Editor's choice

Editor's choice: Research in the BMJ
Fiona Godlee
BMJ 2007;335, doi:10.1136/bmj.39273.529641.47

US editor's choice: Do adverts subvert? Are bacteria good for us?
Douglas Kamerow
BMJ 2007;335, doi:10.1136/bmj.39274.351389.3B

Editorials

The future of the medical profession
Roger Jones
BMJ 2007;335:53, doi:10.1136/bmj.39266.662928.BE

Diarrhoea associated with antibiotic use
Lynne V McFarland
BMJ 2007;335:54-55, doi:10.1136/bmj.39255.829120.47

Surgery for venous leg ulcers
Charles N McCollum
BMJ 2007;335:55-56, doi:10.1136/bmj.39261.651655.47

Treating rheumatoid arthritis
Paul Emery, Tore K Kvien
BMJ 2007;335:56-57, doi:10.1136/bmj.39265.679375.80

Treating painful diabetic polyneuropathy
Edward B Jude, Nicolaas Schaper
BMJ 2007;335:57-58, doi:10.1136/bmj.39261.687650.47

Letters

This week's letters

Oseltamivir's adverse reactions: Fifty sudden deaths may be related to central suppression
Rokuro Hama
BMJ 2007;335:59, doi:10.1136/bmj.39262.448877.BE

FAFfing about: Pandemic preparedness is like house insurance
Peter Dunnill
BMJ 2007;335:59, doi:10.1136/bmj.39269.393356.DE
**FAFfing about:** Evaluating pandemic risk
Susan Chu
BMJ 2007;335:59-60, doi:10.1136/bmj.39269.416435.DE

**HIV:** HIV exceptionalism must end
Martin F Brewster
BMJ 2007;335:60, doi:10.1136/bmj.39269.525116.BE

**HIV:** The societal costs of failing to develop a vaccine
Jeremiah Norris
BMJ 2007;335:60, doi:10.1136/bmj.39269.490255.BE

**Financial incentives and GPs:** What about the impact on patient health?
Mark Strong, John Radford
BMJ 2007;335:60, doi:10.1136/bmj.39269.437176.DE

**News**

Government's plan for NHS review gets mixed response
Michael Day
BMJ 2007;335:61, doi:10.1136/bmj.39269.588738.DB

Polyclinics open till 10 pm proposed for London
Michael Day
BMJ 2007;335:61, doi:10.1136/bmj.39273.467697.DB

Restrictive law on reproduction increases multiple pregnancies
Fabio Turone
BMJ 2007;335:62, doi:10.1136/bmj.39272.373634.DB

GMC hearing against Wakefield and colleagues opens
Owen Dyer

US debates health insurance for millions of children
Janice Hopkins Tanne

Drug industry challenges government's action on generic statins
Clare Dyer
BMJ 2007;335:63, doi:10.1136/bmj.39272.472257.DB

In Brief: News

Orthopaedic departments will have more difficulty meeting 18 week waiting target
Michael Day
BMJ 2007;335:64, doi:10.1136/bmj.39272.408900.4E

Charity challenges decision to refuse eye drug to 84 year old war veteran
Clare Dyer
BMJ 2007;335:64-65, doi:10.1136/bmj.39272.642535.DB

Cambodia faces dengue fever epidemic
Zosia Kmiętowicz
BMJ 2007;335:65, doi:10.1136/bmj.39273.408218.4E
Mental health act "a missed opportunity"
Clare Dyer
BMJ 2007;335:65, doi:10.1136/bmj.39273.354248.DB

Waterborne diseases pose threat in Pakistan as floods strike
Owen Dyer
BMJ 2007;335:66, doi:10.1136/bmj.39272.584688.DB

Consider surgery before IVF, gynaecologists told
Lisa Hitchen

Birth rate drops when obstetricians leave town
Roger Dobson
BMJ 2007;335:66-67, doi:10.1136/bmj.39269.598079.DB

Millennium development goals will not be met until 2282
Peter Moszynski
BMJ 2007;335:67, doi:10.1136/bmj.39273.409132.DB

India reduces estimated count of people with HIV
Ganapati Mudur
BMJ 2007;335:67, doi:10.1136/bmj.39272.563808.DB

Heart failure services in England improve
Susan Mayor
BMJ 2007;335:67, doi:10.1136/bmj.39272.679977.4E

Report calls for better data collection to improve sexual health in England
Susan Mayor
BMJ 2007;335:67, doi:10.1136/bmj.39272.566366.DB

UK residents labelled as "health tourists" have problems accessing health care
Zosia Kmietowicz
BMJ 2007;335:67, doi:10.1136/bmj.39272.371377.DB

Donor countries should ensure donated funds reach health workers
Deborah Cohen, Stephanie Rich
BMJ 2007;335:67, doi:10.1136/bmj.39269.649965.DB

Doctor cleared of act "tantamount to euthanasia"
Owen Dyer
BMJ 2007;335:67, doi:10.1136/bmj.39273.604063.DB

Shortcuts from other journals: Dark chocolate lowers blood pressure
BMJ 2007;335:68, doi:10.1136/bmj.335.7610.68

Shortcuts from other journals: Bed nets protect whole communities from malaria if enough people use them
BMJ 2007;335:68, doi:10.1136/bmj.335.7610.68-a

Shortcuts from other journals: Low cabin pressures are uncomfortable for airline passengers
BMJ 2007;335:68, doi:10.1136/bmj.335.7610.68-a
Shortcuts from other journals: **Time to move on from advanced directives**

Shortcuts from other journals: **Immune deficiency linked to a wide range of cancers**

Shortcuts from other journals: **Dietary counselling is a short term solution to obesity**

Shortcuts from other journals: **New treatments for people with drug resistant HIV**

Shortcuts from BMJPG journals: **Local topography affects annoyance over wind farms**

Shortcuts from BMJPG journals: **Nurse triage in general practice is "efficient but possibly unsafe"**

Shortcuts from BMJPG journals: **Using rear seat belts may save lives**

Shortcuts from BMJPG journals: **French child athletes admit to doping**

Shortcuts from BMJPG journals: **Not placing babies on their side to sleep reduces SIDS**

Feature

**Profile:** Can the ex-postman deliver?
Nicholas Timmins

**175 years of the BMA:** A long way from Worcester
Peter Bartrip

Head to head: **Should medical journals carry drug advertising?**
Yes
Richard Smith
Head to head: Should medical journals carry drug advertising?
No
Gareth Williams
BMJ 2007;335:75, doi:10.1136/bmj.39259.481134.AD

Observations
Border crossing: Who is at the helm on patient journeys?
Tessa Richards
BMJ 2007;335:76, doi:10.1136/bmj.39272.484248.59

Analysis
Analysis: Decline in effectiveness of antenatal corticosteroids with time to birth: real or artefact?
Simon Gates, Peter Brocklehurst
BMJ 2007;335:77-79, doi:10.1136/bmj.39225.677708.80

Research
Use of probiotic Lactobacillus preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial
Mary Hickson, Aloysius L D'Souza, Nirmala Muthu, Thomas R Rogers, Susan Want, Chakravarthi Rajkumar, Christopher J Bulpitt

Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial
Manjit S Gohel, Jamie R Barwell, Maxine Taylor, Terry Chant, Chris Foy, Jonothan J Earnshaw, Brian P Heather, David C Mitchell, Mark R Whyman, Keith R Poskitt

Effects of treatments for symptoms of painful diabetic neuropathy: systematic review
Man-chun Wong, Joanne W Y Chung, Thomas K S Wong

Clinical review
Schizophrenia
Marco M Picchioni, Robin M Murray
BMJ 2007;335:91-95, doi:10.1136/bmj.39227.616447.BE

Practice
Clinical epidemiology notes: Subgroup analyses: how to avoid being misled
John Fletcher
BMJ 2007;335:96-97, doi:10.1136/bmj.39265.596262.AD

Views & reviews
Personal views: Health for London: are we now on the right route?
Stephen Thornton
BMJ 2007;335:98, doi:10.1136/bmj.39272.731470.94
Personal view: How to restructure-proof your health service
Jeffrey Braithwaite
BMJ 2007;335:99, doi:10.1136/bmj.39272.443137.59

Live from London: My brilliant career as health minister
Deborah Cohen
BMJ 2007;335:100, doi:10.1136/bmj.39273.479167.59

Outside the box: Lecturing by remote
Trisha Greenhalgh
BMJ 2007;335:100, doi:10.1136/bmj.39272.454398.59

Between the lines: Talking with crowds, walking with kings
Theodore Dalrymple
BMJ 2007;335:101, doi:10.1136/bmj.39272.693461.59

Medical classics: The Painted Veil
Peter Cross
BMJ 2007;335:101, doi:10.1136/bmj.39265.680683.68

Review of the week: Getting the inside story
Craig Gerrand
BMJ 2007;335:102, doi:10.1136/bmj.39259.540463.34

Obituaries
This week’s obituaries
Arthur Thomas Marshall and Mary Louise Marshall (née Neville)
Tom Marshall
BMJ 2007;335:103, doi:10.1136/bmj.39267.560162.BE

Joseph Patrick Booth
Sara Booth, Brian Bartley
BMJ 2007;335:103, doi:10.1136/bmj.39267.658657.BE

James Wilson Harkess
Donald A L Dick
BMJ 2007;335:103, doi:10.1136/bmj.39262.693229.BE

Peter Kenneth Robinson
Philip Kennedy
BMJ 2007;335:103, doi:10.1136/bmj.39260.529641.BE

Tessa Louise Whitton
Stephen Hill
BMJ 2007;335:103, doi:10.1136/bmj.39259.738218.BE

Minerva
Minerva
BMJ 2007;335:104, doi:10.1136/bmj.39267.646366.801

Minerva
Monika Bajaj, Ulf Clausen, David Nag
BMJ 2007;335:104, doi:10.1136/bmj.39267.646366.80

 Corrections
Managing the menopause
BMJ 2007;335, doi:10.1136/bmj.39272.472801.AD (published 11 July 2007)
Career focus

Read this week’s articles on
The future of the medical profession

Depends on professional unity and respectful dialogue between the government and the profession

This year marks the 175th anniversary of the BMA. The association has been centrally involved in the evolution and stewardship of the medical profession and has made contributions to national and international health that go far beyond its role as a representative and negotiating body. It has had an important role in debates on euthanasia, global conflict and the proliferation of nuclear weapons, AIDS, genetics in medicine, and human rights. It must also take a good deal of the credit for the present ban on smoking and, of course, for this journal.

The BMA took a highly conservative and aggressive stance against Bevin’s plans for the National Health Service (NHS) in the 1940s, but 50 years later found itself almost in step with the health departments after the abolition of the internal market. However, this sense of common purpose is now much more difficult to discern.

The BMA has been faced with many difficulties in engaging with the complexities of 21st century medicine and a highly politicised health service. The Shipman, Bristol, and Alder Hey enquiries and a litany of errors, shook the foundations of public trust and professional confidence. Against a background of escalating healthcare costs, rapidly changing workforce and population demography, and the impact of the European Union, there have been recent difficulties with computerisation of the NHS, the postgraduate training system, doctors’ contracts, and revalidation. The role of doctors’ careers in medicine, and the future of a publicly funded health service have all been questioned.

It is ironic that some countries where the commercialisation of health care has developed unchecked, and others wishing to develop cost effective equitable health systems, have looked to the NHS as a role model. The NHS has, historically, provided universal coverage, ready access, and high quality care for an enviably low proportion of gross domestic product, although this is beginning to change. The reason for this change seems to be the political manipulation of the NHS by a health department that either does not understand or has forgotten what has made the NHS a success. It has disastrously underestimated the extent and importance of hard work, commitment, professionalism, and pride in the service among its workforce. This has resulted in a progressive deconstruction of general practice, the transformation of hospital contracts into a shift system, the introduction of bizarre organisational arrangements in the name of patient choice, and widespread demotivation and demoralisation.

Has the medical profession, in its retreat from out of hours responsibility and personal continuity of care, its support of market values, and its acceptance of central control finally sold out? Or, is it that the NHS reforms have somehow eroded the conditions under which professionalism and altruism flourish? Altruism is, after all, sustained by appreciation on both sides, just as professional respect and esteem are earned by the provision of compassionate care.

To say that the medical profession must unite to reaffirm its core values sounds like a statement of the obvious, but it is probably right. The profession certainly can’t afford division. Ever since the NHS was formed, there has been an inevitable separation between primary care (general practice and community medicine) and secondary care (hospital medicine), which has often caused tension between professionals. Current funding arrangements—including practice based commissioning and payment by results—could aggravate these differences. Similarly, friction between doctors and health service managers needs to be tackled by collaborative working, including greater participation of senior clinicians in the management of health services.

Medical education and the nurturing of professional values have an important part to play, particularly in moving towards a “new compact” between patients and doctors, put forward by Ham and Alberti, which spells out the rights and responsibilities of the government, the profession, and the public. Serious consideration should be given to proposals made recently to take the NHS out of party politics by creating new governance arrangements. All of this must be firmly underpinned by authoritative and consistent dialogue between the profession and the media.

These suggestions do not represent an agenda for a return to some lost, golden age of medicine, but rather an opportunity to reassert its enduring roles and values, which have been obscured by political and organisational turbulence. After the Cabinet Office’s capability review of the Department of Health, there are signs that a new political administration may consider better ways of working with medical leaders and the NHS. The importance of doing so cannot be underestimated.

