and they do not always require concomitant hygiene promotion for their effectiveness. These results support the WHO strategy of promoting the treatment and safe storage of household water as a means of accelerating the health gains of safe drinking water, even though it may not reduce the numbers of people (1.1 billion) currently without access to improved water supplies.

Unanswered questions and future research
Rigorous, multiarm randomised controlled trials in different settings that compare various approaches to improving drinking water quality will help clarify the potential for water quality interventions to prevent endemic diarrhoea. It is particularly important that such trials be blinded, if possible, not only for the methodological reasons that favour blinded trials generally but also because of the ineffectiveness reported in blinded studies of water quality interventions to date. A need also exists for longer term studies in programmatic (non-research driven) settings, especially on household based interventions. Differences in programmatic approaches to optimise the adoption and long term utilisation of these interventions should also be investigated. Finally, as most of the burden from diarrhoeal disease is associated with mortality rather than with morbidity, future research should include studies specifically designed to determine the effectiveness of interventions to improve water quality in preventing death, particularly among vulnerable populations such as the under 5s and people living with HIV/AIDS.

Household interventions require effort on the part of householders to treat their water correctly, to have treated water consistently available, to avoid recontamination, and to refrain from drinking from untreated sources. Each of these conditions creates an opportunity for non-compliance, which we found to reduce effectiveness. Most source based interventions, however, extended to the household’s entire water supply without any additional steps for compliance on the part of the intervention population. It is therefore important to assess whether the target population will use these household interventions correctly and consistently over the long term.

Ultimately the value of water quality interventions in preventing diarrhoeal disease depends not only on their effectiveness but also on their affordability, acceptability, sustainability, and scalability within a vulnerable population—issues that the studies included in this review mainly did not address. Comprehensive cost effectiveness and cost benefit analyses will also help establish the priority that should be attached to water quality interventions by the public sector, donors, and non-governmental organisations.

We thank Greg Allgood, Jamie Bartram, Julia Bohlius, Joseph Brown, Jack Colford, John Grump, Tom Chiller, Val Curtis, Shannon Doocy, Lorna Fewtrell, Carrol Gamble, Bruce Gordon, Stephen Gundry, Bruce Kenwick, Steve Luby, Rob Quick, Mark Salovey, Sara Thomas, and James Wright for their research, advice, assistance, and other valuable contributions; members of the Cochrane Infectious Diseases Diseases Review Group; and the referees of the Cochrane review and its protocol. This is an updated and vastly abbreviated version of the Cochrane review. The authors agreed to change the order of authorship on this paper to reflect their contributions to this paper compared with the full review.

Contributors: SC conceived the review. TC coordinated the review, drafted the protocol and review, carried out the search strategy, retrieved the papers, contacted authors, and prepared the tables and figures. TC is guarantor. TC, TR, and W-PS designed the review. TC and TR screened the search results. TC, TR, and W-PS applied the inclusion criteria. TC, TR, and W-PS extracted the data, calculated estimates of effect, and dealt with the statistics. TC, TR, and IR applied the quality criteria. TC and W-PS entered data into RevMan. IR, TR, W-PS, and SC commented on the review.

Funding: None.
The interventions were effective in people of all ages and in under 5s.

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

Water that is safe at the point of collection often becomes contaminated with faeces during transport, use, and storage in the home.

**WHAT THIS STUDY ADDS**

Interventions to improve the microbial quality of water are effective for preventing diarrhoea. The interventions were effective in people of all ages and in under 5s.

**Competing interests:** TC, W-PS, and SC participate in research supported by Unilever and Vestergaard-Frandsen, which manufacture and sell household or other point of use water treatment devices.

**Ethical approval:** Not required.


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Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials

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ABSTRACT

Objective To explore the extent to which components of composite end points in randomised controlled trials vary in importance to patients, the frequency of events in the more and less important components, and the extent of variability in the relative risk reductions across components.

Design Systematic review of randomised controlled trials.

Data sources Cardiovascular randomised controlled trials published in the Lancet, Annals of Internal Medicine, Circulation, European Heart Journal, JAMA, and New England Journal of Medicine, from 1 January 2002 to 30 June 2003. Component end points of composite end points were categorised according to importance to patients as fatal, critical, major, moderate, or minor.

Results Of 114 identified randomised controlled trials that included a composite end point of importance to patients, 68% (n=77) reported complete component data for the primary composite end point; almost all (98%; n=112) primary composite end points included a fatal end point. Of 84 composite end points for which component data were available, 54% (n=45) showed large or moderate gradients in both importance to patients and magnitude of effect across components. When analysed by categories of importance to patients, the most important components were associated with lower event rates in the control group (medians of 3.3-3.7% for fatal, critical, and major outcomes; 12.3% for moderate outcomes; and 8.0% for minor outcomes). Components of greater importance to patients were associated with smaller treatment effects than less important ones (relative risk reduction of 8% for death and 33% for components of minor importance to patients).

Conclusion The use of composite end points in cardiovascular trials is frequently complicated by large gradients in importance to patients and in magnitude of the effect of treatment across component end points. Higher event rates and larger treatment effects associated with less important components may result in misleading impressions of the impact of treatment.

INTRODUCTION

Composite end points capture the number of patients who have one or more of several events of interest. Clinical trials, particularly in cardiology, often use composite end points to reduce sample size requirements and to capture the overall impact of therapeutic interventions.2

Freemantle and colleagues have highlighted potential advantages and limitations of the use of composite end points.1 Although composite end points may increase the event rate and thus the statistical power of the study, they may mislead if component end points are of widely differing importance to patients, the number of events in the components of greater importance is small, and the magnitude of effect differs markedly across components.3 For example, a statement that an intervention reduces a composite of cardiovascular mortality, myocardial infarction, and revascularisation procedures is problematic if most of the events were revascularisation procedures and investigators found a large apparent effect of treatment on revascularisation but not on death or infarction.

To explore the characteristics of composite end points in common use, we reviewed a consecutive sample of randomised controlled trials that investigated cardiology interventions and were published in six prominent journals. In particular, we were interested in the extent to which components of composite end points varied in importance to patients, the frequency of events in the more and less important components, and the extent of variability in the relative risk reductions across components.

METHODS

Eligibility criteria

We included parallel group randomised controlled trials that involved humans exposed to any cardiovascular therapeutic intervention and reported at least one composite end point. We defined a cardiovascular clinical trial as any randomised controlled trial in which the target population of the study had to
Randomised controlled trials. CEP and IF-G trained in health research methods worked

Seven reviewers (JWB, EAA, DMB, PA-C, AW, SU, and IF-G) trained in health research methods worked

in pairs to extract data independently and in duplicate, using a standardised form and a data collection manual. Reviewers collected information on content area and the type of interventions tested, sample size, the length of follow-up, the number of composite end points presented, and the declared source(s) of funding.

To avoid confounding, we explored only data associated with each trial’s primary composite end point. When authors reported more than one composite end point, we established the primary one by using the following hierarchy: (a) authors’ explicit declaration of primacy, (b) the composite end point used to calculate the sample size, (c) authors’ attribution of importance to the composite end point in their description of the results, and (d) the composite end point that appeared first in the methods section. Two reviewers (JWB and IF-G) independently selected the primary composite end point, resolving discrepancies by discussion.

For each composite end point we extracted the number of components, the effect of the intervention on the composite end point, and the number of events attributed to the composite end point. For the component end points of each composite end point we recorded the effect of the intervention and the number of patients who achieved the outcome. When authors reported results from the same composite end point for more than one time point, we used data from the longest interval. A statistician (DH-A) entered all data into an electronic database and reviewed them for errors and missing data.

Ranking of outcomes according to importance to patients

Patients will typically assign varying importance to different health outcomes.3 We sought, but were unable to find, a published hierarchical categorisation of importance to patients for cardiovascular outcomes. Therefore, to explore the variability in importance to patients across components, we developed a hierarchical categorisation of importance to patients for the component end points included in eligible studies. Two cardiologists (GP-M and IF-G) and nine internists (GHG, HJS, VMM, EAA, RJ, JA, VP-H, PA-C, and AD-S) independently categorised each of 72 outcomes associated with the outcomes guided the process.6 Group members met to resolve disagreements and succeeded in coming to consensus.

Data analysis

The χ statistic provided a measure of interobserver agreement independent of chance on the eligibility of randomised controlled trials. We calculated, for each of the five categories of outcomes, the median event rate and the interquartile range for the control group as well as the effect of the intervention within the category by using the authors’ reporting of relative risk, odds ratio, or hazard ratio. To ensure independence of observations

**Fig 1** Stages of systematic review of cardiovascular randomised controlled trials. CEP=composite end point; RCT=randomised controlled trial

have coronary artery disease, valvular heart disease, arrhythmia, cardiomyopathy, or congestive heart failure on entry. We also included randomised controlled trials investigating primary prevention of cardiovascular disease. We excluded trials that reported composite end points with components relating to toxicity or safety or with no outcomes important to patients (that is, including only surrogate outcomes) or subgroup analyses that ignored random allocation.

**Literature search**

We used Medline to search electronically four high impact general medicine journals (Lancet, Annals of Internal Medicine, JAMA, and New England Journal of Medicine) and two leading cardiology journals (Circulation and European Heart Journal), from 1 January 2002 to 30 June 2003. We used the publication type function to restrict our search to “randomized controlled trial” and “human” subjects; the National Library of Medicine and the US Cochrane Center have collaborated to use these terms to accurately index randomised controlled trials in the Medline database.4

**Study selection**

Eight investigators (JWB, EAA, DMB, PA-C, AW, SU, VP-H, and AD-S), working in pairs, used standardised forms to establish if abstracts of articles identified in our electronic search were parallel group randomised controlled trials studying humans and covered a cardiology topic (as defined above). We retrieved the full text of all potentially eligible articles. The same reviewers independently assessed eligibility of the full text articles with standardised forms and resolved discrepancies by discussion. An arbitrator (VMM) resolved any discrepancies that remained.

**Data extraction**

Seven reviewers (JWB, EAA, DMB, PA-C, AW, SU, and IF-G) trained in health research methods worked
within categories of importance to patients, we selected only one end point in each category for each composite end point to make these calculations; where a composite included more than one end point in the same category, we selected the end point with the highest event rate in the control group. To estimate the effect of the intervention across trials and within each category, we used random effects meta-analyses with an inverse variance approach. This method is conservative, in that it considers both within study and between study differences in estimating the pooled estimate. We used the $I^2$ statistic, the percentage of between study variability that is due to true differences between studies (heterogeneity) rather than sampling error (chance), to quantify inconsistency among studies.

To describe the gradient of importance to patients among component end points, we considered a large gradient to be present when composite end points combined outcomes from categories I or II (fatal and critical) with outcomes from category V (minor). We considered a moderate gradient to be present when composite end points combined outcomes from categories I or II with outcomes from category IV (moderate) without any component from category V. We assigned a minor or absent gradient to composite end points not included in the other two categories.

We limited analysis of the gradient of efficacy across components to those composite end points that provided data on at least two of their individual end points. We assigned a large gradient in the effect of the intervention if the difference between the smallest and largest reported treatment effects (relative risk, odds ratio, or hazard ratio) was $>0.4$, a moderate gradient when the difference was $0.2$ to $0.4$, and a small gradient when the difference was $<0.2$.