For the full versions of these articles see bmj.com

EDITORIALS
Diarrhoea associated with antibiotic use
Evidence supports the use of probiotics, but effectiveness depends on the strain

Diarrhoea is a common side effect of antibiotics; it may prolong hospital stay, increase the risk of other infections, develop into more serious forms of disease (colitis, toxic megacolon), and lead to premature discontinuation of the needed antibiotic. Diarrhoea associated with *Clostridium difficile* is a leading cause of iatrogenic outbreaks of diarrhoea, and considerably increases mortality and healthcare costs for inpatients.1,4 Antibiotic associated diarrhoea may develop in 5-30% of patients, with the rates increasing as the antibiotic spectrum gets broader.4

Diarrhoea associated with antibiotic use may result from the disruption of the barrier of normally protective colonic microflora that are inadvertent targets of the inciting antibiotic. In 20-30% of these cases, an opportunistic pathogen, *Clostridium difficile*, takes advantage of this opening, colonises the intestine, and produces toxins, resulting in diarrhoea or colitis. A strategy to re-establish this microbial barrier is through the use of probiotics.5

In this week's *BMJ* Hickson and colleagues report a randomised, placebo-controlled trial of the effects of a mixture of three different strains of probiotics on prevention of diarrhoea associated with antibiotic use.6

Probiotics are living, beneficial bacteria or yeasts that are taken orally to help restore the microbial balance in the intestinal tract.7 A multitude of probiotic products are available in the global marketplace, but only some are backed by evidence based clinical trials.4,12 The diversity of probiotic products has caused confusion among clinicians and patients as to which are effective and which are not.

The trial by Hickson and colleagues randomised 135 older hospitalised patients receiving a new course of antibiotics to either a probiotic yoghurt drink (containing *Lactobacillus casei* and *Streptococcus thermophilus*) or a placebo milkshake for the duration of the antibiotic plus one week. Patients were followed for an additional four weeks for the development of antibiotic associated diarrhoea or *C difficile* diarrhoea. Significantly fewer patients given the probiotic drink developed diarrhoea than did those given the placebo milkshake (odds ratio 0.25, 95% confidence interval 0.07 to 0.85). Although the rates of *C difficile* diseases were low, the probiotic drink also seemed to prevent this outcome (0% v 17% with placebo; adjusted rate ratio 17%, 7% to 27%). No adverse effects were reported.

The trial has several strengths: the outcomes (diarrhoea associated with antibiotic use and *C difficile* diarrhoea) were defined, the doses (number of bacteria per day) of probiotics were provided, compliance was assessed, and treatments were blinded to patients and assessors.

The trial is limited by its low generalisability due to the small proportion (8%) of people who were enrolled from the target pool of hospitalised patients receiving antibiotics. For a preventive treatment to be practical, it needs to be given widely to the population at risk.

Another limitation is the lack of proper probiotic designs. Closely related bacterial strains have been shown to have differing abilities to act as efficacious probiotics,13,15 so the need to correctly identify the strain (not just the genus and species) of probiotic under investigation is paramount. The authors identified only one strain (*L casei* DN 114 001), and they (inappropriately) cited its brand name as part of its nomenclature. A description of the time of onset would have been helpful (while patient was taking antibiotics or delayed onset after antibiotics were stopped) so that clinicians know when they should expect diarrhoea to develop. The authors also say their analysis was intention to treat, but patients lost to follow-up were not included; although the loss to follow-up was moderate (22 patients; 16%) and the numbers were similar in the two groups.

Despite these limitations, this study supports the findings from other randomised, double blinded, controlled trials that various probiotic preparations are effective for preventing diarrhoea associated with antibiotic use.8,12

So how does this growing body of evidence translate into clinical practice? The study by Hickson and colleagues adds to the findings from recent meta-analyses that probiotics are effective for preventing diarrhoea associated with antibiotics.11,13 Some European hospitals routinely recommend probiotics as an adjunct to high risk antibiotics. Probiotics may be especially useful for patients with chronic infections (such as sinusitis or diabetic foot ulcers) that require repeated courses of antibiotics. Barriers to this practice include choosing an effective probiotic strain, the additional cost of the probiotic, and risks associated with use in immunocompromised patients. Probiotics can easily be given along with antibiotics as an adjunctive preventive treatment and seem to be well tolerated by both paediatric and elderly populations.10,14,16 A word of caution: clinicians need to consider which probiotic strain is supported by evidence from clinical trials, as not all probiotics have equal effectiveness. The evidence that probiotics are effective as a preventive measure for *Clostridium difficile* requires further trials, and more strains need to be tested for their probiotic potential.

Surgery for venous leg ulcers can reduce recurrence, but will have little impact on prevalence

Venous leg ulcers are painful, malodorous sores that impair quality of life and are difficult to treat. An estimated 5%-8% of the world's population have venous disease, and 1% have venous ulcers at some time in their life. The cost to healthcare services is best known for the United Kingdom, where active ulcers affect 1.7% of the elderly population, at a cost to the NHS of around £600m ($890m; $1200m) a year. Available evidence suggests costs are high throughout Europe, the United States, and Australia. These ulcers are caused by sustained high venous pressures due to venous disease, obesity, immobility associated with arthritis, or even old age itself.

Compression using four layer bandaging is the mainstay of treatment—it completely heals ulcers in a mean of 7-8 weeks when delivered by trained leg ulcer nurses in the community. The efficacy of four layer bandaging is not influenced by the underlying venous abnormality. Whether novel “biologically active” dressings can improve these healing rates remains uncertain, as does the role of venous surgery.

In this week's BMJ, Gohel and colleagues report the long term results from the ESCHAR trial, which compared compression alone with compression plus superficial venous surgery in patients with open or recently healed leg ulcers and superficial venous incompetence. This trial was adequately powered and reported on ulcer healing, ulcer recurrence, and ulcer-free time over three or four years. Most previous trials either ignored the role of compression therapy or compared surgery with compression, which is inappropriate as both are effective treatments that should be complementary.

ESCHAR clarifies the role of superficial venous surgery in people willing or able to have an operation. The trial found no significant difference between compression alone and compression plus surgery on ulcer healing at three years—but recurrence, which otherwise happens in a quarter of patients each year, was almost halved. This beneficial effect was most obvious in patients who have incompetence affecting only the superficial veins or those with “segmental” deep venous incompetence, in which reflux is found in limited segments of the deep veins without widespread valve failure. The authors’ use of “isolated superficial” where the deep veins are normal, “segmental deep,” and “total deep” incompetence is unfortunate as most “segmental deep” incompetence is reflux within the common femoral or popliteal vein emptying into the incompetent long or short saphenous vein; valve failure is largely confined to the superficial veins.

The finding of reduced ulcer recurrence after superficial vein surgery in patients with “total deep” incompetence is surprising as valve failure causes widespread deep venous reflux in such patients. However, early results from the ESCHAR study showed that ablating incompetent superficial veins improves deep venous function. This does not mean that all patients with combined superficial and deep incompetence would benefit from superficial surgery. Preoperative assessment in ESCHAR was by duplex imaging, which describes the anatomy of venous disease but not the function. Ambulatory venous pressures would be a more reliable measure of venous function, with a narrow tourniquet obstructing the superficial veins. Many surgeons do not use ambulatory venous pressure measurement because it requires cannulation of the foot, even though it is the only direct measure of venous pressures.

The encouraging results of surgery on ulcer recurrence rates in the ESCHAR trial will sadly have little influence on overall ulcer prevalence. Patients were recruited from specialist, hospital based leg ulcer clinics, whereas many elderly people in the community refuse to attend hospitals for either venous investigations or surgery. Even among the hospital clinic patients screened for ESCHAR, over a third refused to be randomised and a further 20% refused surgery despite consenting to the study. In the community, our experience is that less than half the patients would attend for investigation, and perhaps a third would consider surgery, simple pinch skin grafting being an exception as it can be done in the community by specialist nurses, under local anaesthetic, and speeds the healing of large ulcers.

What does this mean for general practitioners looking after people with leg ulcers? Firstly, people should be referred to a specialist leg ulcer service for investigation of arterial disease before four layer bandaging, if appropriate.
These services should include a local vascular surgeon to manage arterial disease and arrange venous investigations in people being considered for surgery or, in the future, microfoam sclerotherapy or endovenous laser treatment. Referral to a vascular surgeon does not need to be delayed until the ulcer has healed, and nor should a history of deep vein thrombosis be a deterrent since it is found in only 10% of people with leg ulcers, and in a third of those with deep venous incompetence. Superficial venous incompetence, the usual cause of varicose veins, can be detected in most patients with venous ulcers and is a potentially correctible cause of venous hypertension. Neither ESCHAR nor a previous study found that superficial venous surgery accelerates healing. However, there is no need to delay venous surgery where appropriate for uninfected leg ulcers.

Future research should focus on identifying patients at risk of ulceration in order to prevent rather than treat. Superficial venous surgery and compression will almost certainly both have a role in ulcer prophylaxis.


**Treating rheumatoid arthritis**

Antitumour necrosis factor can produce remission if started early

Rheumatoid arthritis is a chronic inflammatory disease affecting the synovial joints. It is characterised by persistent inflammation and destruction of bone and joints. It affects physical functioning and other dimensions of quality of life. Symptoms can be treated with analgesics and non-steroidal anti-inflammatory drugs, which block cyclo-oxygenase. The underlying disease process can be affected by drugs that block or reduce the concentration of cytokines, which are known as disease modifying antirheumatic drugs. These drugs are either conventional small molecules or biological molecules.

The outcome of treatment for patients with rheumatoid arthritis has improved considerably during the past 20 years. People have speculated about the potential to reverse the disease for some time. Treatments that aim to induce remission have been called for since the start of the 1990s. Several approaches have been investigated, including step-up (adding one drug to another) and step-down (starting with a combination of drugs and withdrawing individual ones) regimens and giving three disease modifying antirheumatic drugs at the same time. All approaches have reduced inflammatory activity, delayed radiographic progression, and improved function and quality of life. However, only a few patients have achieved remission. The benefits of cytokine blockers—for example, drugs that antagonise tumour necrosis factor (TNF)—have exceeded initial predictions. Blocking TNF was predicted to reduce symptoms, but to have little structural effect on bone and cartilage, as evidence from animal models indicated that interleukin-1 was a more important bone cytokine than TNF. Clinical studies have shown, however, that TNF blocking agents have long lasting benefit, particularly when combined with methotrexate, and have a major effect on bone damage. There is thus little doubt that the current most effective treatment for patients with rheumatoid arthritis is a combination of methotrexate and anti-TNF. But questions remain, such as whether all patients need this treatment to achieve an adequate response and whether it can be cost effective. The effects of TNF on remission have been assessed in two studies. The first found that 12 months of anti-TNF given early on in the disease process could produce remission, which was sustained one year after ceasing treatment. The second found that six months of TNF blockade showed only short term benefit. Against this background, a single blinded pragmatic study with four treatment arms was started in the Netherlands, and the longer term data from this study have now been published. The first two arms tested the efficacy of conventional disease modifying antirheumatic drugs, with either a switching or step-up protocol, while the third and fourth arms compared anti-TNF plus methotrexate with combination treatment plus corticosteroids.

A crucial feature of the study was that participants were all treated according to prespecified targets (treatment-to-target strategy)—initial drug regimens
The incidence of diabetes is expected to double over the next two decades, which will result in more people with complications of diabetes. Diabetic polyneuropathy is one of the most common, with a prevalence of around 30-50%. It can have a major impact on patients’ quality of life, and treatment is usually needed for many years.

Community based studies report the prevalence of painful diabetic polyneuropathy as around 16-26%, and in one study 80% of the patients had moderate or severe pain. Quality of life is reduced in patients with painful diabetic polyneuropathy, with restriction in daily and social activities, and the condition is associated with depression, sleep disturbances, and anxiety. In this week’s BMJ Wong and colleagues report a systematic review of the effects of drug treatment in painful diabetic polyneuropathy.

Many types of drugs have been studied for relief of pain in diabetic polyneuropathy, as little evidence exists that classic analgesics such as paracetamol or non-steroidal anti-inflammatory drugs are effective. Surveys show that there is substantial scope for improvement in clinical care. In one UK population based study almost 40% of people with painful neuropathy reported that they had never received any treatment, almost a third had been prescribed drugs with no known efficacy in neuropathic pain, and only a minority had been treated with tricyclic antidepressants or anticonvulsants.

Wong and colleagues’ review identified the randomised placebo controlled trials of topically applied and orally administered drugs. Clinical success was defined as a 50% reduction in pain; withdrawal due to adverse events was a secondary outcome. The review found that tricyclic antidepressants were most effective in reducing pain by 50% (odds ratio 3.17; 95% confidence interval 1.88 to 5.32), followed by traditional anticonvulsants (lamotrigine, sodium valproate, carbamazepine; odds ratio 7.59; 2.16 to 26.58), and the newer generation anticonvulsants.
( gabapentin, oxcarbazepine, pregabalin; odds ratio 3.25; 2.27 to 4.66). The newer generation anticonvulsants were most likely to cause withdrawals due to adverse events, followed by tricyclic antidepressants, and the traditional anticonvulsants (odds ratios 2.98, 2.32, 1.51 respectively).

This review can help clinicians make evidence based choices in the management of painful diabetic polyneuropathy, and it also highlights some of the problems in the treatment regimens often prescribed for this condition. The efficacy of pharmacological treatment is limited: with one of the most efficacious drugs in the meta-analysis, amitriptyline, three patients need to be treated to achieve a 50% reduction in pain score in one patient; in the other two patients the drug will have no effect or a limited effect. Adverse effects were not infrequent, and in the analysis of the effects of tramadol the odds ratio for withdrawal due to adverse events was higher than the odds ratio for 50% pain relief. It is difficult to compare the results of different trials in the review since the duration of treatment was highly variable (between 2 to 16 weeks) and could have influenced the number of withdrawals. Unfortunately all the trials in the review were relatively short; many included only a few patients, and for some drugs the confidence intervals were large. Clearly, robust studies with sufficient size and duration, preferably of at least one year, are needed.

Treatment of painful diabetic polyneuropathy is a clinical challenge and requires a treatment plan that should include psychosocial factors, glucose control, and, if necessary, pharmacological treatment. Listening to the patient and explaining the cause of the pain can help to reduce anxiety. Patients’ beliefs and perceptions of the pain and its cause, coping strategies, mood changes, disturbed sleep, and anxiety all need to be addressed.

Several studies have looked at the impact of analgesic treatment on quality of life, sleep patterns, anxiety, and depression and most of them have shown an improvement in quality of life which might be directly related to improvement in pain score.11 Therefore, treating anxiety or depression first might directly related to improvement in pain score. Therefore, treating anxiety or depression first might also reduce the need for analgesics. A few observational studies have indicated that large variations in blood glucose can exacerbate the pain, so glycaemic control should be optimised.12 13

If, despite these measures, the pain persists and is so severe that pharmacological treatment is indicated tricyclic antidepressants seem the best first step, as suggested by Wong and colleagues’ review. But contraindications include cardiac conduction disturbances and glaucoma, and side effects are not infrequent. The dilemma in treating painful diabetic polyneuropathy is what should be done with the many people who do not respond sufficiently to tricyclic antidepressants or in whom tricyclic antidepressants are contraindicated. Wong and colleagues suggest that the next step should be to use one of the older generation anticonvulsants. However, this advice is based on clustering a group of anticonvulsants with very different modes of action; if they are analysed separately, the number of studies for each drug is relatively small and the evidence for efficacy does not seem convincing. Therefore, we and others suggest pregabalin, duloxetine, or gabapentin as second line agents, as these drugs do not seem to differ much in efficacy or in the frequency and severity of side effects.9 Only one or two of these drugs should be included in the local treatment protocol, so that clinicians can develop sufficient experience with them. If this treatment fails, combination therapy or tramadol (or another opioid) can be considered.

Studies that evaluate the efficacy of the combination of two or more drugs to relieve pain are few. Only one study combined gabapentin and morphine in people with neuropathic pain; it showed that the combination gave better pain relief, required lower doses of both drugs, and fewer side effects than if the drugs were used singly.11

Although our knowledge of the treatment of painful diabetic polyneuropathy is growing, there is still no consensus on the most effective protocol. Therefore doctors treating people with diabetes must develop their own local screening and treatment protocols. They should include a treatment algorithm, indications and contraindications for drug treatment, potential adverse effects to look out for, and a simple technique to monitor the effectiveness of treatment.

Fifty sudden deaths may be related to central suppression

In his editorial on the association between oseltamivir phosphate (Tamiflu or oseltamivir-P) and neuropsychiatric disturbance in adolescents Maxwell says that the case is not proved but caution is advisable. On 16 June 2007 the Japanese Ministry of Health Labour and Welfare announced that by 31 May 2007 it had received 1377 reports of adverse reactions and others.

Of these, 567 were serious neuropsychiatric cases, 211 showing abnormal behaviour. The number of deaths reported was 71. These are not only “adverse events” but also “adverse reactions” to oseltamivir because many doctors classed and reported them as probably related or that causality could not be ruled out. However, the ministry classed all but four as “rather negative,” believing that the four were allergic in origin.

In addition to these 71 deaths, there were nine sudden deaths which the ministry did not recognise as adverse reactions.

Of the total 80 deaths, 50 were sudden deaths or deaths from sudden cardiopulmonary arrest (18 in those <10 years old, 32 in those aged 20 or over), while eight were accidental deaths from abnormal behaviour (five in teenagers, three in those aged 20 or over). All 58 deaths were classed as “rather negative” by the ministry—totally different from many doctors’ classifications.

Four deaths were from sepsis following pneumonia after possible respiratory suppression, 10 were possibly related to exacerbation of mainly pneumonia, and eight were from hepatic failure, pancytopenia, gastrointestinal bleeding, etc.

Thus adverse reactions to oseltamivir may be roughly classified into three groups:

(a) sudden onset reactions related to central suppressive action of oseltamivir-P during cytokine storm, including sudden death, abnormal behaviours, and other sudden neuropsychiatric disorders; (b) late onset reactions such as pneumonia, sepsis, hyperglycaemia, and late onset neuropsychiatric disorders possibly related to inhibition of human cytosolic neuraminidase (sialidase) activity by oseltamivir carboxylate; and (c) allergic reactions and others.

Rokuro Hama chairperson, Japan Institute of Pharmacovigilance, No.402 Osaka 2-3-2, Tennoji-ku Osaka, Japan 543-0062 gcco0726@nifty.com

Competing interests: None declared.

3 Hama R. New type of influenza-related encephalopathy or new adverse drug reaction? www.bmj.com/cgi/eletters/328/7433/227#8374
4 Hama R. Limited benefit and potential harm of oseltamivir including sudden death and death from abnormal behaviour. www.bmj.com/cgi/eletters/331/7526/1203-#122513

However, it would require time consuming, though relatively inexpensive, negotiations on intellectual property and technology transfer. The activity has no commercial incentive, so governments would need to enable it. They will not do that if the medical establishment constantly argues it is unnecessary.

Pandemic preparedness is like house insurance: one hopes not to need it, but if a severe pandemic comes, as things stand, the total global vaccine capacity with the best adjuvant could after six months cover only 700 million of the 6400 million global population, and that will not change in the next 10 years. For the rest, the situation would be essentially the same as in 1918 because antibiotics do not seem to be of great importance. Delamothe may be happy to have that on his conscience, I am not.

Peter Dunnill chairperson, Advanced Centre for Biochemical Engineering, Department of Biochemical Engineering, University College London, London WC1E 7JE. p.dunnill@ucl.ac.uk

Competing interests: None declared.

1 Delamothe T. Editor’s choice—faffing about. BMJ 2007;334. 30 June.)

EVALUATING PANDEMIC RISK

Delamothe asks why we should be any more worried about pandemic flu in 2007 than in 1997 or 2017. There are certain observable biological events (such as repeated human infections by a novel avian virus) that are potential precursors to a pandemic and may give us some warning of what might be imminent, a luxury that previous generations did not have. To the extent that advances in virology and epidemiology have made it possible for us to document such changes in the behaviour of viruses, it would be foolish, indeed irresponsible, for us to not make use of the information available.

This is exactly the same as how one would use weather forecasts or flood or hurricane warnings to inform one’s behaviour. With regard to H5N1, I would submit that we are in the same position as New Orleans was 24 hours before Hurricane Katrina hit: we can’t be sure we are going to get a direct hit, but it
HIV

HIV exceptionalism must end

The need for HIV policy reform has again been highlighted, reinforcing earlier claims that HIV testing should not have special status as knowledge about HIV status can be lifesaving. Such opinions are seemingly ignored by the UK government and medical establishment, whereas in the United States reform is under way.

Last week's BMJ featured the cases of two apparently healthy babies who presented later with established HIV. The mothers’ infection had escaped detection. Abolishing exceptionalism would prevent such failure by restoring named feedback. Few mothers realise the importance of this information; namely, the drastic consequences of withholding positive results. Full understanding usually arouses incredulity and anger.

Reform must come soon—litigation costs, stigma, and fear of exposure are probably stemming a tide of legal questioning among relatives unnecessarily bereaved by late HIV diagnosis.

Such trouble was predicted in 1998, yet nine years of General Medical Council and BMA inaction have passed since this well argued case to progress “from exceptionalism to normalisation.”

Less well known is a high court judgment ruling that an infant’s human rights to HIV testing outweigh parental rights of choice. Another court could soon find that the right to be born free of HIV infection outweighs all other considerations.

Doctors and politicians failing to take note do so at their future peril. Waiting for cost effectiveness evidence is unethical. 

Martin F Brewster retired general practitioner, Wigtown DG8 9DZ forreir@brewsterweb.co.uk

Competing interests: None declared.

1 Delamothe T. Editor’s choice: FAflying about. BMJ 2007;334:334. (30 June.)

The societal costs of failing to develop a vaccine

Policymakers should consider not the cost of developing a vaccine against HIV, but the cost to society if it fails to develop one.

In the developed world, some patients on antiretroviral treatment will develop drug resistance and the number will be cumulative each year. Medical care costs will increase exponentially for drug resistant patients, greatly exceeding the price of treatments.

Primary HIV-1 drug resistance ranges from 6.6% in Brazil to 10% in Spain to 27.7% in North America, perhaps because of more frequent testing in developed countries. Yet, this may be a portent of what will come in the developing world. By the end of this year, two million people will probably be on AIDS treatment. Many come from resource limited settings, where initial testing is limited, adherence is problematic, and substandard drugs are used as first line treatment. Suboptimal adherence is the most important factor in virological failure. Adherence is low in resource limited settings, increasing the possibility of early onset of drug resistance.

If the rate of resistance in the developing world is around 10% then 200 000 people would be drug resistant by 2010 and would move on to second line therapies. Second line treatments are over 20 times as expensive as first line ones, and patients on such treatments need care from skilled and relatively well paid medical professionals.

Failing to focus on developing an AIDS vaccine will lead to a sequential increase in the number of chronically sick people whose care and maintenance will prove financially unsustainable for donors and affected governments.

Jeremiah Norris director, Center For Science in Public Policy, Hudson Institute, Washington, DC 20005, USA jeannie@hudson.org

Competing interests: None declared.

1 Tonks A. Quest for the AIDS vaccine. BMJ 2007;334:1346-8. (30 June.)

FINANCIAL INCENTIVES AND GPS

What about the impact on patient health?

McDonald et al’s report of general practitioners’ and nurses’ views of the quality and outcomes framework (QOF) highlights the “box ticking” nature of this pay-for-performance contract. We have therefore proposed that incentives are linked more directly to positive health outcomes.

Rotherham practices achieved highly on the smoking related QOF indicators in 2005 and 2006, costing the primary care trust (PCT) about £276 000 in 2005 and £500 000 in 2006. But the smoking prevalence among those on Rotherham’s QOF chronic disease registers remained unchanged.

We have proposed to the PCT executive and the local medical committee that the QOF contract be renegotiated. We suggested for the smoking related indicators that the four week quit target for us as a PCT is allocated proportionally between practices; then, at year end, practices are rewarded a proportion of the 68 QOF points allocated for the current smoking indicators according to the number of quitters relative to their target.

Moving away from tick box based incentives towards outcome based incentives could seem to be penalising GPs for their patients’ unhealthy behaviours. However, as a PCT, we are responsible for the health of our population, and we believe that this is a sentiment shared by our GPs. We are held accountable as a PCT through the quit target for decisions made by our population, an accountability it seems only fair to share.

Mark Strong clinical lecturer, John Radford director of public health, Rotherham Primary Care Trust, Rotherham S66 1YY m.strong@nrhs.net

Competing interests: None declared.

Plan for NHS review gets mixed response

Michael Day LONDON

The UK government has announced a review of the NHS in a bid to ensure that clinical priorities and local accountability are paramount in the health service’s day to day operations.

The health secretary, Alan Johnson, has asked the junior health minister and surgeon Sir Ara Darzi to lead the review and to consult widely with patients and staff.

The move is widely seen as a bid to mend relationships with health professionals, many of whom feel aggrieved by a decade of non-stop NHS reforms.

Mr Johnson said that providing more accessible and convenient care for patients; achieving better value for money; and ensuring that people with long term illness were “treated with dignity in safe, clean environments” were all key areas that the review would look at.

He also announced an extra £50m (€74m; $100m) to fight hospital acquired infections.

Mr Johnson said, “The past 10 years have seen huge improvements in the NHS, and thanks to record investment and measures to raise standards, nine out of 10 patients rate their care as good to excellent.”

He added, “What was right for the last decade—top down targets and important but sometimes difficult reforms—will not be right for the next, where more local decision making and staff empowerment need to drive the NHS.”

He said that the review could result in an NHS constitution that sets out its values and lines of accountability.

The full report will be published in June 2008. An interim assessment in autumn 2007 will inform the next comprehensive spending review.

Gill Morgan, chief executive of the NHS Confederation, said, “We hope that this is not just another review but a genuine exercise in listening and understanding where the service has got to and where it needs to go. The opportunity to re-engage staff with the NHS reform programme is too important to be missed.”

Polyclinics open till 10 pm proposed for London

Michael Day LONDON

GP supersurgeries that stay open till 10 pm and provide facilities for radiography and trauma care have been called for by the surgeon and newly appointed health minister Sir Ara Darzi, in a report. Healthcare for London: A Framework for Action, commissioned by NHS London, the capital’s strategic health authority, calls for a radical overhaul of the capital’s health services, which it says are “not meeting Londoners’ expectations.”

Topping the list of proposals—and immediately prompting fears of hospital closures—is a network of supersurgeries or “polyclinics,” which would massively expand the role of primary care.

The polyclinics would include GPs’ surgeries; diagnostics such as radiography and pathology; outpatient clinics; facilities for urgent care and minor procedures; and associated services, such as pharmacies.

Professor Darzi said, “Londoners face a stark divide between primary care and hospital care, and we believe the polyclinic will fill that gap. Most GPs provide an excellent and well regarded service, but they do not have the facilities to undertake even quite simple diagnostics on site, which means patients face multiple trips to hospital for quite straightforward procedures.”

The report envisages that the clinics will provide up to half of the outpatient treatment currently carried out in hospital by 2017.

It adds that the size and scale of the new clinics would “allow them to improve accessibility by offering extended opening hours across a range of services.”

Patients requiring “urgent care” would be able to see GPs on rota at the polyclinic up to 10 pm.

See Personal View p 98
New reproduction law reduces success rate

Fabio Turone MILAN

The first official data on the effects of the restrictive Italian law on assisted reproduction, approved in 2004, have been made public by health minister Livia Turco, of the centre left coalition government led by the former president of the European Union Romano Prodi.

According to Ms Turco’s report to parliament, the law has resulted in a decrease in the success rate of the procedures and more multiple pregnancies and adverse outcomes.

The law was approved during the previous centre right government by a cross party majority. It prohibits the use of donated eggs and sperm; limits to three the number of embryos that can be created in each cycle; and bans embryo freezing, making it mandatory to put all fertilised eggs back into the womb. Preimplantation genetic testing is also forbidden.

Attempts to modify the law included a referendum in 2005, which did not reach the necessary quorum (BMJ 2005;330:1405).

The report says that Italian centres that offer assisted reproduction had a 14.5% decrease in the rate of pregnancy for every 100 eggs extracted. It fell from 24.8% in 2003 to 21.2% in 2005, an absolute reduction of 3.6%.