Among composite end points with moderate or large gradients in importance to patients, we explored the impact of the outcomes with less importance to patients on both the total event rate for the composite end point in the control group and the magnitude of effect of the intervention. Our approach was to quantify, in sequence, the impact of adding component end points from importance to patients category III (major end points) and categories IV and V (moderate and minor end points) to end points allocated to categories I and II (fatal and critical end points). This was only possible for those studies that supplied data for each component of the composite in categories I, II, and III (fatal, critical, and major). For each study, we first calculated the event rate in the control group and the relative risk reduction on the basis of a composite of all the end points in categories I and II included in the original composite. We then repeated these calculations for another composite including all end points in categories I, II, and III. When adding the moderate and minor components (categories IV and V), we used the data for the original composite end point reported in the paper to calculate the control event rate and the relative risk reduction. Thus, we did not need component data for end points in categories IV and V.

Calculation of the exact impact would require joint distributions for all the components; because authors did not provide this level of detail, we made estimations by using a conservative approach to assess the impact of the outcomes of moderate and minor importance to patients. To establish the effect on the event rate for the control group, we estimated the impact of fatal and critical end points under the assumption that no patient had both a critical and a fatal event or more than one critical event. For instance, if the rate of death for the control group was 1% and that of large stroke was 2%, we calculated an event rate for the end points within importance to patients category I and II of 3%. We then estimated the effect of adding the events associated with end points grouped in category III (major end points) and the relative risk reduction. Thus, we did not need component data for end points in categories IV and V.

### Table 1 | Characteristics of 114 included studies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Journal</td>
<td></td>
</tr>
<tr>
<td>Annals of Internal Medicine</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Circulation</td>
<td>45 (39)</td>
</tr>
<tr>
<td>European Heart Journal</td>
<td>17 (15)</td>
</tr>
<tr>
<td>JAMA</td>
<td>21 (18)</td>
</tr>
<tr>
<td>Lancet</td>
<td>21 (18)</td>
</tr>
<tr>
<td>New England Journal of Medicine</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Cardiovascular area</td>
<td></td>
</tr>
<tr>
<td>Coronary disease</td>
<td>91 (80)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>12 (11)</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Other*</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>76 (67)</td>
</tr>
<tr>
<td>Coronary intervention (surgery/percutaneous)</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Vascular intervention (surgery/percutaneous)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Other†</td>
<td>23 (20)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No of composite end points per trial (n=111)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65 (59)</td>
</tr>
<tr>
<td>2</td>
<td>28 (25)</td>
</tr>
<tr>
<td>3</td>
<td>12 (11)</td>
</tr>
<tr>
<td>≥4</td>
<td>6 (5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total No of components per composite end point</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>39 (36)</td>
</tr>
<tr>
<td>3</td>
<td>44 (39)</td>
</tr>
<tr>
<td>4</td>
<td>14 (12)</td>
</tr>
<tr>
<td>≥6</td>
<td>17 (15)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effect on components reported</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Every component</td>
<td>77 (68)</td>
</tr>
<tr>
<td>Some components</td>
<td>21 (18)</td>
</tr>
<tr>
<td>No components</td>
<td>16 (14)</td>
</tr>
</tbody>
</table>

*Valvular heart disease, primary cardiovascular prevention, arrhythmia, or cardiomyopathy.
†Rehabilitation or lifestyle intervention (diet, daily activity).
for the control group was 10%, the effect of adding the less important outcomes (categories IV and V) would increase the control event rate from 5% to 10%.

A similar approach allowed assessment of the impact of outcomes grouped according to importance to patients on the effect of the intervention. We calculated the median and associated interquartile range for both the control group event rate and the effect of the intervention. We calculated a test of proportions ($\chi^2$ test) to explore associations between gradients in either importance to patients or of the effect of treatment on components within composite endpoints by declared source of funding (industry versus non-industry funded). We used SAS version 9.1 and S-PLUS version 6.2 (Insightful Corporation, Seattle, Washington) for analyses; we chose a 5% threshold for statistical significance for all analyses.

RESULTS

Results of literature search

Our literature search generated 650 abstracts, from which we identified 242 potentially eligible randomised controlled trials, of which 114 proved eligible on consensus review of the full text publications (fig 1).

Table 2 | Component outcomes by category of importance to patients (114 composite end points)

<table>
<thead>
<tr>
<th>End point</th>
<th>Prevalence—No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Death</td>
<td></td>
</tr>
<tr>
<td>All cause mortality</td>
<td>43 (38)</td>
</tr>
<tr>
<td>Mortality not otherwise defined</td>
<td>32 (28)</td>
</tr>
<tr>
<td>Cardiac death not otherwise defined</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Cardiac death due to coronary heart disease not otherwise defined</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Other fatal end points (n=9)</td>
<td>24 (21)</td>
</tr>
<tr>
<td>II. Critical</td>
<td>18 (16)</td>
</tr>
<tr>
<td>Large myocardial infarction</td>
<td>14 (12)</td>
</tr>
<tr>
<td>Stroke leaving permanent moderate deficit</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Cardiac arrest followed by resuscitation manoeuvres</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Dissecting or ruptured aortic aneurysm</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other critical end points (n=3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>III. Major</td>
<td>95 (83)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>83 (73)</td>
</tr>
<tr>
<td>Stroke leaving permanent deficit, severity not defined</td>
<td>16 (14)</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Cerebrovascular event not otherwise defined</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Other major end points (n=13)</td>
<td>19 (17)</td>
</tr>
<tr>
<td>IV. Moderate</td>
<td>59 (52)</td>
</tr>
<tr>
<td>Coronary revascularisation not otherwise specified</td>
<td>22 (19)</td>
</tr>
<tr>
<td>Coronary revascularisation—angioplasty/stenting</td>
<td>12 (11)</td>
</tr>
<tr>
<td>Non-fatal angina needing hospital admission</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Hospital admission not otherwise specified</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Other moderate end points (n=17)</td>
<td>15 (13)</td>
</tr>
<tr>
<td>V. Minor</td>
<td>12 (11)</td>
</tr>
<tr>
<td>Non-fatal angina, not defined</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Non-fatal arrhythmias, not otherwise specified</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Dyspnoea, not otherwise defined</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Change in blood pressure</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other minor end points (n=10)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

Figure 2 | Variability in magnitude of the effect of intervention across categories of importance to patients

Chance corrected agreement on eligibility was excellent ($k=0.90$). Thus, approximately half of all parallel group cardiovascular randomised controlled trials identified reported an eligible composite end point.

Study characteristics

Table 1 describes the characteristics of the included studies. Most trials appeared in Circulation, the Lancet, and JAMA; focused on treatment of coronary disease primarily through pharmacological intervention; and reported only one primary composite end point. Almost all (98%) composite end points included fatal end points, usually reported as “all cause mortality” (table 2). The median sample size of eligible randomised controlled trials was 840 (interquartile range 238-2334), and the median follow-up time was 1 year (90 days-3.5 years). When a composite end point included only two components, reporting of individual event rates and the composite end point rate made the joint distribution apparent; no eligible trials with three or more components reported the joint distribution of component outcomes.

Most trials (69%; n=79) declared either direct financial industry funding (n=74) or industry having supplied the drug or device under investigation (n=5). Authors of 15 (13%) trials declared not for profit funding alone, and 20 (18%) did not declare a funding source. Of the 74 trials that declared industry funding, 27 trials also reported funding by not for profit sources.

Gradient in importance to patients and effect of intervention across components

Most composite end points (56%; n=64) showed either a large (10%; n=11) or moderate (47%; n=53) gradient in importance to patients. Among the 84 composite end points that reported data for at least two of their component end points, the gradient in the effect of the intervention across component end points was usually large (57%; n=48) or moderate (18%; n=15). Of these 84 randomised controlled trials, 45 (54%) included a composite end point with components that exhibited large or moderate gradients in both importance to patients and effect of intervention across components. Many remaining composite end points (32%; n=27) included a large or moderate gradient in either importance to patients (11%; n=9) or treatment effect across components.
components (21%; n=18). Only 14% (n=12) of composite end points reviewed were composed of end points that exhibited neither gradient or a minor gradient in both importance to patients and the effect of treatment across components. Declared industry funding versus non-industry funding was not significantly associated with either the gradient in importance to patients or in the gradient of effect of treatment across components among composite end points.

Effect of end points of moderate and minor importance to patients

When analysed by categories of importance to patients, the most important components were associated with lower control group event rates, with medians of 3.3% (interquartile range 1.4-6.9%) for fatal outcomes, 3.3% (2.2-5.2%) for critical end points, and 3.7% (1.6-8.5%) for major outcomes. End points of moderate and minor importance to patients had higher event rates: median 12.3% (2.9-26.7%) for moderate and 8.0% (4.5-26.8%) for minor. Similarly, we found that pooled effects for fatal and critical outcomes were small, and end points of lesser importance to patients were associated with larger effects (fig 2).

Of 64 composite end points with moderate or large gradients in importance to patients, 46 had sufficient data to quantify the impact of the less important end points on both the event rates for the composite end point in the control group and the effect of the intervention on the composite end point. The median event rate for the control group when we considered only the most important patient outcomes (fatal and critical end points) was 2.5%. The event rate rose to 8.7% when we added end points of major importance to the composite and to 21.7% when we added end points of moderate and minor importance (table 3). The magnitude of the treatment effect also rose substantially as less important components were included (table 3). Of the 46 composite end points with a large or moderate gradient in importance to patients that provided data on component end points, 59% (n=27) were statistically significant (P<0.05). However, only seven achieved statistically significant when we considered only components of greater importance to patients (fatal, critical, and major end points), whereas most (20/27) achieved statistical significance only when we added end points of moderate or minor importance to the composite.

Our results suggest that a naïve interpretation of composite end points may lead clinicians to overestimate the impact of treatments on preventing adverse events that matter most to patients. Consider, for example, the following statement: "In patients with in-stent stenosis of coronary artery bypass grafts, γ radiation reduced the composite end point of death from cardiac causes, Q wave myocardial infarction, and revascularisation of the target vessel." This result sounds impressive because it suggests that γ radiation reduces the incidence of death and myocardial infarction, as well as the need for revascularisation. The trial that produced this result randomised 120 patients with in-stent stenosis of a saphenous vein graft to γ radiation (iridium-192) or placebo. Death or myocardial infarction contributed only 6/43 events in the placebo arm and 5/22 events in the iridium-192 arm. The investigators have shown the impact of the intervention on revascularisation. The trial provides, however, essentially no information about the effect of the intervention on myocardial infarction or death.

Consider another example—the irbesartan diabetic nephropathy trial that randomised 1715 hypertensive patients with nephropathy and type 2 diabetes to irbesartan, amlodipine, or placebo.9 Results showed a benefit of irbesartan over amlodipine in the primary end point, a composite of a doubling of the baseline serum creatinine concentration, the onset of end stage renal disease (serum creatinine >6.0 mg/dl, initiation of dialysis, or transplantation), or death from any cause. Doubling of serum creatinine provided most events and was the only outcome for which irbesartan was convincingly beneficial. Indeed, in this instance, irbesartan both lowered the incidence of doubling of creatinine and showed a trend towards reduction in end stage renal disease, but it showed a slight trend towards

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**Table 3** | Additive effect of component end points on composite end points, based on category of importance to patients (in composite end points with moderate/large gradient in importance) (n=46)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Most important components (CI, CII)*</th>
<th>Moderately important components added (CIII)†</th>
<th>Less important components added (CIV, CV)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median % (IQR) event rate of composite end point for control group</td>
<td>2.5 (0.8-6.1)</td>
<td>8.7 (5.2-14.5)</td>
<td>21.7 (13.1-33.2)</td>
</tr>
<tr>
<td>Median % (IQR) effect of treatment (RRR)</td>
<td>13 (~4-14)</td>
<td>17 (~9-36)</td>
<td>24 (~4-2)</td>
</tr>
</tbody>
</table>

*CI=category I (death); CII=category II (critical); CIII=category III (major); CIV=category IV (moderate); CV=category V (minor); IQR=interquartile range; RRR=relative risk reduction.
†Reflects event rate in control group and RRR for only most important components included in composite end point.
‡Moderate components, when present (n=35), have been included with most important components to calculate event rate in control group and RRR.
§Event rate in control group and RRR results for full composite end point; reflects addition of least important components to data in previous column.
WHAT IS ALREADY KNOWN ON THIS TOPIC
Clinical trialists use composite end points, outcomes that capture the number of patients who have one or more of several events, to increase event rates and statistical power. When the gradient of importance to patients is large, and the more important events are uncommon and show negligible treatment effects, use of composite end points can be misleading.