The decrease in the rate of pregnancies per embryo transfer was similar, from 27.6% in 2003 to 24.5% in 2005. Conversely, the rate of negative outcomes, including spontaneous abortions, grew from 23.4% to 26.4%, and the number of multiple deliveries also grew, from 22.7% to 24.3%, because in 2005 more than 50% of transfers involved three embryos (because all three eggs had been effectively fertilised).

“All the figures are statistically significant,” said Giulia Scaravelli, head of the registry at the Istituto Superiore di Sanità, the national institute of health, in Rome.

But she recognised that the overall scientific value of the current report was not fully satisfactory. Because the law lacks specific authorisation establishing the registry, privacy laws prevail. As a result, it is impossible to know how many Italian women repeat the treatment before obtaining a child—or before giving up—or move to a better equipped public centre in another region in addition to women who go to private centres abroad (BMJ 2006;333:1192).

“We are trying to overcome the current limits through a voluntary survey,” said Dr Scaravelli.

Fertility centres had a 14.5% decrease in the pregnancy rate

GMC hearing against Andrew

Owen Dyer LONDON

The UK General Medical Council will this week hear charges of serious professional misconduct against three authors of a study published in 1998 in the Lancet that triggered a public health scare by suggesting a link between autism and the combined measles, mumps, and rubella (MMR) vaccine (1998;351:637-41).

Andrew Wakefield, John Walker-Smith, and Simon Murch are accused of carrying out research in 1996-9 without proper ethical approval and of failing to carry out the research as described in the application to the ethics committee.

The formal charges will not be released until the case starts on 16 July, but in a statement the GMC said that the three researchers will also be accused of carrying out potentially harmful tests on the children that were not clinically indicated, including colonoscopies and lumbar punctures.

In one case, the GMC will allege, Dr Wakefield and Professor Walker-Smith “administered a purportedly therapeutic substance to a child for experimental reasons prior to obtaining information about the safety of the substance.”

On another occasion Dr Wakefield allegedly took “blood from children at a birthday party to use for research purposes without ethics committee approval, in an inappropriate social setting, and whilst offering financial inducement.”

Dr Wakefield also faces charges in relation to a research grant he received from the Legal Aid Board to investigate a possible link between the MMR vaccine and autism on behalf of parents involved in litigation.

He failed to declare this funding to the Lancet. When the payment was exposed by the Sunday Times newspaper in an investigation in February 2004, the Lancet’s editor, Richard Horton, declared it a “fatal conflict of interest.”

The GMC will also examine allegations of Dr Wakefield’s involvement in a patent relating to a new vaccine.

The study and Dr Wakefield’s comments at a press conference at the Royal Free Hospital, north London, in 1998, caused a

US debates health insurance for millions of children

Janice Hopkins Tanne NEW YORK

A successful US programme to insure children in poor families is coming up for its five year renewal in Congress at the end of September, amid controversy between Democrats and Republicans.

The situation is examined in a commentary in the New England Journal of Medicine by John Iglehart, the journal’s national correspondent (2007;357:70-6), and in a review by the not for profit Commonwealth Fund.

The Democrats want to expand the programme to cover more families, but the Republican president, George Bush, wants to reduce it, giving families tax incentives to buy private insurance. The programme may, therefore, be renewed for only a year or two.
An estimated seven or eight million US children don’t have health insurance. The number has dropped from about 11 million in the 10 years since the federal government set up the state children’s health insurance programme. The programme is about 70% funded by the federal government and 30% by the states. Some eligible children haven’t been signed up by their parents.

The programme expanded on the Medicaid programme, which provides health care for children and others in families below the poverty line. For 2007 this is an income of about $21000 (£10400; €15400) for a family of four.

The programme enrolled children in families that earned up to double the amount assessed as the poverty line (about $41000 in 2007). Many were working poor people, with jobs but no health insurance or health insurance that they couldn’t afford. The programme’s payments to healthcare providers are more generous than Medicaid. Some states with high living costs allowed families earning up to 350% of the poverty level to enrol. Other states allowed parents of children in the programme to enrol.

When the programme expires on 30 September, Democrats have proposed expanding the programme by $50bn over five years to include children in middle class families who don’t have health insurance.

Republicans called for an increase of about $5bn over five years. President Bush said that attempts to expand the programme would be “incremental steps down the path to government-run healthcare,” which he said was “wrong . . . for our nation.” He said a single payer healthcare system would end choice and competition; increase federal spending and taxes; and lead to rationing.


The government is determined to cut the £7bn (€5bn; $3.5bn) a year the NHS pays for branded drugs. With nearly two million Britons taking statins to help lower their cholesterol, the Department of Health estimates that at least £84m a year could be saved if doctors prescribed generic statins.

But a spokesman for the association said that although it supports the government’s desire to get the best value for money, it has “serious concerns” about the methods adopted to persuade doctors to switch their patients to the cheaper drugs. It questioned the legality of offering doctors money as an incentive and cast doubt on the adequacy of safeguards for patients.

The Department of Health’s guidance to primary care trusts last month stated that any change to a patient’s treatment regime “should be based on good quality evidence or guidance” and that payments under an incentive scheme “should go into practice funds and not to individuals.”

It added, “It is good practice to specify appropriate use of the money—for example, for the benefit of patients of the practice.”

The association said that its first concern was the lack of central guidance “to ensure that such switches were not being made without proper regard to the welfare of individual patients.”

The second was that “additional payments to doctors were being made as a direct financial inducement to prescribe certain medicines in substitution for other named medicines, which the ABPI considers is illegal under European law.”

Orthopaedic surgeons will have most difficulty meeting targets

Michael Day LONDON
Experts have highlighted considerable hurdles facing the NHS as it prepares to meet the government’s 2008 deadline for eliminating waiting times of more than 18 weeks.

At a meeting of clinicians and Department of Health civil servants last week, however, warnings were sounded about poor progress in several areas.

Sue Hill, the department’s chief scientific officer, admitted that the situation for audiology services was “pretty dire,” with some patients waiting more than 50 weeks.

The gynaecologist Clive Pickles, from the Royal National Orthopaedic Hospital, in Stanmore, Middlesex, noted that less than 25% of orthopaedic patients were currently admitted within 18 weeks.

Less than 25% of orthopaedic patients are currently admitted within 18 weeks

Experts have highlighted considerable hurdles facing the NHS as it prepares to meet the government’s 2008 deadline for eliminating waiting times of more than 18 weeks.

At a meeting of clinicians and Department of Health civil servants last week, however, warnings were sounded about poor progress in several areas.

Sue Hill, the department’s chief scientific officer, admitted that the situation for audiology services was “pretty dire,” with some patients waiting more than 50 weeks.

The gynaecologist Clive Pickles, from the Sherwood Forest Hospital NHS Trust, said that organisation within his department had been “a complete and utter shambles,” with a lack of interest from clinicians and managers. He added that only when it had become an official Department of Health pilot site for testing new systems for implementing the 18 weeks pledge had senior staff shown any interest.

Speakers at the meeting, a practical guide to delivering the 18 week patient pathway,” noted that trusts have only until the end of November this year to ensure that plans are in place for delivering maximum waits of 18 weeks.

Of all specialties, orthopaedics accounts for the most operations, and experts at the meeting, organised by Healthcare Events, expressed concern about the scale of the problem facing this specialty.

Ian Bayley, a consultant surgeon at the Royal National Orthopaedic Hospital, in Stanmore, Middlesex, noted that less than 25% of orthopaedic patients were currently admitted within 18 weeks.

For further progress to meet the December 2008 deadline, primary care organisations would also have to cooperate with acute trusts by reducing unnecessary referrals.

Charity challenges decision to refuse drug to 84 year old

Clare Dyer BMJ
An English primary care trust (PCT) that refused to fund sight saving treatment for an 84 year old war veteran agreed to reconsider its decision this week after it was threatened with legal action.

Oxfordshire Primary Care Trust said it would look again at the case of Dennis Devier, whose legal challenge is being funded by the charity the Royal

Charity challenges decision to refuse drug to 84 year old

Clare Dyer BMJ
An English primary care trust (PCT) that refused to fund sight saving treatment for an 84 year old war veteran agreed to reconsider its decision this week after it was threatened with legal action.

Oxfordshire Primary Care Trust said it would look again at the case of Dennis Devier, whose legal challenge is being funded by the charity the Royal
Dengue fever epidemic in Cambodia affects 17 000

Zosia Kmietowicz LONDON
Cambodia is facing an epidemic of haemorrhagic dengue fever, aid agencies have warned.

The Cambodian Red Cross says that there have been 16 986 unconfirmed cases of dengue haemorrhagic fever and 174 deaths throughout the country since the start of the outbreak. In June alone there were 132 deaths from dengue fever, a fivefold increase compared with the previous month.

Dengue fever is transmitted by the Aedes mosquito and causes a severe flu-like illness. No vaccine or specific drug treatment exists, although intravenous fluids are given to maintain fluid volume.

Although dengue fever itself rarely causes death it can lead to dengue haemorrhagic fever, which can be fatal. This complication can cause a rash, high fever, headache, muscle and joint pain and haemorrhagic shock.

The Cambodian authorities have been spraying insecticide in the streets to try to control the Aedes mosquito, which breeds primarily in manmade containers where water collects, such as discarded tyres and metal drums. Local radio stations have also been warning people to cover water containers.

Last month the Cambodian government called on its neighbours to help contain and manage the outbreak. Thailand responded by sending supplies and medical teams. Warmer weather and heavy rains seem to be helping to spread the virus through the region with Vietnam, Malaysia, Indonesia, and Singapore all reporting a rise in cases.

A mother prays over her child, who is suffering from dengue fever at Phnom Penh’s Kantha Bopha VI hospital

Mental health act becomes law after concessions are made

Clare Dyer BMJ
The UK government’s controversial mental health bill was finally passed into law last week. Months of confrontation with the House of Lords and lobbying by pressure groups had ended in substantial concessions by ministers.

The Mental Health Alliance, an umbrella group for 77 organisations, accused ministers of missing “a historic opportunity to achieve a modern and humane act” but welcomed “important concessions to protect patients and their families from abuse and neglect.”

Andy Bell, the alliance’s chairman, called on the government to “start listening to the people who are affected by the act when it writes the new regulations and to ensure that sufficient resources are made available to mental health services to implement the changes fairly.”

He also urged ministers to “take seriously the warnings made by the Commission for Racial Equality about the impact of the act on black communities and to take action before it is too late to put this right.”

The new mental health act, which replaces the 1983 act, will allow people with serious personality disorders to be detained—even if they have committed no crime—if they are deemed to be a danger to themselves or others. It also allows patients who have been detained in hospital to be compulsorily treated in the community, under new community treatment orders.

The legislation was introduced after several high profile murders involving people with mental health problems, but critics maintain its powers are too draconian.

National Institute of Blind People (RNIB).
The charity accuses the trust of operating an illegal blanket ban on providing the drugs despite its own stated policy of treating “exceptional” cases, pending full guidance from the National Institute for Health and Clinical Excellence (NICE).

Mr Devier, from Henley, Oxfordshire, who is the main carer for his disabled wife, has wet, age related macular degeneration; Paget’s disease; and diabetes, and he is already blind in one eye.

The trust refused to pay for antivascular endothelial growth factor drugs, which can slow sight loss from wet, age related macular degeneration. One drug, Macugen (pegaptanib), costs about £10 000 (€15 000; $20 000) a year, and the other, Lucentis (ranibizumab), about £12 000.

Steve Winyard, the charity’s head of campaigns, said, “Oxfordshire PCT has told Dennis that for him to be eligible for sight saving treatment he must be an ‘exceptional case.’ In our view he is.

“Oxfordshire PCT claim to be operating a policy where they consider treatment on an individual basis, but as far as we understand they have not funded a single case of [this] treatment. Dennis has had his appeal turned down three times now. If Dennis isn’t an ‘exceptional case,’ then my question to Oxfordshire PCT is, ‘Who is?’” Mr Winyard said that the trust had 70 patients who might benefit from the treatment.

Primary care trusts in England and Wales are formulating their own policies on the drugs while waiting for final guidance from NICE, which is expected in September. Its draft guidance last month recommended a total block on pegaptanib. It said that ranibizumab should be funded only for patients with a specific type of the wet form of age related macular degeneration—about 20% of the total. Patients to be treated would also have to have the condition in both eyes.

“If Dennis isn’t an ‘exceptional case,’ then my question to Oxfordshire PCT is ‘who is?’”
Waterborne diseases pose threat in Pakistan as floods cause chaos

Owen Dyer LONDON
Hundreds of thousands of people are living in the open as large tracts of India, Pakistan, and China have been struck by lethal floods after weeks of torrenital monsoon weather and a direct hit from a tropical cyclone on Pakistan’s southern coast.

Cyclone Yemyin narrowly missed Karachi on 26 June, just three days after the city was struck by another storm that caused widespread damage and killed 228 people. The cyclone instead hit land in the province of Balochistan, one of Pakistan’s most deprived areas.

The Balochistan relief commissioner, Khuda Bakhsh Baloch, says that roughly 200,000 houses in the province have been destroyed by flooding, and confirmed 130 people were dead. Estimates of the number of people affected by the floods in the province swiftly grew to more than 800,000, of whom more than 100,000 lack shelter. Hundreds of thousands more people are affected in Sindh province.

Some remote areas of Balochistan have not yet been reached except by air, as flood waters have still not fully subsided. Health kits and mobile clinics stored by the World Health Organization in the town of Lasbella were inspected from the air and found to be flooded. The townspeople were seen taking refuge on rooftops.

Aid agencies and Pakistani authorities are primarily concerned about the risk from waterborne diseases, said Antonia Paradela of Unicef Pakistan. “In some of the districts worst affected by the floods, when we had previous assessments, we had found that half of the children had diarrhoea in the prior two weeks,” she said.

Consider surgery before IVF, gynaecologists told

Lisa Hitchen LONDON
Surgical options should be considered before clinicians offer women in vitro fertilisation (IVF), experts recommended at a conference last week on obstetrics and gynaecology.