WHAT THIS STUDY ADDS
Almost half of a sample of recent prominently published cardiovascular trials used composite end points, which were often inadequately reported and showed large gradients in importance to patients. End points of least importance to patients typically contributed most events. Composite end points, as currently used in cardiovascular trials, may often be misleading.

increased all cause mortality (fig 3). These examples highlight the challenges that clinicians face when making decisions on the basis of the results of cardiovascular trials that report composite end points.

DISCUSSION
Findings
Our analysis of a sample of 114 randomised controlled trials on cardiovascular interventions found that the use of composite end points is common. Reporting is not optimal: authors failed to provide the effect of treatment for all the components in almost one third of the articles. Most randomised controlled trials showed a large or moderate gradient in importance of end points to patients, and in 54% of the 84 trials in which data were available the component end points exhibited substantial gradients in both importance to patients and the effect of treatment across components. Less important components showed higher event rates and larger treatment effects.

Limitations and strengths
Our review has potential limitations. Our conclusions depend on clinicians assigning importance to patients to cardiovascular end points, a challenging process. Previous analyses have considered component end points in one of two categories, fatal or non-fatal; patients are, however, unlikely to attach similar importance to all non-fatal end points. Several authors have suggested weighting end points to reflect their relative importance when constructing composite end points. Lubsen and Kirwan have outlined a theoretical classification scheme for ranking components of composite end points. Trialists, however, rarely use these strategies. Published data examining the utilities that patients attribute to a variety of cardiovascular outcomes guided our classification, and 11 clinicians knowledgeable in cardiovascular care worked independently in generating the classification and were able to achieve consensus. Our decisions on categorisation are available (table 2 provides examples), and readers can independently judge their credibility.

Our analysis of the effect of treatment across components was limited to trials that reported data on component end points in categories I (fatal) to III (major) of importance to patients. This may have led to a biased sample. Our analytic approach was, however, conservative in that when three or more components were present and the joint distribution of results was unavailable we assumed distributions that attributed the maximum number of events to the end points of greater importance to patients.

One might question our application of meta-analytic approaches to data across a wide variety of interventions (fig 2). The variability in results, represented by the $I^2$, proved to be 0% for fatal end points and was below a commonly used threshold of 50% for other end points. The increasing treatment effect with decreasing importance seems to be a real phenomenon.

Our work has additional strengths. Our sample of 114 composite end points is the result of a systematic search completed in duplicate with excellent agreement. Our data collection was comprehensive and careful, including independent judgment and abstraction of data at all stages by reviewers trained in the methodology and use of targeted, relevant analyses. We excluded composite end points containing efficacy and safety outcomes because their inclusion would have overestimated the proportion of composite end points with large gradients in the effect of the treatment. We included only one composite end point for each randomised controlled trial to avoid clustering, as multiple reported composite end points within a single trial commonly share components.

Implications
Use of composite end points appeals to clinical trialists because it increases event rates and statistical power. The fundamental problem with composite end points is, however, the difficulty in interpreting results when the gradient of importance to patients is substantial and a substantial gradient in the magnitude of the treatment effect also exists. Conversely, confident interpretation of composite end point results requires relatively small gradients of importance to patients and similar relative risk reductions across components. Our findings suggest that most composite end points used in cardiovascular randomised controlled trials have substantial gradients in both importance to patients and treatment effects across component end points. Furthermore, less important outcomes provide larger contributions to the composite end point event rate and show larger treatment effects. In particular, mortality outcomes, present in almost all cardiovascular composite end points, provide the lowest event rate and show the smallest treatment effects. Thus, an important and plausible risk of misleading conclusions associated with the use of composite end points is to attribute reductions in mortality to interventions that do not, in fact, reduce death rates.

The common use of inadequately reported composite end points with large gradients in importance to
patients, in which end points of least importance contribute most events, and in which treatment fundamentally affects these same components, is problematic. Trialists should report complete data on individual component end points to facilitate appropriate interpretation; clinicians should view with caution the results of cardiovascular trials that use composite end points to report their results. Clinicians and patients are best served when trialists restrict their use of composite end points to end points of similar importance to patients and contexts in which they anticipate that more important end points will contribute a large proportion of study events. If they do not, they risk misleading their audience.

We thank Lisa Buckingham for assistance in creating the database used to capture the information extracted from eligible trials.

Contributors: IF-G, JWB, GP-M, VMM, and GHG were involved in the study design and concept. JWB, EAA, IF-G, DMB, PA-C, AW, and SU collected all data. OH-A, IF-G, JWB, and GHG did the analysis. All authors offered critical revisions to the manuscript, and all approved the final version. GHG is the guarantor.

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Competing interests: None declared.

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CLINICAL REVIEW

Post-traumatic stress disorder

Jonathan I Bisson

Post-traumatic stress disorder (PTSD) is a disorder that occurs in response to a traumatic event. PTSD is diagnosed when a person experiences symptoms of re-experiencing, avoidance, and increased arousal that are severe enough to cause significant distress or impairment in functioning.

The DSM-5 criteria for PTSD include:
1. Re-experiencing the trauma
2. Avoidance
3. Increased arousal

Re-experiencing phenomena includes:
- Recurrent distressing dreams about the event
- Acting or feeling as if the events are recurring
- Intense psychological distress to cues
- Physiological reactivity to cues

Avoidance includes:
- Avoidance of thoughts, feelings, and conversations
- Avoidance of reminders
- Psychogenic amnesia
- Greatly reduced interest in related activities
- Detachment or estrangement feelings
- Restricted range of affect
- Sense of foreshortened future

Increased arousal includes:
- Difficulty sleeping
- Irritability or outbursts of anger
- Difficulty concentrating
- Hypervigilance
- Exaggerated startle response

Vivid descriptions of reactions to traumatic events span many centuries, although their nature has changed over time. PTSD was first recognised as a diagnosable psychiatric disorder in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) and ICD-10 (International Classification of Diseases, 10th edition). Its very existence continues to attract debate, with several authors arguing that culturally determined, understandable emotions to traumatic events are being pathologised. However, even its most ardent critics recognise as a diagnosable psychiatric disorder in the DSM-III and ICD-10. PTSD is now widely accepted as a legitimate and treatable disorder.

In the DSM-IV-TR, PTSD is diagnosed when a person experiences symptoms of re-experiencing, avoidance, and increased arousal that are severe enough to cause significant distress or impairment in functioning. The symptoms must be persistent and cause significant distress or impairment in functioning.

Methods
I consulted recent systematic searches used to prepare Cochrane reviews and BMJ Clinical Evidence on prevention and treatment of post-traumatic stress disorder, as well as those used to prepare the National Institute for Health and Clinical Excellence (NICE) guidelines for post-traumatic stress disorder. I searched PubMed using the terms “epidemiology”, “neurobiology”, and “neuroimaging” in conjunction with “post-traumatic stress disorder”. I also used a personal archive of references.

What is post-traumatic stress disorder?
Box 1 shows the characteristic features of the disorder. It occurs after a traumatic event that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others. For the DSM classification, the person must also have experienced intense fear, helplessness, or horror when the event occurred. The symptoms must have been present for at least one month (the one month criterion does not apply in the ICD-10 classification) and, crucially, they must also cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. Acute post-traumatic stress disorder becomes chronic if it lasts for longer than three months. Symptoms usually begin shortly after the trauma, but they are said to have delayed onset if they start at least six months later. Most people diagnosed with delayed onset post-traumatic stress disorder actually had symptoms within six months of the trauma, but they presented late or their symptoms were not recognised initially. For a few patients the onset of symptoms truly is delayed.

Psychological models of the disorder
Traumatic experiences can usually be assimilated without the development of a pathological response. If this is unsuccessful, post-traumatic stress disorder can develop, with pathological fear structures characterised by excessive response elements such as avoidance, physiological reactivity, and resistance to modification. Central to cognitive theories of post-traumatic stress disorder are pre-existing beliefs and models of the world, and the difficulty of assimilating information provided by a traumatic experience into them. One prominent theory distinguishes between memories that are easily verbally recalled and give rise to emotions related to the trauma and memories that cannot be deliberately accessed and give rise to symptoms such as dreams and flashbacks. Another theory suggests that the disorder develops when the traumatic

Box 1 | Characteristic symptoms of post-traumatic stress disorder adapted from DSM-IV-

<table>
<thead>
<tr>
<th>Re-experiencing phenomena (at least one required)</th>
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<tbody>
<tr>
<td>• Recurrent and intrusive distressing recollections</td>
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<tr>
<td>• Recurrent distressing dreams</td>
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<tr>
<td>• Acting or feeling as if the events are recurring</td>
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<tr>
<td>• Intense psychological distress to cues</td>
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<tr>
<td>• Physiological reactivity to cues</td>
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<table>
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<tr>
<th>Avoidance and numbing (at least three required)</th>
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<tr>
<td>• Avoidance of thoughts, feelings, and conversations</td>
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<td>• Avoidance of reminders</td>
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<td>• Sense of foreshortened future</td>
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<th>Increased arousal (at least two required)</th>
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<tr>
<td>• Difficulty sleeping</td>
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<tr>
<td>• Irritability or outbursts of anger</td>
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<td>• Difficulty concentrating</td>
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<tr>
<td>• Hypervigilance</td>
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<tr>
<td>• Exaggerated startle response</td>
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</tbody>
</table>
memory induces a sense of current threat promoted by excessively negative appraisals of what happened.6

**Biological models of the disorder**

Although still in its infancy, with many findings still needing confirmation, our knowledge of the neurobiology of post-traumatic stress disorder is improving. The amygdala receives information about external stimuli and determines their importance. This then triggers emotional responses including a “fight, flight, or freezing” response and alterations in stress hormones and catecholamines. The hippocampus and medial prefrontal cortex (fig 1) influence the response of the amygdala in determining the final fear response. Hippocampal lesions have been associated with a stronger fear response and smaller hippocampal volume has been associated with post-traumatic stress disorder,7 although whether this is a cause or an effect of the disorder is unknown.w6 Neuroimaging studies have shown decreased activity in medial prefrontal and anterior cingulate areas to be correlated with increased activity in the amygdala.8 It has therefore been suggested that post-traumatic stress disorder represents a failure of medial prefrontal and anterior cingulate networks to regulate the activity of the amygdala, which results in hyper-reactivity to threat.9

One of the most enduring neurophysiological theories has been that of enhanced negative feedback in the hypothalamic-pituitary-adrenal axis. Several studies have found low cortisol concentrations in people with post-traumatic stress disorder and an opposite response to the dexamethasone suppression test than that seen with severe depression. However, this finding has not consistently been supported by more recent studies.10 The increased catecholamine concentrations in people with the disorder have also caused much interest. It has been suggested that an initial adrenergic surge may be associated with the consolidation of traumatic memories.11

**Who is affected?**

The recent replication of the US national comorbidity survey of 5692 adults found that the lifetime prevalence of post-traumatic stress disorder was 6.8%12 and the 12 month prevalence was 3.5%; about a third of those affected had a severe form of the condition. However, similar epidemiological studies of adolescents and young adults in Germany w7 and adults in Australia w8 produced far more conservative estimates — prevalence at 12 months was 0.7% and 1.2%, respectively. Comorbidity rates are often more than 80%.14 The most common comorbid conditions are depressive disorders, panic disorder, other anxiety disorders, and substance misuse or dependence. Anyone can develop the disorder after a traumatic event, but the incidence increases with the severity of the trauma. Studies have reported an incidence of more than 50% for rape,14 w9 30-40%w10 for disasters, and around 19% for veterans of the Vietnam war.w11 Rates for other traumas including accidents and non-physical assaults tend to be lower.14 w9 Factors associated most closely with the development of post-traumatic stress disorder are perceived lack of social support and peritraumatic dissociation, but neither increase the risk by more than 50%.15 16 Box 2 lists the factors associated with the disorder across several studies.