In vitro fertilisation is not a “universal panacea” for all fertility problems, said William Ledger, professor of obstetrics and gynaecology at the University of Sheffield.

He showed data from York University Health Economic Consortium on the most cost effective preferred solution for infertility. Out of tubal disease and endometriosis, anovulation, male factor, and unexplained infertility, in vitro fertilisation came out top only for severe tubal disease and endometriosis.

“The media’s fascination with IVF is as if there is no other option,” he said. “Many patients pick that up, and you have to try to convince them to try something else because they think, ‘I’m infertile, I have to do IVF.’ This is not the case. In an audit of our practice in Sheffield only just over half of the pregnancies we had in a year were IVF, the rest come from these easier techniques.”

The problem is that many junior doctors won’t get sufficient training to carry out techniques such as surgery for adhesions or fibroids in the future he told delegates.

“My concern is that if we don’t train younger doctors in these techniques, they will disappear and all we will have to offer is IVF.”

Nor was preimplantation genetic screening the

Birth rate drops when obstetricians attend national conferences

Roger Dobson ABERGAVENNY
New research shows that when obstetricians and gynaecologists are away at national conferences the number of births drops (Social Science and Medicine 2007 Jun 27 doi: 10.1016/j.socscimed.2007.05.034).

Researchers found that the number of births dropped by up to 4% during five day key annual conferences in the United States and Australia, with nearly 1000 births affected.

“Since it is unlikely that parents take these conferences into account when conceiving their child, this suggests that medical professionals are timing births to suit their conference schedule,” say Joshua Gans from the University of Melbourne and coauthors from the Australian National University, in Canberra.

They say that although medical conferences have become a normal part of the career of many doctors, little has been written about how hospitals and others manage the effects on the supply of available staff.

In the study the authors looked at daily birth rates in the two countries and matched them with the annual meetings of the largest conferences of obstetricians and gynaecologists in each country, the annual scientific meetings of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists and the American College of Obstetricians and Gynaecologists, over a 12 year period.

In Australia conferences were associated with a 3.8% fall in births and in the US with a 1.5% fall in births. “To give some sense of the magnitude of these effects, the results
India reduces estimated count of people infected with HIV

Ganapati Mudur NEW DELHI
India has lowered its estimate of people infected with HIV to 2.47 million for 2006, but health officials and public health experts have warned that the real reduction in HIV prevalence is only marginal.

“The revised figure is more reliable than the 5.2 million estimate for 2005 and results from new estimation methods using data from a population survey to complement sentinel surveillance, senior health officials said last week.

India’s HIV counts have long been controversial, with projections ranging in recent years from 3.4 million to 9.4 million. Five years ago, a US agency predicted that India could have 20 million people infected with HIV by 2010 (BMJ 2002;325:1132).

“India still has one of the largest numbers of HIV infected populations,” said Sujatha Rao, director general of the National AIDS Control Organisation. “The epidemic has shown a decline in some areas where intervention has been strong, but there are pockets of high HIV transmission,” Ms Rao said.

Epidemiologists have long attributed the earlier overestimates to the exclusive use of sentinel surveillance data—HIV prevalence among patients in clinics for sexually transmitted diseases and antenatal clinics—to calculate national estimates.

Public health experts said that the lower count is expected to translate into more resources for prevention. The National AIDS Control Organisation last week also launched the third phase of its AIDS control programme for the period 2007-12.

The 115 billion rupees (£1.4bn; €2.1bn; $2.9bn) programme funded by the Indian government, international agencies, and private foundations, will expand education in youth and high risk groups, promote more condoms, increase voluntary testing and give free antiretroviral treatment to 340000 people by 2012.
Dark chocolate lowers blood pressure

One small square of dark chocolate a day could have a clinically relevant effect on blood pressure, according to a preliminary trial from Germany. People aged 56-74 who ate 6.3 g of dark chocolate for 18 weeks dropped their systolic blood pressure nearly 3 mm Hg more than those given a matching portion of white chocolate (−2.9 mm Hg, 95% CI −3.9 to −2.0).

The dark chocolate, which contained 30 mg of polyphenols, reduced diastolic blood pressure by a mean of 1.9 mm Hg (1.1 to 2.7).

The researchers think a specific subgroup of polyphenols called flavanols are probably responsible, mediated by the vasodilator S-nitrosoglutathione. At the end of the trial, serum concentrations of S-nitrosoglutathione were significantly higher in the group given dark chocolate.

The 44 participants had baseline blood pressures between 130/85 and 160/100. They were healthy, reasonably affluent non-smokers with normal body weight and a habitually low intake of alcohol and chocolate. Dark chocolate won’t necessarily work the same way in other populations, say the authors. But these findings pave the way for bigger, longer, and more diverse studies, preferably looking for the effects of cocoa flavanols on heart disease.

Bed nets protect whole communities

Bed nets treated with insecticide protect people from malarial mosquitoes. They can also provide herd protection by killing some mosquitoes and diverting others to feed on non-human mammals that are not hosts of the malarial parasite. Both mechanisms reduce the burden of malaria in a community, reduce transmission between humans, and prevent disease even in people with no access to a net. But at what level of coverage do these community wide effects offer the same protection as sleeping under a net? This question is especially important for pregnant women and children, those most likely to die from falciparum malaria.

Using mathematical modelling, researchers estimated recently that pregnant women and children would be well protected if 35-65% of the population slept under a net. These estimates support the growing consensus that wider distribution of nets might help control malaria better than the current strategy of targeting pregnant women and young children. At the least, this more equitable option should be explored further while targeted net distribution continues, say the researchers.

Low cabin pressures are uncomfortable for airline passengers

The cabins of commercial aircraft are maintained at an air pressure equivalent to a moderately high altitude on land—up to about 8000 ft (2438 m). Because it is possible to get acute mountain sickness at or even below this altitude, the Boeing Company in collaboration with a US university did a study of acute mountain sickness during simulated long haul flights to assess the risk to passengers.

Volunteers took 20 hour “flights” in a hypobaric chamber pressurised to the terrestrial equivalent of 650, 4000, 6000, 7000, or 8000 ft. The volunteers’ oxygen saturation fell significantly as cabin altitude increased—those at 8000 ft dropped their saturation by a maximum 4.4 percentage points. But air pressure had no measurable impact on the risk of acute mountain sickness, which affected 7.4% (37/502) of volunteers overall.

Those at simulated altitudes (lower air pressures) of 7000 or 8000 ft were significantly less comfortable than the other groups, reporting more malaise, muscle discomfort, and fatigue. The differences appeared after three to nine hours in the hypobaric chamber.

Aircraft cabins are kept at low pressures to save energy and increase fuel efficiency, say the authors. Higher pressures won’t prevent mountain sickness, but they could make flying more comfortable.

Time to move on from advanced directives

Advance directives promise much but deliver little, writes one doctor from Texas. They were developed more than three decades ago to give patients a say in their future care, but the original concept was overoptimistic. Even the most thorough advanced directive can be derailed in the end by the complexities of modern care, the poor preparation of proxy decision makers, the ambiguity of the patient’s wishes, or the strong will of other parties, he writes. Complete control over the manner of death is an unattainable goal.

Despite decades of encouragement, most people fail to complete advanced directives, preferring instead to ignore the uncomfortable reality of death or leave end of life decisions...
to someone else, or to fate. Even when an advance directive exists, it may not be accessible at a time of crisis. Some are signed once but never updated, leaving relatives unsure of a patient's current wishes.

Some kind of advance care planning will always be important, writes the doctor, but advance directives don’t work. Until we come up with something better, doctors should prepare patients and their families for the uncertainty that lies ahead, and support them courageously through difficult decisions when they finally come. *Ann Intern Med* 2007;147:51-7

**Immune deficiency linked to a wide range of cancers**

Patients with HIV have an increased risk of many cancers, not just the familiar AIDS defining cancers such as Kaposi’s sarcoma, a meta-analysis has found. The pattern of cancers that emerged looked similar to that found in patients with organ transplants, suggesting that immune deficiency is the common cause in both populations.

A close look at data from more than 400 000 people with AIDS and more than 30 000 people with transplants showed that both groups were significantly more likely than the general population to develop 20 of the 28 types of cancer examined. The risks were most obvious for cancers with a definite or probable infectious cause, including Hodgkin’s and non-Hodgkin’s lymphomas (Epstein Barr virus), liver cancer (hepatitis viruses), stomach cancer (*Helicobacter pylori*), and anogenital cancers associated with human papilloma viruses. Most of the common epithelial cancers such as those of the breast, prostate, and colon were not associated with HIV or organ transplantation. But the researchers noted a significant excess of lung cancers in both groups.

People with HIV are living longer than ever thanks to highly active antiretroviral therapy, say the researchers. Cancer could become an increasingly important cause of morbidity for these patients. *Lancet* 2007;370:59-67

**Dietary counselling is a short term solution to obesity**

Dietary counselling is the mainstay of many weight loss programmes. To measure how well it works, researchers from the US undertook a meta-analysis of 46 randomised controlled trials. Forty two of the trials included exercise as part of the package. When compared with usual care, dietary counselling helped overweight and obese people lose just under two units of body mass index (1.9, 95% CI 1.5 to 2.3), or 6% of their initial body weight in one year. But weight crept back on once counselling finished. Participants regained about half their initial weight loss in three years. Weight gain accelerated towards the end of follow-up, starting with 0.02 to 0.03 units of body mass index a month between 12 and 18 months and increasing to 0.04 units a month between 24 and 30 months.

Whether these small benefits make a lasting difference to people's risk of cardiovascular events or death is unclear. The researchers found no trials of dietary counselling with clinically useful end points.

The trials they did find were generally of average or poor quality and tested a mixed bag of interventions. So there’s likely to be some uncertainty around the final combined result. *Ann Intern Med* 2007;147:41-50

**Drug resistance is a big problem for many people with HIV.** Fortunately at least two new drugs in the pipeline have been developed specifically for patients whose treatment is failing. Darunavir (a protease inhibitor) and etravirine (a non-nucleoside reverse transcriptase inhibitor) both performed well in recent randomised trials, controlling viral replication significantly better than comparator drug regimens with no extra side effects. Participants in the etravirine trials had drug resistant disease.

The authors of a linked comment (p 3) say these new trials show that innovation is still alive and kicking in HIV research, and that one day there will be effective drugs of one sort or another for everyone. They are less upbeat, however, about the presentation of key data on etravirine, which were published in two separate papers. By failing to combine the data in one analysis, the researchers missed a golden opportunity to look at the outcomes that matter most to patients—opportunist infections and death, they write. Divided data mean lower statistical power and an over reliance on surrogate measures of success, such as laboratory results. After pooling the data themselves, the comment’s authors calculate that etravirine really can slow the progression of HIV disease. But the studies in isolation were too weak to report a significant result.

This kind of split publication does nothing for patients, but plenty for researchers (who get two chances to be first author), drug companies (who get two papers to submit to the regulatory authorities), and medical journals (who get twice the number of citations and twice the income from reprints), they write. Influential journals should insist on combining studies with such similar protocols. *Lancet* 2007;370:29-38, 39-48, 49-58

**INCIDENCE RATIOS OF CANCERS WITH A DEFINITE OR PROBABLE INFECTIOUS CAUSE**

<table>
<thead>
<tr>
<th>Epstein Barr virus related cancers</th>
<th>Cohort</th>
<th>Standardised incidence ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s lymphoma HIV</td>
<td>11.03 (8.4 to 14.4)</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma HIV</td>
<td>76.67 (59.4 to 149)</td>
<td></td>
</tr>
<tr>
<td>Human herpesvirus B related cancer</td>
<td>8.07 (6.4 to 10.2)</td>
<td></td>
</tr>
<tr>
<td>Kaposi’s sarcoma HIV</td>
<td>1640.0 (1326 to 1976)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B/C virus related cancer</td>
<td>Liver HIV 5.32 (3.2 to 8.2)</td>
<td></td>
</tr>
<tr>
<td>Helicobacter pylori related cancer</td>
<td>Stomach HIV 1.90 (1.5 to 2.3)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Epstein Barr virus related cancers</th>
<th>Cohort</th>
<th>Standardised incidence ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir-ritonavir (n=297)</td>
<td>64000 (4336 to 976)</td>
<td></td>
</tr>
<tr>
<td>Darunavir-ritonavir (n=298)</td>
<td>208.0 (114 to 349)</td>
<td></td>
</tr>
</tbody>
</table>

**Adapted from Lancet 2007;370:59-67**
Local topography affects annoyance over wind farms

People living near wind turbines in Sweden may notice and be annoyed by the noise. Of 754 respondents to a questionnaire, 307 noticed the sound, of whom 31 were annoyed by it. Country dwellers complained more than those in urban areas, and although perception and annoyance correlated with decibel level, complex (hilly or rocky) local terrain was also a major influence in rural areas, as was being able to see the turbines and complainants having renovated their house.

The investigators pointed out that it is not enough for regulatory authorities to consider simple dose-response relations when judging noise pollution; authorities need to consider the effects of differing local topography.

Nurse triage in general practice is “efficient but possibly unsafe”

When telephoned by trained simulated patients, triage nurses in four large general practice cooperatives in the Netherlands correctly estimated the degree of urgency (as determined previously by a consensus group of expert general practitioners) in 242/352 (69%) of cases.

Sensitivity for predicting potentially life threatening illness was 0.76 (63/83) and specificity 0.95 (256/269). The positive predictive value was 0.83—much higher than the a priori probability of this degree of severity of 0.24. The negative predictive value was 0.93 (a priori 0.76).

The authors conclude that nurse triage was highly efficient but possibly not safe. They add that no comparison study has been conducted of the competence of general practitioners in telephone triage and that this method of selection may be inherently unsafe. Although nurses who had been trained in using nationally agreed telephone guidelines were less likely to underestimate urgency than those who had not, the authors recommend safety rules such as arranging a personal consultation for any patient who telephones twice about the same event.