**Immediate reactions after trauma**

Many people experience traumatic stress symptoms shortly after traumatic events. More than 90% of female victims of sexual assault satisfy the symptom criteria for post-traumatic stress disorder within a week of the event,w12 and 31% of 1010 Londoners described substantial stress 11-13 days after the bombings in London on 7 July 2005.17 Prospective research suggests that rates reduce rapidly over time. After the 11 September terrorist attacks in New York, probable post-traumatic stress disorder in people living south of

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**Box 2 | Factors associated with post-traumatic stress disorder**15 16

**Pretraumatic factors**
- Previous psychiatric disorder
- Sex (more prevalent in female patients than in male patients)
- Personality (external locus of control greater than internal locus of control)
- Lower socioeconomic status
- Lack of education
- Race (minority status)
- Previous trauma
- Family history of psychiatric disorders

**Peritraumatic factors**
- Severity of trauma
- Perceived threat to life
- Peritraumatic emotions
- Peritraumatic dissociation

**Post-traumatic factors**
- Perceived lack of social support
- Subsequent life stress
The most researched complex early interventions have used trauma focused cognitive behaviour therapy over four to 12 sessions, starting from one to three months after the traumatic event. These contain components similar to those used to treat the chronic disorder (box 4). No research has suggested a formal role for the early prescription of drugs. However, guidelines from the United Kingdom’s National Institute for Health and Clinical Excellence suggest that acute phase symptoms, such as severe insomnia, could be managed with hypnotics or antidepressants. Concern about prescribing of benzodiazepines has resulted in many prescribers preferring to recommend a sedative antidepressant or an α agonist, such as prazosin.

Managing chronic post-traumatic stress disorder

A wide range of psychological and pharmacological approaches have been used to treat the chronic disorder. Unfortunately, no good direct comparisons of the two approaches have been carried out, making it difficult to determine their relative efficacies.

Psychological treatment

The psychological treatments with the best evidence are trauma focused cognitive behaviour therapy, which comprises varying combinations of exposure therapy and trauma focused cognitive therapy, and eye movement desensitisation and reprocessing (box 4). Both are individual treatments usually provided over the course of up to 12 sessions (box 4; fig 2). Exposure therapy commonly involves the patient describing the traumatic event in great detail, tapping this account, and listening to it repeatedly. In trauma focused cognitive therapy, distorted beliefs and misinterpretations about the traumatic event and its consequences are considered and challenged. In eye movement desensitisation and reprocessing, the recipient focuses on the traumatic experience, associated thoughts, emotions, and

**Box 3 | Items on trauma screening questionnaire**

<table>
<thead>
<tr>
<th>Re-experiencing</th>
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<tr>
<td>Upsetting thoughts or memories</td>
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<td>Upsetting dreams</td>
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<tr>
<td>Feeling that the event is happening again</td>
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<td>Upset by reminders</td>
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<tr>
<td>Symptoms of physical anxiety</td>
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<table>
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<tr>
<th>Hyperarousal</th>
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<tr>
<td>Difficulty sleeping</td>
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<tr>
<td>Irritability</td>
<td></td>
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<tr>
<td>Difficulty concentrating</td>
<td></td>
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<tr>
<td>More aware of dangers</td>
<td></td>
</tr>
<tr>
<td>Easily startled</td>
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**Box 4 | Trauma focused psychological treatments**

**Exposure therapy**
- Repeated confrontation of traumatic memories, often through detailed recounting of the traumatic experience
- Repeated exposure to avoided situations and those that elicit fear that are now safe but which are associated with the trauma

**Trauma focused cognitive therapy**
- Modification of misinterpretations that lead to overestimation of current threat
- Modification of other beliefs related to the traumatic experience and the individual’s behaviour during the trauma (for example, guilt and shame)

**Eye movement desensitisation and reprocessing**
- Standardised procedure using bilateral physical stimulation (eye movements, taps, or tones) while the patient focuses on memories and associations
- This form of treatment is thought to stimulate information processing to help produce an adaptive contextualised memory

110th Street reduced from 7.5% at one month to 1.6% at four months and 0.6% at six months. This recovery trajectory is important when deciding how best to provide for individuals after traumatic events.

**Detecting the disorder**

Despite the associated factors it is difficult to predict exactly who will develop post-traumatic stress disorder after a traumatic event. Various screening instruments have been developed, and one of the simplest—the 10 item trauma screening questionnaire—is one of the best validated. This questionnaire is probably more helpful in detecting people with the chronic disorder than as a predictive screening instrument shortly after a traumatic event. This is because it produces a high number of false positives unless a high incidence of the chronic disorder is expected. A full assessment that equates to a standard mental health assessment is needed to diagnose the disorder. This should look at presentation, background, mental state examination result, risk assessment result, social factors including support network, and information from other sources including relatives.

**Preventing the disorder**

Formal psychological interventions targeted at everyone involved in traumatic events have been ineffective. Meta-analyses have indicated no differences between people who received an intervention and those who did not in the first six months. Some studies have reported more negative outcomes in people who receive one-off individual interventions based on critical incident stress debriefing, particularly those with higher levels of symptoms. This has led to concerns about this form of input and recommendations that it should not be used. More attention is now being focused on developing stepped or stratified models of response in which immediate practical, social, and emotional support is offered by non-mental health professionals. People with severe ongoing symptoms are offered a formal assessment and a more complex intervention if post-traumatic stress disorder that is not improving is detected.
sensations while receiving bilateral physical stimulation, most commonly by following the therapist’s finger as it is moved from side to side.

Non-trauma focused stress management has a positive but less pronounced effect. Group treatment seems to be less effective than individual treatment. A recent meta-analysis found no significant benefits over waiting list controls for non-trauma focused treatments such as supportive therapy, non-directive counselling, psychodynamic therapies, and hypnotherapy. Using a predetermined threshold, only trauma focused cognitive behaviour therapy and eye movement desensitisation and reprocessing produced significant clinical improvements, and no major differences were found between the two in head to head comparison studies.

Drug treatment
The efficacy of various drugs has provoked considerable debate and conflicting recommendations. A Cochrane review and the American Psychiatric Association reported benefits for selective serotonin reuptake inhibitors—sertraline and paroxetine. NICE do not recommend sertraline, mainly because data from unpublished studies were included in their meta-analysis, and no drug satisfied their predetermined threshold for significant clinical improvement. Paroxetine, mirtazapine, amitriptyline, and phenelzine were all significantly better than placebo, although studies of all but paroxetine had small sample sizes. Adding olanzapine to an antidepressant also seemed to be better than adding placebo to augment treatment in people with chronic post-traumatic stress disorder who did not respond fully to antidepressant drugs alone.

Management guidelines for the chronic disorder
The NICE management guidelines for the chronic disorder recommend that all patients should be offered a course of trauma focused cognitive behaviour therapy or eye movement desensitisation and reprocessing, normally on an individual outpatient basis. Trauma focused psychological treatment should usually be given for eight to 12 sessions, with some sessions lasting for 90 minutes if the trauma is considered during the session. The number of sessions may need to be increased, especially after multiple traumatic events and when accompanied by comorbidity or traumatic bereavement. An alternative trauma focused treatment or augmentation with drug treatment should be considered if no improvement is seen. Paroxetine and mirtazapine are recommended for general use, and amitriptyline and phenelzine under specialist supervision. Other factors may precipitate prescription of drugs including patient choice, serious ongoing threat, and lack of immediate availability of psychological treatment. Caution is needed when prescribing because of the well documented problems associated with some antidepressants in recent years.

Prognosis
Few longitudinal follow-up studies of post-traumatic stress disorder have been carried out. In one of the largest cross sectional studies, more than a third of people reported having the disorder six years after they first developed it, with a 50% chance of remission at two years. However, these results are of limited value in determining prognosis accurately. Whatever the true figure, for many people with the chronic disorder their condition is severe and enduring. Treatment can help some people many years after they developed the
SUMMARY POINTS

Post-traumatic stress disorder is a major cause of distress and reduced functioning after traumatic events in people of all ages.

No routine intervention has been shown to prevent this disorder.

Trauma focused cognitive behaviour therapy is the treatment of choice within three months of a traumatic event.

Trauma focused cognitive behaviour therapy or eye movement desensitisation and reprocessing are the treatments of choice for chronic post-traumatic stress disorder.

Drug treatment is a second line treatment for the disorder.

where appropriate, and they conclude that there is currently no good evidence for widely used treatments such as play therapy, art therapy, or family therapy for post-traumatic stress disorder.21

Competing interests: None declared.


The patient
A previously well 22 year old woman presented acutely to the accident and emergency department with collapse after several days of insidious onset headache. No focal neurological signs were seen, but she was sleepy, with generalised apathy. The remainder of the clinical examination was normal. As the patient’s father had factor V Leiden deficiency, she was referred for imaging to detect cerebral venous thrombosis.

What tests should I order?
Cerebral venous thrombosis is an uncommon but important diagnosis, as it is potentially reversible when promptly recognised and treated. Diagnosing this condition, which accounts for <1% of strokes, is challenging, as the clinical manifestations and aetiological factors are many and varied. Imaging is mandatory to confirm the diagnosis.

Imaging findings of cerebral venous thrombosis can be direct, with visualisation of the thrombus, or indirect, with oedema, infarction, and haemorrhage as a consequence of ischaemia from obstructed venous flow.

Unenhanced scanning
Standard computed tomography (CT) of the brain should be done first to exclude common causes of neurological symptoms, such as subarachnoid haemorrhage and tumours. Parenchymal infarction or haemorrhage inconsistent with an arterial vascular territory should raise the suspicion of venous thrombosis.

In the first two weeks of its development, thrombus may be seen as linear high density in the vein or sinus on the non-contrast scan (fig 1). Polycythaemia or normal non-myelinated brain in infants may mimic this. After two weeks, thrombus is isodense to brain parenchyma and is usually seen only on contrast enhanced scans.

Contrast enhanced scanning
Contrast enhanced scanning will show the thrombus as a filling defect within the vessel, whereas the dura surrounding the clot are enhanced. This radiological “empty delta” sign is found in 25-75% cases, and is more readily detected if the clot is located in the superior sagittal sinus or torcular. Over time, organised thrombus can also enhance, and the empty delta sign is no longer apparent.

CT venography
CT venography may be done if the diagnosis is in doubt or if the initial unenhanced scan suggests venous thrombosis. This technique uses fast, thin slice, helical acquisition following a bolus of iodinated intravenous contrast; the timing of the scan coincides with optimal opacification of the cerebral venous circulation. The source images are reviewed, and appropriate software allows subtraction of adjacent bony structures, and excellent multiplanar and three dimensional visualisation of the enhanced veins.
Computed tomography (CT) and magnetic resonance (MR) venography in diagnosing cerebral venous thrombosis

<table>
<thead>
<tr>
<th></th>
<th>CT venography</th>
<th>MR venography</th>
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<tr>
<td><strong>Advantages</strong></td>
<td>Can be performed immediately after standard computed tomography</td>
<td>No radiation exposure (consider use in paediatric or pregnant patient)</td>
</tr>
<tr>
<td></td>
<td>Quick (1-2 minutes)</td>
<td>Use where CT contrast medium is contraindicated</td>
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<tr>
<td></td>
<td>Readily available</td>
<td>Sensitive test</td>
</tr>
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<td></td>
<td>Fewer motion artefacts</td>
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<tr>
<td></td>
<td>Can use if patient has cardiac pacemaker or claustrophobia</td>
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<tr>
<td></td>
<td>Good spatial resolution</td>
<td></td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Exposure to ionising radiation</td>
<td>Time consuming; image quality more prone to patient movement</td>
</tr>
<tr>
<td></td>
<td>Use of iodinated contrast medium</td>
<td>Not as readily available as CT venography</td>
</tr>
<tr>
<td></td>
<td>(increased risk of contrast reactions in patients with asthma, renal failure, and allergy to iodine)</td>
<td>Need to be aware of potential technical pitfalls in diagnosis</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>Overall accuracy 90-100%, depending on vein or sinus</td>
<td>Comparable to CT venography</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;90% when various MR sequences are combined with MR venography</td>
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Compared with conventional digital subtraction angiography, CT venography is a sensitive (95%), specific (91%), and reliable technique. It provides better venous anatomy than time of flight MR (magnetic resonance) venography, and detects thrombosis with equal accuracy. A recent study quotes sensitivity of 75-100%, specificity of 81-100%, positive predictive value of 75-100%, and negative predictive value of 89-100% for CT venography, using MR venography as the reference standard. The difference in range of values depends on the sinus or vein involved; overall accuracy is 90-100%.

**USEFUL READING**


The main advantage of CT venography is that it can be done immediately after the unenhanced CT scan, thereby enabling a prompt diagnosis.

**MR venography**

Normal blood flow results in a “black” signal void within vessels on standard magnetic resonance imaging (fig 2). Phase contrast, time of flight (fig 3), and contrast enhanced MR venography are commonly used for detecting cerebral venous thrombosis. Parenchymal changes, including microhaemorrhages, can be detected earlier with magnetic resonance imaging than with computed tomography (table).

Differences in intensity of the signal within cerebral vessels depend on the evolution of the thrombus, physiology of normal flow, and artefacts of imaging. Knowing the potential pitfalls in diagnosis is essential when interpreting the images.

**Patient outcome**

The patient was initially imaged with unenhanced computed tomography, cerebral venous thrombosis was diagnosed promptly, and intravenous heparin, the mainstay treatment, was started. She subsequently had MR venography to define the extent of the thrombus and any associated parenchymal changes and was also found to have factor V Leiden deficiency. We give anticoagulants even if a haemorrhagic venous infarct is seen on imaging, and thrombolysis is advocated only if the patient clinically deteriorates despite adequate intravenous heparin.

**Contributors** Both authors equally contributed to the research, design, content, and editing of the manuscript.

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**Competing interests** None declared.

**Provenance and peer review** Commissioned and peer reviewed.

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A PATIENT’S JOURNEY

Intensive care

Emilie Perrier

I am a 27 year old French woman and have lived in London since 2002. I came here to learn English, to meet people from other countries and to work. I had never been ill in my life, never been allergic to anything, and had no worries about my health.

In February 2003, on holiday in France, I had severe diarrhoea. After a few days, I was admitted to hospital with peritonitis. A few weeks later I was diagnosed with Crohn's disease. It changed my life completely. I spent three months in hospital before returning to England, where my husband was waiting for me.

As I learnt about my new life and new diet, I also started to become an old lady in my body. I developed a lot of joint pain from arthritis. At the end of October, back in France, my gastroenterologist prescribed sulphasalazine for my pain. The treatment went well for two weeks and I returned to London, but then I began to feel really sick. I had a high fever, pain everywhere in my body and I vomited everything I ate. I had shivers, could not sleep, and collapsed repeatedly.

On 20 November, we called an ambulance, but they said it was probably flu and that I should see my general practitioner, who prescribed paracetamol. Within two days, I was very ill; my skin had become very red and I was collapsing more frequently.

At the St Charles Hospital in London, the doctor gave me penicillin, believing I had meningitis. I was sent to St Mary’s Hospital, where I saw several doctors, who thought my illness could be a bladder problem related to Crohn’s disease. I had several CT scans and was told I was a “very interesting case.” Nobody wondered about the fact that I had a rash. I began to feel better; the rash disappeared and I wanted to go home.

I was discharged on 28 November, with a check-up appointment for the following Monday. I started my treatment again. On the Monday, my skin was very itchy and red. I told the doctor, who gave me anti-itch pills and I had some blood tests done.

That night the fever returned. I felt terribly tired and had no appetite. I was supposed to see my general practitioner on the Tuesday afternoon but was far too tired and sick. I called my husband and told him I needed to go to hospital.

When I arrived I began to feel really unwell and very hot; I collapsed in front of the lift. A doctor who saw me put me straight in a wheelchair and sent me to the accident and emergency department, where I was admitted. During the night I collapsed again and vomited a lot. I had a fever, and the on-call doctor became very worried.

The next morning the consultant arrived but really did not know what to do; the medical team still believed my illness had something to do with my Crohn’s disease and I was scheduled for surgery the next morning.

My fingers started to swell, and the nurse had to cut one of my rings. Even at this point, we did not ask ourselves why I was swelling up. That night, the nurse needed to take some blood and tried to find a vein. Desperately she tried and tried again but with no success. I began to lose consciousness.

At this point I became really spaced out. I knew I had been moved to intensive care and that there were people talking to me, but I didn’t care; my mind was elsewhere. The nurse told me I had to be brave as they were going to put some lines between my legs. I didn’t care—I was so sick, they could do anything they wanted. I didn’t feel the pain, I was in another world. I could hear and see people, but my mind was not there. On Thursday, I went for surgery.

After surgery, my skin blew up and burned. I was slipping into a coma, unaware of everything around me. I was put onto a life support machine and transferred to Intensive care.

During my coma I dreamed a lot. Strangely, I was somewhere else. The nurse told me I had to be brave as they were going to put some lines between my legs. I didn’t care—I was so sick, they could do anything they wanted. I didn’t feel the pain, I was in another world. I could hear and see people, but my mind was not there. On Thursday, I went for surgery.

I was discharged on 28 November, with a check-up appointment for the following Monday. I started my treatment again. On the Monday, my skin was very itchy and red. I told the doctor, who gave me anti-itch pills and I had some blood tests done.

That night the fever returned. I felt terribly tired and had no appetite. I was supposed to see my general practitioner on the Tuesday afternoon but was far too tired and sick. I called my husband and told him I needed to go to hospital.

When I arrived I began to feel really unwell and very hot; I collapsed in front of the lift. A doctor who saw me put me straight in a wheelchair and sent me to the accident and emergency department, where I was admitted. During the night I collapsed again and vomited a lot. I had a fever, and the on-call doctor became very worried.

The next morning the consultant arrived but really did not know what to do; the medical team still believed my illness had something to do with my Crohn’s disease and I was scheduled for surgery the next morning.

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After surgery, my skin blew up and burned. I was slipping into a coma, unaware of everything around me. I was put onto a life support machine and transferred to the intensive care unit in St Thomas’ Hospital.

During my coma I dreamed a lot. Strangely, I was always in a hospital bed during my dreams. I remember my father speaking to me, saying my mother and my family were there. My husband was my guide, speaking to me by telepathy. It was never scary, but I know I prayed a lot, asking the Lord to help me. It’s funny because I dreamed of doctors and nurses who were good or bad during my coma; when I woke up, there they were, for real.

I have no clear memory of my first awakening. It was
A DOCTOR’S PERSPECTIVE

Emilie Perrier’s story was striking. She was a healthy 24 year old who had been well until April that year, when she was diagnosed with Crohn’s disease. This was well controlled with mesalazine until October, when she had started to experience joint pains, and she was switched to sulfasalazine. Four weeks later she developed a diffuse maculopapular rash and abdominal pain. She was admitted to hospital, and a computed tomogram showed bilateral pleural effusions and free fluid in the abdomen and pelvis. She was treated on a presumptive diagnosis of intra-abdominal infection with cefuroxime and metronidazole. Notably, during admission the sulfasalazine was stopped and she improved. On returning home, she restarted all drugs, and within 24 hours she collapsed. On readmission she was noted to have diffusely “flushed” skin and a low blood pressure of 89/49 mm Hg. She had right upper quadrant tenderness. Her sulfasalazine was again stopped. In view of her abdominal pain she had a laparotomy. This showed no abnormality. She rapidly deteriorated, developing marked erythroderma and facial oedema. She developed bullous lesions over pressure points. There was no oral or genital involvement. Nikolsky’s sign was negative (Nikolsky’s sign is positive if there is intradermal blistering, which can develop when apparently normal skin is rubbed (this can be seen in toxic epidermal necrolysis)). On admission to intensive care she had a metabolic acidosis, with a bicarbonate concentration of 14. Her white cell count was raised, with a neutrophilia 9.3×10⁹/l. Notably she had a raised eosinophil concentration was 198 µmol/l and albumin concentration was 19 g/l. Creatinine concentration was 198 µmol/l and alkaline phosphatase 178 U/l. Her liver function tests were deranged (alanine aminotransferase 357 U/l and alkaline phosphatase 178 U/l). Creatinine concentration was 198 µmol/l and albumin concentration was 19 g/l. Her chest radiograph showed bilateral pleural effusions with interstitial shadowing. Acute respiratory distress syndrome was diagnosed, and the patient was intubated. The differential diagnosis included toxic epidermal necrolysis, but the negative Nikolsky’s sign and lack of oral and genital involvement suggested otherwise. The neutrophilia and relapsing remitting nature of the presentation also argued against this diagnosis. With the combination of rash, peripheral eosinophilia, and hepatic and pulmonary symptoms, we diagnosed DRESS (drug reaction eosinophilia and systemic symptoms) syndrome in response to sulfasalazine.

It is important to make the differential diagnosis between DRESS and toxic epidermal necrolysis, as steroids are successful in the former but can be deleterious in the latter, where they have been associated with infection and gastrointestinal bleeding.

We started pulsed methylprednisolone 500 mg daily for two days, followed by cyclosporin 50 mg twice daily. Fortunately for this patient, she made a full recovery, although she now has an increased sensitivity to various drugs, and needs longer term cyclosporin.

What can we learn from this case?

• At first presentation, start from the beginning; don’t rely on previous notes.
• In retrospect, the relation between Emilie’s deterioration and starting and restarting sulfasalazine is compelling.
• All clinical signs are important even if you can’t at first explain them. She had a rash from first presentation.
• The differentiation between toxic epidermal necrolysis and DRESS syndrome was vital in this case. Clear history taking and examination of clinical and laboratory findings went against our initial diagnosis of toxic epidermal necrolysis (which we had made on the basis of her being very sick with a severe skin reaction). This allowed vital steroids to be given. In my view, this turned the case around.

Back in St Mary’s, I met my dermatologist. She was so kind and told me that everything would be OK. I started to become really thin and lose all my fluid. I couldn’t sleep. Every time I went to sleep I woke up again, brutally. I had terrible diarrhoea and was unable to control myself. I was so weak I couldn’t move. I was totally dependent on the medical staff and my family. I was terrified I was going to have a breakdown.