Using rear seat belts may save lives

A US analysis of 10 736 fatal road crashes involving passenger vehicles (carrying more than 26 000 rear seat passengers) suggests that using a safety belt in rear seats may reduce risk of death by about 60% in a car and 70% in a light truck. The difference between the two types of vehicle was explained by the latter being more likely to roll over in a crash, so the belt prevents a passenger from being ejected. During the study period (2000-4) 57% of drivers wore belts, but, among passengers in the rear seats, only 15% of those in centre seats and 29% of those in side seats wore belts.

In countries whose laws require the use of belts in the front seats of vehicles, fewer occupants die. This study suggests that laws requiring rear seat passengers to use belts, coupled with educational campaigns, could lead to a similar outcome.

French child athletes admit to doping

Some preadolescent athletes are using prohibited substances (“doping”) including those engaged in leisure, rather than competitive, sport. A prospective study of all 3564 pupils (mean age 11.2 years) entering secondary education in the Vosges region of eastern France in 2001-2 has shown that by 2005, 3% (95% confidence interval 2.3% to 3.7%) admitted taking doping agents at least once in the preceding six months, compared with 1.2% (0.8% to 1.6%) at study entry. The main substances were salbutamol, corticosteroids, and cannabis, as well as other stimulants and anabolic agents. The investigators state they took account of the exemption for therapeutic use granted to asthmatic athletes by making it clear to the young people that they were not asking about medication for ill health.

Of those taking doping agents, 44% considered they had won at least one event as a result and 18% did not know whether they had. Compared with non-users, users were more likely to be male, spend a lot of time in training, and report low self esteem and high levels of trait anxiety. The authors recommended adults supervising young athletes should be alert to this last two signs.

Not placing babies on their side to sleep reduces SIDS

Researchers in New Zealand suggest that the continuing fall in sudden infant death syndrome (SIDS)—a decade after the “Back to Sleep” campaign proved successful—is probably the result of a decrease in putting babies down to sleep on their side. Prone sleeping in New Zealand was negligible by 1992, but the rate of sudden infant death syndrome has fallen by a further 30% since then, with “side sleeping” falling from 75% to 28% in the general population.
Can the ex-postman deliver?

Alan Johnson arrives as secretary of state for health charged with pouring oil on troubled waters. How far the current beneath them will continue to flow in the direction of Tony Blair’s market-style reforms to the National Health Service—with choice, competition, and the private sector being seen as the key to improving services—remains to be seen.

The 57 year old former postman and trade union leader brings an easy style and a fine line in self deprecation to the job. He has a reputation for being a Blairite who also gets on with Gordon Brown, although the new prime minister has given him what may seem to be a somewhat thankless task.

General secretary of the Communication Workers Union at the age of 42, he was about the only trade union leader publicly to back the dumping of Labour’s clause IV—which committed the party to nationalisation—during Tony Blair’s and Gordon Brown’s construction of New Labour ahead of the 1997 general election.

Rapid rise

Entering parliament as a Hull MP that year, he instantly acquired the most junior of government jobs as parliamentary private secretary to Dawn Primarolo, financial secretary to the Treasury. She is now to be Mr Johnson’s junior as minister of state for public health. Two years later he began a whirlwind trip through six ministerial jobs in seven years, starting out at the Department of Trade and Industry, through education, on to being secretary of state for work and pensions, and back to trade and industry as secretary of state before becoming secretary of state at education and skills in 2006, where he pushed ahead with city academies and other private sector involvement in schools.

For a brief period last September, when Tony Blair’s supporters in Labour’s ranks were going through an “anyone but Brown” frenzy, he was touted as a possible contender for the Labour leadership contest that never happened, opting instead to run as deputy leader and losing narrowly to Harriet Harman.

His biggest single achievement as a minister has probably been the deployment of his undoubted charm on Labour backbench rebels in 2004 to get the government’s controversial introduction of higher university tuition fees through the House of Commons. Working with Charles Clarke, the then education secretary, he famously remarked afterwards that “I was the charm and Charles was offensive.” His least notable achievement, certainly in the eyes of some colleagues, was when he was handed the problem of sorting out—that is, cutting—the future cost of public sector pensions. He took colleagues aback by agreeing with little consultation that all current staff with a retirement age of 60 should be able to keep that, when emerging government policy on the state pension was to see it pushed up from 65 to an eventual 68. He vigorously argues that the deal he did will still deliver the bulk of the savings the government was seeking.

He is one of Labour’s relatively few “log cabin to White House” politicians, orphaned at 12, brought up by his 15 year old older sister, starting as a Tesco shelf stacker before delivering the post to Dorneywood—the ministerial grace and favour residence near Slough—and bringing up three children on a council estate before becoming a union official and eventually a minister. While at the education department he had a T shirt on his desk declaring: “I went to a London state school and still deliver the bulk of the savings the government was seeking.

Alan Johnson has come a long way since his years delivering letters. Nicholas Timmins examines his career and asks whether he can deliver NHS reform

Nicholas Timmins public policy editor Financial Times, London nicholas.timmins@ft.com Competing interests: None declared.
A long way from Worcester

As the BMA reaches its 175th anniversary, Peter Bartrip considers the journey so far

The BMA has now been in existence for a century and three quarters. Such longevity is impressive. Rival bodies, including an earlier British Medical Association unrelated to Charles Hastings’ creation, proved transient. The BMA of 2007 is, of course, a very different creature from its earlier incarnation, the Worcester based Provincial Medical and Surgical Association of 1832. Now, headquartered far from its place of origin and operating under a different name, it performs different functions in a much changed medical context. It has faced numerous challenges in the past, and its continued existence has not always been assured. It seems safe to assume, however, that it is well on its way to a bicentenary.

Foundation
The BMA, originally named the Provincial Medical and Surgical Association (PMSA), was established by some 50 medical men in the boardroom of Worcester Infirmary on 19 July 1832. Charles Hastings, “the best known physician in the Midlands,” was the driving force behind the new body and the dominant personality within it for over 30 years. The association was not set up to act as a professional ginger group or press the case for medical reform, then a topical issue under the influence of Thomas Wakley’s Lancet. Nor was it created to advance public health agenda. Its main purpose was to provide a “friendly and scientific” forum that would allow provincial practitioners to advance and exchange medical knowledge.

Medical politics did not reach the forefront of the association’s activities for some years. Initially, the Lancet welcomed the PMSA’s foundation, but before long the acerbic Wakley turned hostile, describing the association as “a most disgraceful abortion.” Such invective did not stall the association’s growth. Ten years after that first gathering in Worcester its membership had reached a healthy 1350. The association was also well on the way to acquiring control of a weekly journal, the Provincial Medical and Surgical Journal (called British Medical Journal from 1857), through which members could communicate.

Medical reform
Wakley’s disillusionment with the PMSA owed much to its failure to adopt his radical views about medical reform—that is, the way in which the profession was educated, certified, and regulated. He favoured confrontation with the professional elites, whereas Hastings and his colleagues preferred a more emollient approach. In time, however, Wakley recognised the merit of the PMSA—he even became a member—and praised the association’s efforts as the reform question came to a head. The BMA, as it was known from 1855, played an important role in securing the passage of the Medical Act 1858 which, for all its flaws, established the General Medical Council, drew a line between qualified and unqualified practitioners, reserved public appointments for the former, and created a system of professional self regulation. Of the GMC’s 24 founder members, eight, including Hastings, were BMA members. The association had, once and for all, become a potent force in medical politics.

National health insurance
Once it became active in medical politics the 19th century BMA was an effective campaigner in many spheres, including Poor Law medical practice, quackery, alternative medicine, public health, military medicine, and contract practice. The defence of professional interests was one consideration, but protecting the public—for example, from the manufacturers of fraudulent, sometimes harmful, “patent” medicines—was another. In the early 20th century the association faced its biggest challenge to date when Asquith’s Liberal government, mainly in the person of the chancellor of the exchequer, Lloyd George, proposed a system of national health insurance for manual workers and other employees with earnings of less than £160 a year. The BMA was not opposed to an insurance scheme. Indeed, in 1909 it published plans of its own for “the organisation of medical attendance on the insurance principle.” But the association was adamant that its members would not be exploited as they had been under the Poor Law and by sick clubs in the past. Confrontation with the government ensued and thousands of BMA members voted to refuse service in the new scheme. Lloyd George offered concessions but the association overplayed its hand and was ultimately obliged to climb down as it became clear
that many doctors actually were willing to serve. Once the new system was in place it proved a boon not only to patients but to the many doctors who escaped that bane of private practice, the unpaid fee. When the prospects of an NHS loomed in the 1940s, many practitioners were reluctant to see the end of National Health Insurance.

Birth of the NHS
Early in the second world war it was widely recognised that arrangements for the provision of medical services to the British people were likely to change with the return of peace. The BMA has sometimes been seen as wholly opposed to the introduction of a national health service, but in reality its annual representative meeting approved a state system “for the whole community” as early as 1942, baulking only at any suggestion of a full time salaried service. Until the election of Labour in 1945 the BMA and wartime coalition had little difficulty in agreeing the terms of the new service, but with the firebrand Welsh socialist Aneurin Bevan at the Ministry of Health, association and government were soon on a collision course. Before and after the passage of the National Health Service Act 1946, acrimonious negotiations took place, with Charles Hill (the “radio doctor”) and Guy Dain to the fore for the BMA. For a time it seemed that practitioners would decline to enter the service. But with concessions from both sides, wiser counsels eventually prevailed. Weeks before the new service was due to begin, a special representative meeting voted to cooperate. It was not long before the profession came to see the merits of the NHS; when, in 1962, the American Medical Association attacked the service, the BMJ deplored the Americans’ “cheapness and vulgarity,” insisting that the United States had much to learn from Britain and Europe.

NHS practice
Recognition of the merits of the NHS did not mean universal approval of its terms and conditions of service. For years, many general practitioners felt undervalued, under-resourced, professionally isolated, poorly paid, and overworked. The 1950s and 60s in particular saw a spate of inquiries into general practice, some of which led to improvements—at least for a while. The BMA’s record in negotiating change was chequered, with the occasional embarrassment and several triumphs. Agreement on the charter for the family doctor service (1966), with its emphasis on group practice, suitable premises, employment of ancillary staff, and the prioritising of preventive medicine, was a high point. “The BMA,” the Lancet noted, “has won a clear victory.” A subsequent fight concerned hospital “pay beds” and consultants’ private practice within the NHS. The Labour government that came to power in 1974 was committed to phasing out both. Barbara Castle, the minister responsible, had a personal commitment to the cause and was determined to confront the profession. But the BMA had more cause than the minister to be satisfied with the outcome. As Charles Webster has noted, by the end of James Callaghan’s administration more than five years later, Labour had failed to eliminate pay beds from the NHS while succeeding “in stimulating rather than repressing the private sector of health care.”

Peter Bartrip is reader in history, University of Northampton, and associate research fellow, Centre for Socio-Legal Studies, University of Oxford. peter.bartrip@socio-legal-studies.oxford.ac.uk
Should medical journals carry drug advertising?

Richard Smith executive director, UnitedHealth Europe, London SW1P 1SB richardsmith@yahoo.co.uk

YES  The central argument for carrying advertising in medical journals is independence. Ironically, the main argument against may also be independence, but you can place greater trust in a journal that carries advertising than one that does not.

Price of independence  Independence is a journal’s most precious asset, and independence means financial independence. “He who pays the piper calls the tune.” So to be able to play multiple tunes a journal needs multiple sources of income—and drug advertising is one of the most important and profitable. The beauty of drug advertising is that there are many companies who want to advertise in a journal that has a wide circulation. This means that none of them alone has the power to influence the journal.

Advertisers may huff and puff in response to articles that upset them, and they may for a while take away their advertising. But the journal doesn’t depend on any one advertiser—and so can ignore the protests. Furthermore, the multiple advertisers keep a close eye on each other. If an advertiser breaks any of the many codes that regulate them, the first protest is often from a competitor.

But what about the joint power of the drug companies? Can’t they together influence the journal? Again, it’s back to money. If the sole source of income for a publication is advertising, and we are conditioned to discount it. I’m not arguing that it has no influence, but advertising in a journal will have only a small influence on the average doctor. He or she is bombarded with messages from drug companies—through drug representatives, advertising in free newspapers, studies in medical journals, direct mail, and “education” funded by the industry.

Consequences of banning  If advertisements in medical journals were the only way that drug companies could influence doctors, then the question of banning drug advertising would be much more serious.

If advertising were banned, publishers of journals would have to find other sources of income. Publishing more drug company sponsored studies in order to boost reprint sales would be deeply damaging. If subscriptions were raised, many doctors would simply switch to what is free—and, as I argued above, much more likely to be influenced by drug companies. (All the evidence shows that given a choice between having a publication funded by advertising or paying for it themselves almost all doctors will accept the advertising—which is perhaps a killer argument.) Or, for open access journals like the BMJ, it might mean putting the research articles on websites behind access controls—something far worse in my mind than carrying advertising.

A ban on advertising might also mean financial dependence on the owners of journals—and this is the greatest threat to independence. Journal owners have got rid of the editors of JAMA, the New England Journal of Medicine, the Canadian Medical Association Journal, the Annals of Internal Medicine, the Irish Medical Journal, and others because they didn’t like what they published or how they behaved.

The BMJ has not yet had this experience, and one of the most important reasons is that money flows from the BMJ to the BMA. Not one penny of the subscription that members pay to the BMA reaches the BMJ. The journal funds itself, and drug advertising is an important source of revenue. If the BMA had to support the BMJ financially, my bet is that it would be much more bothered about anything that upset members (and there are—and should be—many such pieces).

My advice to readers is to flip over the adverts, which you probably do anyway, and enjoy the independence that they bring.

Competing interests: RS was editor of the BMJ and chief executive of the BMJ Publishing Group. His pension from the BMA (if he lives that long) will be funded in part by income from drug advertising. He is on the board of the Public Library of Science, a position for which he is not paid.
No one can fail to notice the adverts in medical journals but are they really necessary? Richard Smith maintains they are essential to editorial independence, whereas Gareth Williams argues that they undermine a journal’s integrity.