My husband brought me a small television, which was amazing. I began to rediscover the world.

On 24 December, my dermatologist explained to me what had happened (see the doctor’s perspective box for her explanation). I felt really lucky and grateful. I asked the doctors when I would be able to go home and they said, when I could walk on my own and if I had some help at home. I was determined to go back to my place as soon as possible, to begin my own battle, the one with my body. The physiotherapist showed me some easy exercises to start my muscles functioning again. It was hard work; I felt as if all my physical and mental energy had been taken away.

Eventually, on 16 January, I was allowed home under supervision. I was so happy and proud of myself. I weighed 40 kg, was very weak, but was standing. This was my victory.

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10-MINUTE CONSULTATION

Chronic obstructive pulmonary disease

Andrew McIvor,1 Paul Little2

A 58 year old female smoker presents with a complaint of dyspnoea associated with chronic cough and sputum production during the winter months. Her general health is good. She recently took early retirement to spend more time with her grandchildren but found that she is too breathless to lift and carry them or to look after them safely in the park.

What issues you should cover

Chronic obstructive pulmonary disease (COPD) is largely caused by smoking and is characterised by progressive, partially reversible airflow obstruction, systemic manifestations (skeletal muscle dysfunction, depression, and secondary polycythaemia), and increasing frequency and severity of exacerbations. The main symptoms—usually insidious in onset and progressive—are shortness of breath and inability to tolerate physical activity.

History—Take a careful history to determine whether she has COPD, focusing on the main symptoms. Does she smoke or have significant exposure to secondhand smoke or occupational dust? Ask about history of exacerbations: urgent care visits, prescriptions for antibiotics or oral corticosteroids, and frequency of exacerbations.

Comorbidity—Ask about symptoms that suggest common comorbidities such as heart and circulatory diseases, asthma, anaemia, and depression.

Referral—Look out for worrying features associated with COPD that merit referral to a specialist: diagnostic uncertainty; COPD in people under 40 or in those who have a first degree relative with history of α1-antitrypsin deficiency; severe COPD; frequent exacerbations; haemoptysis; and difficulty in controlling symptoms or a need for oxygen therapy, pulmonary rehabilitation, or surgery.

What you should do

• In examining her look for signs of a hyperinflated (barrel shaped) chest, absent apex beat, hyper-resonance, and reduced diaphragmatic excursion, which are usually present in advanced disease. Although a physical examination is an essential part of assessment it is an insensitive means of detecting air flow obstruction.

• Record her height and weight. Look for signs of poor nutrition or muscle wasting (especially in the thighs), which commonly accompany severe COPD.

• Explain that to confirm the diagnosis you will have to perform spirometry, the gold standard for diagnosis and assessment of COPD related impairment. It should be considered in all patients aged 40 or over who are smokers or ex-smokers and who have shortness of breath after activity, persistent cough and sputum production, or frequent respiratory tract infections.

• Arrange chest radiography to rule out other comorbidities such as lung cancer, bronchiectasis, heart failure, tuberculosis, and interstitial lung disease.

• Strongly encourage smoking cessation at every opportunity.

• Remember that COPD is amenable to treatment. Be positive and supportive.

• Educate and advise her on any necessary or helpful lifestyle modifications (dietary change and exercising more).

• Use of inhalers is not intuitive and devices differ, so you should carefully explain their use and show her how to use each inhaler.

• Encourage partnership in care with the practice nurse and the primary care team and arrange a follow-up visit. This will allow you to assess her compliance, inhaler technique, and—by assessing how much her dyspnoea and overall lung function have improved—response to initial therapy. Use the Medical Research Council dyspnoea scale to assess shortness of breath and disability in the follow-up evaluation. If no improvement has occurred, adjust the treatment regimen to provide optimal symptom relief.

• Consider referring her to an airways clinic if one is nearby.

• Continue to review her progress, and if none is seen continue the referral to a specialist.

Competing interests: AMcI has received honoraria for speaking and consulting from Altana, AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline.

LONG TERM MANAGEMENT OF COPD

• Encourage collaborative self management

• Encourage smoking cessation

• Give annual influenza vaccination

• Give pneumococcal vaccination at least once, and possibly every 5-10 years

• Inhaled bronchodilators are the mainstay of COPD pharmacotherapy: titrate to relieve dyspnoea

• Prescribe short acting β2 agonists as needed, supplemented by stepwise addition of regular short or long acting anticholinergic inhalers

• Add a long acting β2 agonist inhaler (LABA)

• Add an inhaled corticosteroid (ICS) or a combination of ICS and LABA as a single inhaler

www.goldcopd.com

Canadian Thoracic Society. COPD guidelines. www.copdguidelines.ca


Masking is better than blinding

PERSONAL VIEW Daniel Morris, Scott Fraser, Richard Wormald

Consider this scenario. An elderly woman has agreed to be part of a clinical trial testing a new drug for age related macular degeneration. Her left eye has poor vision, and the sight in her previously good right eye is rapidly declining. She is told that she is part of a double blind trial in which she and the doctor will be blinded to the treatment. Taking fright, she withdraws her consent and goes home, terrified that this “blinding” experiment may deprive her of what little vision she has left.

The term “blinding”—commonly used in clinical trials—is particularly inappropriate in the ophthalmological setting, not least because an outcome measure of a particular trial could indeed be blindness. What an odd situation when the word used to describe trial allocation is also used to describe one of the trial outcomes. As a medical term blindness does not really have a strict definition, but it has a much greater resonance in its sociocultural meaning.

This common meaning is emotive enough outside eye care services, but within them the word is rarely used by practitioners and is dreaded by patients.

One of the earliest trials that described masking of allocations seems to have been performed by a commission of inquiry appointed by Louis XVI in 1784 to investigate the medical claims of “animal magnetism.” The commission’s goal was to assess whether the purported effects of this new healing method were the result of any real force or were illusions of the mind, and the participants were given what we would now call placebo or dummy treatments.

In the 19th century the concept of concealment of allocation was developed further with the Nuremberg salt test of 1835. Annoyed by the rise in popularity of homoeopathy among the upper classes of Bavaria, the leading public health official challenged a prominent homoeopath to publicly test a C30 (100⁹) dilution of salt. One hundred and twenty citizens met in a local tavern. In front of everyone, 100 vials were numbered, shuffled, and split into two lots of 50. They were filled with either distilled water or the homoeopathic remedy. The coding list was sealed and the vials distributed by a commission of people unaware of their contents. Those conducting the experiment stressed that the crucial element of its design was that anything that might enable the participants or those responsible for the trial to guess whether or not the actual medicine was given must be avoided; this concept still stands today.

Current use of the word “blinding” covers a variety of situations in a trial. Concealment of treatment allocation from those administering and those receiving it is obviously vital. Depending on the trial design, those assessing the treatment effects and the study statistician may also be unaware of allocation until the analysis is completed. Thus the word blinding is deeply ingrained in the language of trial design and evidence based medicine. To replace this word with a less emotive one requires a term that conveys the same obvious meaning of concealment of treatment.

“Concealment of allocation” is a better term for the prevention of selection bias, while “masking” is better used for the prevention of performance and detection bias. Masking is where neither the patient nor the investigator knows who is getting which treatment. Allocation concealment is preventing the subversion of the randomisation process. If the sequence of allocation is known, it is possible to select who goes into which group. It is true that proper double masking will usually deal with allocation concealment, but allocation concealment is mainly concerned with selection bias rather than detection bias.

If you are not an eye care practitioner you probably come to the conclusion that ophthalmologists are either too “politically correct” or far too precious about their patients. However, if we look at the origin of the term “blinding,” one dictionary defines it as “to deprive of perception or insight” but also as “partial or complete loss of sight.” Neither of these terms are ones that we would wish to associate with a rigorously designed trial. In contrast, the term “masking” is defined as “to cover in order to conceal, protect, or disguise.” We can see that the word masking in itself is a better description of what we intend to do in a trial—no matter what specialty is involved.

Thus we suggest that the term blinding is avoided in trial design. If this is thought too drastic, we would at least ask practitioners to take care when using it, either when describing a trial to a patient or within consent forms or patient information leaflets.

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The full version of this article with references is available on bmj.com
The refresher course

The setting is the Mengo hospital for plastic and reconstructive surgery in Kampala, the meeting the Ugandan Society of Anaesthesia’s annual refresher course. I am working with Andrew Hodges, who has established the charity Interface Uganda and moved to Kampala with his wife and family to set up a plastic surgical training programme. Sarah Hodges is an anaesthetist and is coordinating the refresher meeting. There are a handful of speakers from Britain for the two courses, held back to back, which are attended by nearly all of the anaesthetists and anaesthetic officers in the country.

That’s a total of 280 of the 330 anaesthetic officers, 11 consultant anaesthetists, and three trainee anaesthetists currently in Uganda. The population of Uganda is 24 million. The Royal College of Anaesthetists has 13000 anaesthetists on its books in the United Kingdom.

We give a series of lectures and workshops with the local anaesthetists and debate common problems: anaesthesia for caesarean sections, paediatric emergencies, acute abdominal pain. We encourage discussion from an audience that is polite, listens intently, and objects if we flick to the next slide too quickly. After all, if you have no textbook to refer to, how else will you retain what we have imparted some knowledge, but we will not be disposed of: how else can you administer anaesthesia safely to the children in your hospital?

We discuss the importance of careful postoperative monitoring in a high dependency area. There is no question here of intensive care to ventilate sick patients, because when the electricity goes off—which is the same as in many other parts of sub-Saharan Africa and that the remedies are bleeding, magnesium is the treatment of choice for eclamptic fits. The prizes are handed out. It is humbling; the most coveted prize is an anaesthetic T piece, a basic piece of disposable equipment. These T pieces will not be disposed of: how else can you provide a safe service. The delegates all have a copy of the Oxford Handbook of Anaesthesia, donated by the Association of Anaesthetists of Great Britain and Ireland under the “books for anaesthetists in Africa” scheme.

And we know that the situation in Uganda is the same as in many other parts of sub-Saharan Africa and that the remedies are not expensive. We have been moved by the dedication of this group of professionals, and by the efforts of individuals such as Andrew and Sarah Hodges and their colleagues, in the face of such difficulties.

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It is always good to be able to ask a respected source a question and get a useful reply. On the Johns Hopkins AIDS service for the clinician forum [http://3a.hopkins-aids.org/forum/main.htm] you can see the questions that have been posted recently, search the database, or check by category. It is easy to ask a question, and you can read the online biographies of those responding. Case histories are an appealing and challenging way to learn, and if you are interested in paediatric radiology check out the weekly quiz at [www.bedsradiology.com/default.aspx] Answers are provided in the archive.

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We welcome suggestions for websites to be included in future Netlines. Readers should contact Harry Brown at the above email address.
Afterwards gives us an important glimpse of how veterans who are psychologically damaged by their war experiences struggle to cope after returning to civilian society. Seiffert, one of many new writers nurtured by the creative writing course at Glasgow University and whose first novel, The Dark Room (2001), was shortlisted for the Booker prize, has written Afterwards in an understated, almost skeletal style that paradoxically seems to make her work all the more powerful.

At the centre of the story is the developing relationship between Alice, a physiotherapist, and Joseph, a former infantryman who now works as a plasterer and decorator. As the story unfolds it becomes clear that Joseph has been struggling to cope with psychological harm resulting from service with the army in Armagh. Alice, who was abandoned by her father as a baby and is still grieving for her beloved grandmother, enlists Joseph’s help to redecorate her grandfather’s house. During the redecoration, David, her grandfather, seems to welcome the opportunity to confide in Joseph about his war experiences in Kenya, where as an RAF officer he bombed Mau Mau villages. The effect of this is to rekindle the terrors in Joseph’s mind about his own experiences in Armagh in the early 1990s.