NO

There is no escape from them and their quaint little catch-phrases: the woman with a toilet for a head (“It’s always on my mind”), the blurred bloke on a beach (“A feeling says a thousand words”), the kayak in the waterfall (“The big drop”). Like it or not, drug advertisements have embedded themselves deep in the fabric of medical journals. You can almost understand why: they help drug companies to recoup the huge costs of developing new drugs while providing medical journals with a useful income stream. And why not? Adverts may be an irritating distraction, but surely they are harmless—all, no doctor could be gullible enough to prescribe a drug because of a picture of a toilet-headed woman and a puerile lavatorial pun.

I believe, however, that drug advertising is no more acceptable than a drug representative’s foot around the doctor’s door, and that it has no place in medical journals.

Distortion

Drug advertisements exist only to sell a product and inevitably, like all marketing copy, are biased. For many new drugs, an honest appraisal is that they seem no better than existing alternatives, are grossly overpriced, and may turn out to have dodgy side effects. A clear statement of those facts is unlikely to send sales into the stratosphere. Hence the hype, which in many cases far outstrips the hard evidence. All too often, reading the fine print will show that the wonder drug’s credentials are worryingly threadbare. The big headline claims may rest only on a poster presentation, an article in a journal supplement paid for by the company, the company’s summary of product characteristics, or the enigmatic “data on file.” The poverty of evidence makes a striking contrast with the obvious wealth of the advertising campaign and raises some important questions. Do they have something to hide—or perhaps nothing to show? If this is the best evidence they can roll out, is the drug really ready to go into patients?

Predictably, drug advertisements project the positive, while the negative gets little coverage. You never see a full-page colour spread announcing the demise of a wonder drug that didn’t turn out to be so wonderful after all; instead, bad news tends to creep out in a “Dear prescriber” letter that follows the discreet withdrawal of the discredited product. The story of the ill-fated troglitazone, which was withdrawn after it was found to cause liver failure, is illuminating in this regard.

Doctors, as the targets of the advertising, are a key part of the problem, because they help to perpetuate the culture that makes drug advertising both acceptable and profitable. Doctors should prescribe a drug only because they have a sound understanding of its indication, benefits, shortcomings, and value for money; all that information is readily available in authoritative, balanced, and up to date publications such as the British National Formulary. Patients should not have to take a drug because their doctor’s eye has been caught by an advertisement while leafing through a journal. Sadly, the fact that the toilet-headed woman and her associates still ply their trade can only mean that there are enough impressionable doctors out there to justify the companies’ vast advertising budgets.

Medical journals, being the Trojan horse that brings drug advertisements into the doctor’s home and workplace, also need to examine their collective conscience. They have to survive in a competitive market but exist for a higher purpose that requires them to be totally objective and untainted by conflicts of financial interest; unfortunately, some have found it difficult to live up to those noble ideals. Editors set high standards for their publications, and contributors who fall short on evidence, honesty, clarity of writing, and professionalism can expect to face the full wrath of peer review. How peculiar that the journals feel able to relax their principles and print, alongside the research papers, material that would not look out of place in a glossy tabloid and that often raises two fingers to evidence based medicine.

Moral high ground

So what should be done? As a minimum, drug advertisements should be vetted independently and much more stringently than at present and barred from publication if they make inflated or substantiated claims. Ideally, though, drug advertising should be banned completely from medical journals. This would be a big financial hit on some journals—some of which raise 20-30% of their income from advertising—but comes at a time when doctors, institutions, and patients are under increasing pressure to re-examine the morality of their links with the drug industry. It would be fitting for the journals, especially those that hold the respect of the profession, to lead the march to the moral high ground.

Fifty years ago, the American Journal of Medicine regularly ran advertisements for Camel cigarettes, improbably peddled by Pasteur and other big names from medical history. It took many years for the ethical arguments to outweigh the lucrative, but eventually they won and tobacco advertising in medical journals—which would be unthinkable today—became nothing more than an embarrassing memory. It’s high time that drug advertising went the same way.

Competing interests: GW has received numerous research grants and honorariums for advisory work with several drug companies active in diabetes and obesity.

References are in the full version on bmj.com

WHERE DO YOU STAND ON THE ISSUE? Vote now on bmj.com

Gareth Williams, dean, Faculty of Medicine and Dentistry, University of Bristol, Bristol BS2 8DZ Gareth.Williams@bris.ac.uk

Richard Smith
BORDER CROSSING Tessa Richards

Who is at the helm on patient journeys?

Doctors know that poor communication and lack of continuity of care are behind many medical errors. So why aren’t they doing more to coordinate care?

Two years ago a 41 year old English journalist died from septicaemia. Her case haunts me. Two days before the Easter weekend Penny Campbell had an injection for haemorrhoids. During the weekend she became progressively unwell and called the out of hours medical service eight times. None of the doctors she contacted realised how ill she was. By the next day the die was cast; within 24 hours she was dead.

Her case hit the headlines and continues to do so. Four months ago London’s Evening Standard (14 March) used it to lambast the “costly shambles” of GP out of hours services and called for GPs to resume running Saturday surgeries. I shudder at the distress Penny must have felt and that expressed by her husband in a Daily Mail article (“The eight doctors who failed to diagnose my dying wife,” 29 May). I relate to it too: over the weekend before my father died I also made eight calls to a service with no memory.

Five weeks ago the inquiry into her case reached its conclusion. Only one of the eight doctors was deemed to have failed to provide “reasonable” care. The problem, the inquiry found, was lack of continuity of care. Each episode was treated as a new one, and the doctors concerned had no access to their colleagues’ notes. In the wake of this judgment the Department of Health has asked primary care trusts to “review their arrangements for how clinicians relay information to each other” (BMJ 2007;334:1130).

Exhortations to look at what you do and do it better seldom solve entrenched problems. All health professionals know that continuity of care matters—and that it depends on good communication among those providing immediate care, timely and rigorous “handover” of information between teams, and coordination of care over time. Equally we know that the NHS is not good at providing continuity. Patients know it too, for they are constantly being asked to supply “missing” bits of their medical jigsaw.

Not many professions manage their clients’ affairs blindfolded to key information. Commercial lawyers take continuity very seriously, and not only because changes of team upset clients, who are paying a lot for their services. The same people may manage individual cases over years, seeking other opinions when needed. They may take out insurance on a judge’s life against the risk that the judge dies before the case concludes.

Leaving apart patients’ preference for continuity, not to mention the vast human cost of poor “relaying” of medical information, the financial toll is surely high. We know that medical error is costly and common, scarily common. One in 10 medical encounters is said to result in harm, as the US Institute of Medicine’s landmark 1999 report To Err is Human: Building a Safer Health System and many reports since have shown. We also know that poor communication is a common cause of medical error. In their book Internal Bleeding: The Truth Behind America’s Terrifying Epidemic of Medical Mistakes (2004) Robert Wachter and Kaveh Shojania argue that “behind every error there is a second story, one with a complex mix of miscommunication, low cultural expectations and poor teamwork.”

Why the NHS and those who use it tolerate a service where communication is so poor is hard to answer. The low expectations cited in Internal Bleeding may come into it, or maybe the business case for putting more resources into tackling error that is due to poor communication and lack of continuity has not gone far enough.

Initiatives to tackle medical error are certainly not lacking. Over the past 10 years the number of organisations, national and international, committed to improving the quality and safety of health care has burgeoned. In most healthcare systems, and the NHS is no exception, data on errors and near misses are routinely collected; how systematically and effectively the data are used as a learning tool to reduce error is open to question. Some would argue that the proliferation of initiatives to improve safety suggests that we are some way from getting on top of the problem.

Establishing common electronic health records in the NHS and sharing these with patients ought to help solve many of our communication problems, but they are a long time coming. Furthermore, Glyn Elwyn, professor of primary care at Cardiff University, says that Connecting for Health may be more focused on producing a data processing tool than one that promotes case coordination.

Time will tell—but while we wait for the Holy Grail we can surely pursue some simple measures. Professor Elwyn suggests providing incentives for GPs to appoint a personal doctor to maintain continuity of care for acutely ill, dying, or complex patients, and the quality and outcomes framework (QOF) springs to mind as a mechanism to achieve this. Another approach would be to adopt the social services model where case managers are responsible for collating information on patients’ access to diverse services. What is certain is that we need a more energetic debate on how to develop local solutions to tackle local communication problems.

No one should underestimate how stressful it is to be left, as Penny Campbell was, to steer your own patient journey. Doctors can’t guarantee a good outcome but they can, and should, help patients navigate their way as safely as possible through our complex and fragmented health systems.

Tessa Richards is assistant editor, BMJ trichards@bmj.com
Decline in effectiveness of antenatal corticosteroids with time to birth: real or artefact?

The widely accepted notion that the benefits of antenatal corticosteroids decline with time to birth may not be correct, argue Simon Gates and Peter Brocklehurst, as the evidence is based on unsound subgroup analyses.

The effectiveness of antenatal corticosteroids to prevent neonatal lung disease in women at risk of preterm birth was established by systematic reviews. In addition, subgroup analyses suggested that treatment was most effective in babies born one to seven days after administration. This belief led to widespread use of repeated courses of corticosteroids in women who did not deliver within a week or two of initial treatment. However, the notion that effectiveness declines after seven days may be incorrect, as the analyses that it is based on are unreliable. Here, we discuss the methodological problems of these analyses and their relevance to current randomised controlled trials of repeated versus single courses.

So, what is the evidence?

Babies born before 32 weeks’ gestation often have neonatal lung disease, a major cause of neonatal mortality and morbidity—the earlier the birth, the greater the risk. Corticosteroids given to mothers at risk of preterm delivery accelerate fetal lung development, and the effectiveness of this treatment for preventing neonatal lung disease was investigated in a series of randomised controlled trials from the 1970s onwards. Some trials showed a significant benefit of antenatal corticosteroids, but some showed no significant effect. A landmark systematic review resolved the apparent discrepancies in the results and established that this treatment reduced death and respiratory distress syndrome in the babies of these women. A forest plot from this review is used in the Cochrane Collaboration’s logo, and the intervention is now used routinely in clinical practice.

Another clinically important question is whether (and how) the effectiveness of antenatal corticosteroids changes with time after administration. This question was investigated by a subgroup analysis in the first randomised controlled trial conducted. Women were divided into subgroups on the basis of the interval between treatment and delivery—less than 24 hours, 24–48 hours, two to seven days, and more than seven days. Respiratory distress syndrome was significantly reduced only in babies born two to seven days after the first dose of corticosteroids. The somewhat inconsistent conclusion was that steroids should be given at least 24 hours before delivery to have a noticeable effect on lung function, and that effectiveness does not persist for more than a week. This conclusion appears to be consistent with the results of laboratory studies, although corticosteroids act in several different ways, and how they affect growth and development of the lungs is not certain. Subsequent trials and four systematic reviews found similar results—a large and statistically significant reduction in respiratory distress syndrome in the subgroup given corticosteroids one to seven days before delivery and a smaller (usually non-significant) effect in the other subgroups (table). This evidence led, in the 1990s, to a widespread practice of repeating treatment in women who did not deliver within seven to 10 days of receiving it. Courses were often repeated weekly until 34 weeks’ gestation, resulting in prolonged exposure of babies to corticosteroids. More recently, use of multiple courses has declined, because of worries about adverse effects of exposure to corticosteroids, especially in the developing brain. At least nine randomised controlled trials have been initiated to determine the efficacy and safety of repeated courses. The studies reported so far have shown no conclusive evidence of short term benefit for repeated courses, but long term follow-up is needed to assess the neurodevelopmental effects of this treatment and fully understand its risks and benefits.

### Meta-analyses of trials of corticosteroid treatment for preventing neonatal respiratory distress syndrome in women at risk of preterm delivery

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Time period subgroup</th>
<th>No of trials</th>
<th>Intervention group</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crowley 1989</td>
<td>&lt;24 h</td>
<td>10</td>
<td>Treatment*</td>
<td>0.72 (0.49 to 1.06)</td>
</tr>
<tr>
<td></td>
<td>24 h to 7 days</td>
<td>12</td>
<td>Control*</td>
<td>0.80 (0.56 to 1.15)</td>
</tr>
<tr>
<td></td>
<td>&gt;7 days</td>
<td>6</td>
<td></td>
<td>0.69 (0.50 to 0.94)</td>
</tr>
<tr>
<td>Crowley 1990</td>
<td>24 h to 7 days</td>
<td>Not stated</td>
<td>Not stated</td>
<td>0.31 (0.23 to 0.42)</td>
</tr>
<tr>
<td></td>
<td>&gt;24 h or 7 days</td>
<td>Not stated</td>
<td>Not stated</td>
<td>0.62 (0.35 to 1.08)</td>
</tr>
<tr>
<td>Crowley 1995</td>
<td>&lt;24 h</td>
<td>12</td>
<td>Treatment*</td>
<td>0.80 (0.56 to 1.15)</td>
</tr>
<tr>
<td></td>
<td>24 h to 7 days</td>
<td>13</td>
<td>Control*</td>
<td>0.35 (0.26 to 0.46)</td>
</tr>
<tr>
<td></td>
<td>&gt;7 days</td>
<td>7</td>
<td></td>
<td>0.63 (0.38 to 1.07)</td>
</tr>
<tr>
<td>Roberts</td>
<td>&lt;24 h</td>
<td>9</td>
<td>Treatment*</td>
<td>0.82 (0.55 to 1.22)</td>
</tr>
<tr>
<td>and</td>
<td>24 h to 7 days</td>
<td>9</td>
<td>Control*</td>
<td>0.36 (0.25 to 0.51)</td>
</tr>
<tr>
<td>Dab Chileo</td>
<td>&lt;24 h</td>
<td>8</td>
<td>Treatment*</td>
<td>0.80 (0.48 to 1.33)</td>
</tr>
<tr>
<td></td>
<td>24 h to 7 days</td>
<td>9</td>
<td>Control*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;7 days</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Number of events/number of babies.
What are the problems?