Enlisting in the army had, to Joseph, “felt like something real,” allowing him to escape the estate where he grew up; but Seiffert slowly describes the effect on Joseph’s mental health of his military experience, and we learn that Joseph had killed a suspected gunman in front of his wife and child. We begin to understand how lasting and psychologically scarring the effects of Joseph’s military experience have been.

Seiffert describes well Joseph’s disorientation when he leaves the army and becomes homeless: “It took over everything sometimes and there wasn’t anywhere he could settle. Only a few days in any one place, if that. Friends’ houses, then friends of friends, sometimes hostels. He was in a place for veterans for over a week once and that was easy at first, familiar . . . but the man in the next bed had screaming nightmares, and the day room was full of bitter talk about compensation and pensions. A lot of Gulf War blokes there, all of them angry.”

Alice becomes increasingly aware that Joseph studiously avoids talking about his army past and is prone to “disappear” regularly as a means of trying to cope. She also becomes curious to know what her grandfather and Joseph had discussed together.

Concern about the quality of care available for injured veterans who are psychologically damaged by their war experiences struggle to cope after returning to civilian society is increasing in the United States and the United Kingdom. Recent testimony to the US Senate’s Armed Forces Committee described the struggle of many veterans to have mental health problems taken seriously by military review boards seeking to limit costs. In the UK, the ex-services mental welfare charity Combat Stress and the Royal British Legion have each reported a significant increase in numbers of returning service personnel with post-traumatic stress disorder and other psychological illnesses. As described in Afterwards these mental problems often result in anxiety and depression, substance abuse, violence, and homelessness.

There has also been concern that the UK’s “military covenant”—namely, the historical obligation, recognised since the Napoleonic wars, for the state to care for military personnel who have served their country—is being less than fully honoured or is even ignored. This resulted in the publication of an open letter to the prime minister, signed by national figures and relatives of members of the armed forces who have died recently in the Middle East, following Ministry of Defence plans to close the UK’s only dedicated military hospital at Haslar in Gosport and replace it with a military ward at Selly Oak Hospital, in Birmingham. Throughout the rest of the country NHS services will be expected to provide outpatient services for injured service people. Whether or not these new services will provide adequate support for the growing number of mentally traumatised veterans from Iraq and Afghanistan remains to be seen; but as Afterwards illustrates, such services will have little or no effect on the many subclinical cases of battle shock.

Afterwards is an important and timely new work that avoids political viewpoints but will make readers think beyond the headline figures of war fatalities, terrible as these are, to the effect of war on ordinary lives, relationships, and families.

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See also Clinical review, p 789

Afterwards will make readers think beyond the headline figures of war fatalities to the effect of war on ordinary lives
Call of the curlew

My face clung to the seats as I crossed the Pentland Firth for the first time. I was unable to raise my head for fear of heaving. The Orcadians, welly booted and boiler suited, laughed and joked through cigarette smoke as they chewed on bacon rolls. I wanted to bawl.

Ten years later I stood on the deck, drenched in sea spay. I chewed a bacon roll as the boat heaved and rolled fiercely. Basketball booted and stretch jeans suited, I clung to my new PVC Woolworths suitcase. In life it is often easier knowing what you don’t want—I turned my back on Orkney.

City life is different from the remote island life of my childhood. Cities are polarised communities, divided by deprivation and wealth, and foreign to each other in almost every way—schools, health care, transport, and lifestyles. In theory all general practitioners do the same job, but in reality urban and suburban practices are different countries, with their own language and customs.

A friend of mine returned to take up a GP position in Orkney, and many other professional people have returned home to Orkney over the years. Why would they choose such a small and closed environment?

Remote communities offer limited choice in all things but especially in education and health care. There is therefore a strong vested interest in making public services work, with the most influential people in the community having no opt out clause. There is also a lack of anonymity in remote communities—people know you from primary school. Whether you become a doctor, lawyer, or member of the Scottish parliament, you have little scope to take up pretensions on an island, or you will soon be reminded of the time you cried for your mummy. Lastly, families are more stable because they have remained for generations in certain areas—consequently there is no faceless crime in a small community. The bottom line is that a community that is raised together stays together—it works.

Many of our social and medical problems are a product of the widening schisms in our society—and all communities are the worse for it. Despite all the sophistication of our urban life, there is much to learn from rural communities. With the absolute certainty of youth long gone, I wonder if I was right to leave.

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No miracles in the NHS

“It’s Our Lord,” said my receptionist, “and before you ask, He has ID, a gold credit card.”

“Hang on,” He said as He entered the surgery, “I’d asked for a doctor that believes in Me.”

“Nothing personal, Lord,” I said, “but to rational people you’re slightly less believable than Santa Claus or homeopathy, all that Samson and Goliath stuff.”

“Hey,” He said, “Samson was a decent hardworking man; runs a barber shop now—or was it then? Omnipresence can be confusing.

“I’m feeling a bit depressed,” He continued, idly bringing my dead budgie back to life. “Two thousand years, and very little gratitude; when things go well they take it for granted—when they go badly I get the blame.”

“Boy, could I sing a few bars of that,” I said. “The real question is, just how depressed are you?”

“Oh, not too bad, I suppose,” He said gamely. “So I thought . . . maybe a few tablets . . . ”

“Alas,” I said, “the latest guidelines from the National Institute for Health and Clinical Excellence (NICE) on mild to moderate depression are unequivocal; no medications for you, Lord. Take plenty of exercise, eat a balanced diet, and try and get out some more.”

“What else do they suggest?” He said, visibly unimpressed by my lifestyle advice, further evidence of His human side.


“Hey, we can put the show on right here in the barn,” I said, hoping a Mickey Rooney reference might cheer him up. I patted his knee and said, “There, there.”

He seemed to find this unhelpful.

“Anything else?”

“Of course,” I said, “Do you think the fine people at NICE are idiots, that they have no idea what’s really going on out there, on the streets? Cognitive therapy is a very effective treatment.”

“Great,” He said, “I’ll have that?”

“I have more bad news,” I sympathised. “Because your depression is only mild to moderate, you’re not an urgent case. I can’t refer you directly, you’ll have to see a psychiatrist first, and non-urgent psychiatric cases are usually not seen for about six months, and the waiting list for cognitive therapy is another six months after that.”

“About a year in total,” He calculated, biting his lip. “That’s a long time to be depressed. Any other treatment options?”


“So what NICE are saying, in effect,” He reasoned painfully, “is that there are no treatments for mild-to-moderate depression.”

“It is you that say it, Lord, not me. Have a NICE day,” I said, getting up and washing my hands.

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Life unlimited

It is an old hobby horse of mine that what drives many people to seek medical assistance, when they have nothing much wrong with them, is not so much fear of illness as fear of meaninglessness. This is what drives them also to such extravagant and obvious self-destructiveness: for the crises that result from their conduct at least lend to the vacuity of their existence the patina of drama. Unfortunately, we doctors are not experts in the meaning of life.

The well known literary academic Terry Eagleton has just published a book entitled The Meaning of Life (Oxford University Press). I do not think it is any criticism of it that it does not provide a definitive answer to the conundrum, that we could profitably push into our patients’ hands and say, “Here, read this,” in the pious expectation that, having read it, they will not bother us again with their trilling complaints.

Here I must confess, in the spirit of declaring an interest, to an irrational and base prejudice against academics and intellectuals who publish under diminutives of their own first name. I mean, who could have taken seriously A Treatise of Human Nature or The Decline and Fall if they had been written by Dave Hume and Ted Gibbon?

But if Professor Eagleton’s occasional lapses into politico-linguistic correctness irritated me, and I found his conclusions utopian and therefore fatuous, I was none the less impressed by his lucidity and (more surprisingly) his fair mindedness. He claims not to be a philosopher, but he does a fair imitation of one.

A passage in the book that stirred me to my childhood, concerned disability: “In Aristotle’s eyes, the reason why you could not be really happy sitting in a machine [that delivered pleasurable stimuli directly to the brain] all your life is much the same reason why you could not be fully happy confined to a wheelchair . . . it is simply that to be disabled is to be stymied in one’s ability to realize certain powers and capacities . . . .”

As a child, my closest friend, from whom I was virtually inseparable for several years, was struck down by polio. It was all the more tragic because it happened immediately before the advent of immunisation against polio. He was rendered paraplegic; my parents, as I now realise, lived in mortal terror with illness, which she regarded as a kind of death-pall. “His sticks,” as we called his crutches, became just a normal part of our lives. I can still hear in my mind’s ear the clicking sound they made as we went everywhere together.

He went on to have a much more interesting career than the majority without his disability. Here, then, is a paradox, if a fortunate one: no one would choose such a disability, and yet it did not in the least prevent him from living life as fully as his contemporaries.

The solution, perhaps, is this: that, within quite wide limits, limitations do not limit us. Infinity is our glory, as it is our burden.

Theodore Dalrymple is a writer and retired doctor.

BETWEEN THE LINES

Theodore Dalrymple

No one would choose such a disability, and yet it did not prevent him from living as fully as any of his contemporaries

La Belle Dame Sans Merci By John Keats

First published 1820

Keats, it is well known, had some medical training. He completed his house jobs at Guy’s Hospital after becoming one of the first people to pass the licence of the Society of Apothecaries. His experience of the family tuberculosis that would kill him at the age of 25 and his early years of surgical assistance gave him knowledge and experience of death, the only clue to his medical background that can be seen in his work.

In La Belle Dame Sans Merci, an imitation of a medieval ballad, an alluring, otherworldly damsel has fatally tempted the “knight-at-arms” who is found, at the poem’s beginning, “alone and palely loitering.”

The narrator who addresses the opening line to the knight could be a medic taking a history—“Oh what can all thee”—and goes on to a physical inspection of the lovelorn and possibly hallucinating knight: “I see a lily on thy brow/With anguish moist and fever-dew.” The flower, a symbol of death, connects in the next line to another flower, a rose, seen fading on his cheeks, which “fast withereth too.”

When consumption was at its height, the pallor of the skin was felt to be in beautiful contrast with the rosy cheeks. These changes, however attractive, Keats knew were a death warrant. Tuberculosis had no cure. Indeed it was steeped in mythology involving spirits and even vampires.

The knight’s reply to these inquiries—the rest of the poem—is his story of the faery lady, followed by his recounting a sinister dream populated by “pale warriors, death-pale were they all,” who inform him ghoulishly that “La Belle Dame Sans Merci/Hath thee in thrall.” He finishes by reflecting on his captive, hopeless state, repeating the famous first verse with a subtle change in rhythm, “And this is why I sojourn alone and palely loitering/Though the sedge is withered from the lake/And no birds sing.”

A mysterious poem of seemingly endless interpretations, it uses images of death to straddle the supernatural and make it eerily present. Keats, by his own account, was not the most attentive student: “The other day, during the lecture, there came a sunbeam into the room, and with it a whole troop of creatures floating in the ray; and I was off with them to Oberon and fairy-land.” Eventually he deemed himself unfit for surgery, saying of his last operation, “The opening of a man’s temporal artery . . . I did it with the utmost nicety, but reflecting on what passed through my mind at the time, my dexterity seemed a miracle, and I never took up the lancet again.”

Not every desultory junior doctor has such insight. Keats was a doctor for whom medicine could not compete with poetry. Our literature is the greater for it.

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MEDICAL CLASSICS

La Belle Dame Sans Merci By John Keats

First published 1820

Keats, it is well known, had some medical training. He completed his house jobs at Guy’s Hospital after becoming one of the first people to pass the licence of the Society of Apothecaries. His experience of the family tuberculosis that would kill him at the age of 25 and his early years of surgical assistance gave him knowledge and experience of death, the only clue to his medical background that can be seen in his work.

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Aires Agnelo Barnabé Barros D’Sa

Pioneer of vascular surgery during the troubles in Belfast

Aires Barros D’Sa was a pioneer of vascular surgery and trauma, who in 2000 was awarded the OBE for services to vascular surgery in Northern Ireland. He died suddenly in the cardiac surgical intensive care unit in the Royal Victoria Hospital, Belfast, where he had spent most of his career playing a pivotal role in establishing vascular services regionally, nationally, and internationally. He founded one of the first vascular laboratories in the United Kingdom, which in 2005 was named the Barros D’Sa Vascular Laboratory.

Born to a Goan family in 1939 in Nairobi, Aires Barros D’Sa grew up in Kenya. He gained a scholarship to medical school in Mumbai. However, he was caught up in the Indian blockade of Goa, which heralded the end of Portuguese rule there, and couldn’t reach Mumbai, so in 1959 he took up a scholarship to Queen’s University, Belfast. One of a handful of overseas students in Belfast in the 1960s, Aires emerged as a social and academic leader. His future in Northern Ireland was ensured when he met and married Libby, a fellow medic.

In 1978, after a year at Providence Medical Center, Seattle, Aires was appointed consultant vascular surgeon in the Royal Victoria Hospital, Northern Ireland’s primary teaching hospital. He quickly stood out for his charm, warmth and humour, thirst for knowledge, and clinical acumen. A loyal champion of his nurses and junior staff, he fought continually to ensure the best resources for them and for his patients, with scant patience for red tape. He expected his own high standards to be met; lazy, incompetent staff were not tolerated, and patients found terrorising nurses were simply wheeled off the ward, not to be readmitted.

The troubles reached their height in the 1970s, and the Royal Victoria Hospital received the majority of victims. Many required treatment for horrific bomb blast, shrapnel, and gunshot injuries. During this time, Aires gained an international reputation for his pioneering use of shunts in the management of complex limb vascular injuries. His surgical technique was unparalleled and, aligned with his courage, stamina, and coolness under pressure, undoubtedly saved many lives and limbs. While Aires, along with colleagues, applied impeccable standards of care to all patients, he despised terrorism and had no time for extremists from either side.

In recognition of his pioneering work in vascular trauma he was appointed Hunterian professor of the Royal College of Surgeons in 1979. Over the next decades he travelled extensively worldwide as an invited lecturer, notably in 1983 as the 77th James IV surgical traveller representing the British Isles.

A visionary, Aires recognised clear advantages in developing vascular surgery as a specialty. In 1978 he initiated the establishment of a dedicated regional vascular surgery unit in the Royal Victoria Hospital, only the third of its kind in the UK, and in 1979 instituted a clinical vascular laboratory. In 1996 he established a registry for vascular surgical patients in Northern Ireland; among the UK’s earliest regional databases, it is still in use today.

Despite increasing national and international commitments, Aires retained a love of teaching. Students learnt from his example exceptional care and thoughtfulness towards patients in pain and anticipating major surgery. As a lecturer, his dynamic delivery vivified the driest subjects. He would arrive early for lectures and cover the blackboards with superb anatomical drawings, and his detailed operating notes often resembled sketches from Leonardo Da Vinci’s notebook. He designed crests for the Ulster Surgical Club and the Joint Vascular Research Group, one of five national and European societies of which he was a founding member.

Hugely committed to vascular research, Aires published extensively, in particular on vascular trauma: 209 pieces of original research, 187 communications to learned societies, and 34 book chapters. He authored and edited three books, most recently Emergency Vascular and Endovascular Surgical Practice, co-edited with Tony Chant; the second edition was highly commended in the 2006 BMA medical book competition. He sat on the editorial board of several vascular journals and was a reviewer on many more.

The latter years of Aires’ career brought many accolades. For example, in 1999 he was made honorary professor of vascular surgery (personal chair) at Queen’s University, and in 2001 he was elected president of the Vascular Society of Great Britain and Ireland and in 2003 deputy lieutenant, County Borough of Belfast.

Health problems prompted his premature retirement in 2001. His interests spanned politics, literature, and the arts; he was an orchestra patron, an environmentalist, a keen supporter of Irish rugby, and loved travel. Above all, he was a passionate family man and held that his life’s greatest achievement was raising his four daughters. In his final year, the arrival of a grandson brought him enormous joy. He leaves Libby, four daughters, and one grandson.

Lisa Barros D’Sa, Paul Blair
Aires Agnelo Barnabé Barros D’Sa, consultant vascular surgeon Royal Victoria Hospital, Belfast; honorary professor of vascular surgery Queen’s University, Belfast (b 1939; q Belfast 1965; OBE, DL, MD, FRCS, FRCS Ed), died on 29 January 2007 from bronchopneumonia secondary to pulmonary hypertension associated with CREST syndrome, a week after having had heart surgery.
George’s Medical School, as well where she stayed for 20 years. After qualifying, Mary Cameron travelled to the United Kingdom, particularly the university club. He was an active researcher in embryology and heterotopic ossification. He was active in the Council of the Anatomical Society of Great Britain and Ireland, represented university teachers and medical researchers locally and nationally, and was chairman of the local BMA in 1986. In 1975-7 he was appointed Queen’s honorary physician and awarded honorary chairman of the local BMA in 1986. Barry was a founder member of the Royal College of Obstetricians and Gynaecologists. He was a founder member of the Royal College of Physicians and Surgeons of Edinburgh (FRCP). In 1975-7 he was appointed Queen’s honorary physician and awarded honorary professorship of obstetrics and gynaecology. Barry was educated in classics and modern history and listener to his death. He was an avid smoker and whisky and wild enthusiasms were features of his personality. His cigarettes and whisky were always at hand, and he never lost his immense enthusiasm for conventional medicine. His passion was for truly integrated medicine. For it to be more widely available in the NHS, he leaves a wife, Pat; three children; and two grandsons.

Jennifer Boyle

Doreen Mary Tillotson
(née Robertshaw)

Former general practitioner Menston, West Yorkshire; assistant medical officer of health Skipton; schools medical officer Leicester (b 1905; q Leeds 1928), d 15 December 2006. Doreen was one of only four girls in her year at medical school. In 1929 she started a general practice in Menston amid cries from the main practice (of men) that she wouldn’t last six months. Twenty years later she moved to Ilkley to become assistant medical officer of health for Skipton. As founder member and president of Ilkley Soroptimist Club, she worked with and inspired the Methodist Homes for the Aged to establish “Glen Rosa.” Around 1958 Doreen was asked by Save the Children Fund’s headquarters to start a committee in Leicester; she was still its vice president when she died. Predeceased by her husband, Ambler, in 1984, she leaves two sons and five grandchildren.

Peter Tillotson

ADVICE We will be pleased to receive obituary notices of around 350 words. In most cases we will be able to publish only about 100 words in the printed journal, but we can run a fuller version on our website. We will take responsibility for shortening. We do not send proofs. Please give a contact telephone number and, where possible, supply the obituary on a disk or by email to obituaries@bmj.com.
Referral for NHS dental implant treatment is reserved for people who have lost teeth through trauma or were born with too few. It's expensive, and demand vastly outweighs resources. An audit of referral and selection in six months in one London hospital found that only 80% of referrals were in the approved categories (Annals of the Royal College of England 2007;89:247-51). As many as a quarter of patients had untreated caries or periodontitis, which are both contraindications for NHS implant treatment. The proportion of patients with caries was more than double among patients referred by general dental practitioners than among patients referred from hospitals.

In the aftermath of the Modernising Medical Careers debacle, a letter writer in the Journal of the Royal Society of Medicine (2007;100:164) points out that there’s value in holding interviews for both employers and future employees. Junior doctors should regard the process as much for them to have the opportunity to find out more about their potential employers, and to decline a job if the red flags start waving, as it is for consultants to choose their juniors.

The Netherlands recently introduced a standardised medicinal cannabis product. Because it was anticipated that this would probably be taken with anticancer drugs, researchers did a drug interaction study (Oncologist 2007;12:291-300). They looked at the effect of medicinal cannabis on irinotecan and docetaxel, which are both metabolised by cytochrome P450 isozyme 3A. The cannabis product was given as a herbal tea to patients with cancer being treated with these drugs. The researchers found that the plasma pharmacokinetics were not significantly altered by the cannabis, leaving the required chemotherapy doses unchanged.

A prospective randomised trial of oral betamethasone versus intramuscular dexamethasone for treating mild to moderate viral croup found no difference between them (Academic Emergency Medicine 2007;14:e76). The study was presented as an abstract at the first inter-American conference on emergency medicine. The oral steroid is clearly palatable and doesn’t require a nurse to give it, say the authors, making it a good alternative for ambulatory management.

The consumer correspondent for the Journal of Family Planning and Reproductive Health Care had the arguably enviable job of writing about sex products, much to her friends’ amazement (2007;33:129-30). Apparently they were shocked that such a “highbrow periodical should have commissioned a piece about what can be viewed as such a lowbrow industry.” The correspondent’s biggest warning is that even the better informed outlets promote costly sex products that are useless or even harmful. Health professionals “may giggle but it may cause our more innocent clients to reach inadvisedly for the credit card.”

The first ever conference on blogging in healthcare took place last year. Typically blogs—from “web logs”—are defined as “personal journals posted on the internet,” with entries in reverse chronological order and an invitation for readers to contribute, turning the diary entries into conversations. Medical blogs are sprouting up everywhere and are becoming seen more as tools for communication of complex science—albeit without peer review—and not just for entertainment (European Science Editing 2007;33:13-4).

A 21 year old man saw his GP in London for a non-itchy skin rash. The GP found abnormal results in liver function tests and referred him to a gastroenterologist. While waiting for a liver biopsy the patient moved to Swansea University and consulted the university doctor, who had some experience of working with HIV. The patient was born in Africa and had immigrated to the United Kingdom aged 12 years. His father had died from tuberculosis in Africa. He denied ever using intravenous drugs, although he’d had several injections in Africa for malaria. Severe acne prompted an HIV test, the result of which was positive. Genotype testing showed subtype C, which is common in Africa. His viral load indicated advanced HIV disease. Worsening of previous acne, late onset, or severe forms of acne have all been reported in patients infected with HIV.

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A meta-analysis in the Journal of Bone and Joint Surgery (Am) reports that releasing tourniquets early to obtain haemostasis after knee arthroplasty increases the blood loss (2007;89:699-705). And releasing a tourniquet after wound closure can increase the risk of early postoperative complications, with the need for further surgery. What’s not known is what happens with the late release of a tourniquet and whether this is also associated with early postoperative complications.

The health secretary, Patricia Hewitt, clearly belongs to the “no pain, no gain” school of theory. Interviewed in the Health Service Journal, she said the “pain has been worth it” (29 Mar, p 12-3). The pain she’s referring to is the pressure placed on chief executives to balance the books in the past year. So much pressure, said some, that they were forced to make short term savings that affected patients’ care.

The placebo response is important in the treatment of depression. But how much is contributed by different factors remains hazy. Double blind, placebo controlled trials of antidepressants show that follow-up assessments incur a significant therapeutic effect for patients taking placebo, which represents 40% of the placebo response (British Journal of Psychiatry 2007;190:287-92). Two additional visits were associated with twice the reduction in depression score than one visit, making them cumulative.