Although the notion of an optimal period of administration persists, certain features of the analyses on which this conclusion is based could make them unreliable and the conclusion unsound. We describe four ways in which misleading results could have arisen.

Arbitrary choice of time period subgroups

The choice of 24 hours and seven days as the cut-off points for determining the subgroups was totally arbitrary. These time points were used by the first trial to be published and have been followed by others, but the reasons for choosing them are not clear. They may have been chosen to maximise the difference between the subgroups, and different cut-off points might have produced different results. If a period of maximum effectiveness does exist, it may not be a plateau between days one and seven.

Babies born at term were all in one subgroup

Most trials recruited women with a gestational age of less than 36 weeks. Almost all babies born at term (>37 weeks) were therefore in the subgroup of babies delivered more than seven days after randomisation. Death and respiratory distress syndrome are rare in babies delivered at term; fewer outcomes would therefore occur in this subgroup, so a statistically significant difference would be less likely to be found. Hence, the lack of evidence of a difference in this group may simply reflect the much lower incidence of outcomes in babies born at term. The overall incidence of respiratory distress syndrome in the three subgroups in the most recent review is consistent with this argument—27.5% in the less than 24 hours subgroup, 16.4% for one to seven days, and 7.0% for more than seven days.

Subgroup comparisons did not use interaction tests

Subgroups with fewer trials or fewer events have greater uncertainty and are less likely to give statistically significant results than those with more trials or events, even if their treatment effects are exactly the same. Hence, using statistical significance to assess differences between subgroups is unreliable. Instead, statistical tests of interaction should always be used to assess subgroup differences, both in trials and systematic reviews.

The time to delivery subgroups contained different sets of trials, which complicates the performance of interaction tests in these reviews. It would be expected that some women would deliver in each time period after randomisation in almost all trials, so that data should be available for each subgroup for each trial. However, in the Cochrane review, only five of 11 trials reported data for all subgroups. This could introduce bias. Firstly, one subgroup may, by chance, contain trials with larger treatment effects or more participants, making that subgroup more likely to show a significant treatment effect. This would give an impression of a difference between the subgroups, which would not be seen if data from all the trials were included in all subgroups. Secondly, a potential reporting bias exists—subgroup results may have been reported in the original trial papers because they were statistically significant, with non-significant subgroup results not being reported. Reviews would then tend to contain those subgroups that had significant results.

Subgroups were classified by an outcome variable

The time between randomisation and delivery is not known at trial entry, as it is not determined until birth. Subgroup analyses classified by variables that arise after randomisation are known to have a high risk of producing misleading results. Normally, subgroups are defined by variables known at randomisation (figure), and comparison between the arms of the trial within each subgroup is determined by randomisation. When subgroup analysis is classified by a variable determined after randomisation (bottom), the composition of the two groups is determined by the presence or absence of outcome 1.
PB is a clinical trialist with a background in multiple versus single courses or we risk repeating the reports of other trials and systematic reviews of be misleading. Such analyses should be omitted from courses in babies born at less than 28 weeks. This may be caused by differences in the composition of subgroups. None of the antenatal corticosteroid trials provided data comparing the baseline characteristics or other outcomes of the time to delivery subgroups, so the likelihood of bias cannot be assessed.

Whether the effects of antenatal corticosteroids change with time to delivery cannot be adequately investigated by the existing analyses, but a valid and straightforward method of analysis has been suggested. This uses standard techniques to determine which baseline characteristics, including randomised treatment, are related to the interval between randomisation and delivery, followed by standard subgroup analyses on any such variables identified. The original (individual patient) data from each trial would be needed; this would also allow analysis to be based on the exact time to birth rather than the arbitrary categories used so far. Reanalysis of individual patient data may help clarify whether the hypothesised association is real, and if so, suggest how long the effects of antenatal steroids persist.

The way forward
The widely accepted notion that the benefits of antenatal steroids decline with time to birth is based on analyses with various colleagues while running a pilot study of this treatment. SG is guarantor.

Provenance and peer review: Non-commissioned, externally peer reviewed.

18 Van Walraven C, Davis D, Forster Al, Wells GA. Time-dependent bias was common in survival analyses published in leading clinical journals. J Clin Epidemiol 2004;57:672-82.
Use of probiotic *Lactobacillus* preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial

Mary Hickson, research dietitian,1 Aloysius L D’Souza, research fellow,2 Nirmala Muthu, research nurse,3 Thomas R Rogers, professor of clinical microbiology and honorary consultant (Hammersmith Hospitals NHS Trust),4 Susan Want, clinical scientist,5 Chakravarti Rajkumar, senior lecturer,2 Christopher J Bulpitt, professor of geriatric medicine2

**ABSTRACT**

**Objective** To determine the efficacy of a probiotic drink containing *Lactobacillus* for the prevention of any diarrhoea associated with antibiotic use and that caused by *Clostridium difficile*.

**Design** Randomised double blind placebo controlled study.

**Participants** 135 hospital patients (mean age 74) taking antibiotics. Exclusions included diarrhoea on admission, antibiotic use in the previous four weeks, severe illness, immunosuppression, bowel surgery, artificial heart valves, and history of rheumatic heart disease or infective endocarditis.

**Intervention** Consumption of a 100 g (97 ml) drink containing *Lactobacillus casei*, *L bulgaricus*, and *Streptococcus thermophilus* twice a day during a course of antibiotics and for one week after the course finished. The placebo group received a longlife sterile milkshake.

**Main outcome measures** Primary outcome: occurrence of antibiotic associated diarrhoea. Secondary outcome: presence of *C difficile* toxin and diarrhoea.

**Results** 7/57 (12%) of the probiotic group developed diarrhoea associated with antibiotic use compared with 19/56 (34%) in the placebo group (P=0.007). Logistic regression to control for other factors gave an odds ratio 0.25 (95% confidence interval 0.07 to 0.85) for use of the probiotic, with low albumin and sodium also increasing the risk of diarrhoea. The absolute risk reduction was 21.6% (6.6% to 36.6%), and the number needed to treat was 5 (3 to 15). No one in the probiotic group and 9/53 (17%) in the placebo group had diarrhoea caused by *C difficile* (P=0.001). The absolute risk reduction was 17% (7% to 27%), and the number needed to treat was 6 (4 to 14).

**Conclusion** Consumption of a probiotic drink containing *L casei*, *L bulgaricus*, and *S thermophilus* can reduce the incidence of antibiotic associated diarrhoea and *C difficile* associated diarrhoea. This has the potential to decrease morbidity, healthcare costs, and mortality if used routinely in patients aged over 50.

**Trial registration** National Research Register N0016106821.

**METHODS**

The hypothesis was that a probiotic *Lactobacillus* preparation would reduce the incidence of antibiotic associated diarrhoea and *C difficile* associated diarrhoea. Our primary outcome was the occurrence of diarrhoea, which was recorded by the nursing staff and authenticated by the researchers. Diarrhoea was defined as more than two liquid stools a day for three or more days in quantities in excess of normal for each patient. The secondary outcome was the occurrence of *C difficile* infection, defined as an episode of diarrhoea combined with the detection of toxins A or B, or both,
from a stool sample (enzyme immunoassay kit, Meridian Bioscience, OH, USA).

Participants
We recruited patients from three London hospitals: Hammersmith, Charing Cross, and Hillingdon. Patients were recruited mainly from orthopaedic, medical, and care of the elderly wards, and included inpatients aged over 50 who were prescribed antibiotics (single or multiple antibiotics, oral or intravenous) and were able to take food and drink orally. Initially patients had to be able to give written informed consent, though half way through the trial we received ethical approval to recruit patients with cognitive impairment. Nevertheless, only seven patients had an abbreviated mental test score less than 7 (four in the control group and three in the probiotic group).

Our exclusion criteria were diarrhoea on admission or within the preceding week, reported recurrent diarrhoea, or bowel pathology that could result in diarrhoea; intake of high risk antibiotics (clindamycin, cephalosporins, aminopenicillins) or more than two courses of other antibiotics in the past four weeks to exclude pre-existing diarrhoea associated with antibiotic use; severe life threatening illness, immunosuppression, bowel surgery, artificial heart valve, history of rheumatic heart disease, or history of infective endocarditis; regular probiotic treatment before admission; and lactose intolerance or intolerance to dairy products.

Interventions
The treatment group received a probiotic yoghurt drink (Actimel, Danone, France) containing Lactobacillus casei DN-114 001 (L casei imunitass) (1.0×10^8 colony forming units/ml), S thermophilus (1.0×10^9 cfu/ml), and L bulgaricus (1.0×10^9 cfu/ml). The placebo group received a longlife, sterile milkshake (Yazoo, Campina, Netherlands). We carried out general lactobacillus counts on a sample of the probiotic drinks to ensure they were active. L casei imunitass has been shown to travel through the human gut and survive into the large intestine, thus meeting one criterion of a probiotic. Participants began using the drinks within 48 hours of starting antibiotic therapy and continued doing so for one week after they stopped taking antibiotics. They drank 100 g (97 ml) twice daily half an hour before or one to two hours after meals. Researchers verified participants’ consumption and recorded missed or refused drinks to assess compliance.

Study plan
The admitting medical team identified potential patients who had been prescribed antibiotics and the researchers approached them within 48 hours of the first antibiotic dose. Once they obtained informed consent, they collected baseline data and prescribed the randomised study drink. The hospital pharmacy dispensed the drug. A baseline stool sample was collected to screen for asymptomatic C difficile carriage. Bowel movements were monitored with stool charts, which were checked every weekday for accuracy. When there was evidence of diarrhoea a stool sample was analysed for C difficile toxin.

Once the antibiotic course was finished a final week of study drug was dispensed and a final follow-up date fixed for four weeks later. Patients who were discharged taking antibiotics were provided with enough drink on discharge to cover the period they had to take antibiotics plus one week. Researchers followed up participants for four weeks from discharge with weekly phone calls to ask about diarrhoea and compliance. If participants had diarrhoea, the researchers collected a further stool sample to check for C difficile toxin.

Sample size
With α=0.05 and a power of 90% to detect an absolute difference of 20% between the proportion of patients with antibiotic associated diarrhoea in the placebo (assumed at 30%) and probiotic (assumed at 10%) groups we estimated that we needed a sample size of 164 (82 in each group).

Randomisation
An independent statistician generated the random allocation sequence, which was stratified for hospital, sex, and two age groups (50-69 and ≥70). The sequence was given to the pharmacy on each site.

Blinding
Actimel is sold in 100 g white plastic bottles with removable labels; Yazoo is packaged similarly but in 200 ml bottles. We chose Yazoo as placebo because it looks identical in colour and consistency to Actimel but is an ultra high temperature treated product and has no
bacterial content. The pharmacies removed the commercial labels, then applied study labels to identify the patient, the drink’s “use by” date, and storage instructions. We could not find a placebo in an identical bottle to Actimel.

Patients and researchers were blind to the study drink as they did not see the bottle the drink came in. Nursing staff dispensed the drinks and were instructed to pour 100 ml into a cup for the patient; they were not told which bottle contained which drink. Older people in the UK are not generally familiar with these products, but it is possible some patients might have recognised the taste. However, we had excluded people who regularly took this or other probiotic products from the study.

Potential bias through unblinding was possible but unlikely, and the outcome measure was checked and agreed between two or more people. Microbiology staff who were blind to the study grouping assessed occurrence of *C difficile* by analysis of a stool sample from patients who had diarrhoea.

**Statistical methods**

We used Fisher’s exact test to compare rates of antibiotic associated diarrhoea and *C difficile* associated diarrhoea and logistic regression (block entry with removal of non-significant variables) to establish which factors influenced the occurrence of diarrhoea and to estimate the adjusted odds ratio for treatment effect.

**RESULTS**

From November 2002 to January 2005, 135 patients entered the study (figure). The most common reason for exclusion (61% of patients) was the likelihood of diarrhoea from causes unrelated to antibiotics. A further 21% of patients were excluded because of possible safety concerns, and 18% were not able to give informed consent nor were relatives willing or available to give assent. Only one patient was excluded because of a dairy allergy.

There were no reported adverse events related to the study drinks. In the 24 samples we tested for lactobacillus the mean count was \(2.2 \times 10^8\) CFU/ml (range \(0.35 \times 10^8\) to \(4.6 \times 10^8\)). We found no bacterial content in the Yazoo samples.

There were no clinically important differences between the two groups at baseline (table 1). Most patients received one antibiotic, but about 40% received two (table 1). The most common reasons for antibiotic use were respiratory infection (49%) or prophylaxis before or after surgery (25%) (usually orthopaedic). Compliance was assessed by the percentage of prescribed drinks that were consumed: 75% (interquartile range 55-91%) of the probiotic and 79% (63-94%) of the control drink. The main reason for compliance rates falling below 100% were delivery and distribution failures, rather than palatability. One patient in each group was positive for *C difficile* toxin at baseline but had no diarrhoea; neither patient subsequently developed diarrhoea.

The primary analysis was intention to treat and included all patients with available end point data (table 2). We could not complete follow-up on 16% (22/135; 12 in probiotic group, 10 in placebo group) as we were unable to contact them at home despite numerous phone calls and written communications (16) or they had withdrawn (6) from the study, thus the analysis for occurrence of antibiotic associated diarrhoea included 113 patients (56 in control and 57 in probiotic group). Four patients were not tested for *C difficile* (one in probiotic group, three in control group) and thus were not included in the analysis for occurrence of diarrhoea associated with *C difficile*. We found a significant reduction in both the incidence of antibiotic associated diarrhoea and *C difficile* associated diarrhoea (P=0.007) and *C difficile* associated diarrhoea (P=0.001) in the probiotic group. The absolute risk reduction for occurrence of antibiotic associated diarrhoea was 22% (95% confidence interval 7% to 37%), and the number needed to

---

**Table 1** Baseline characteristics of study participants. Figures are numbers (percentages) of patients unless stated otherwise

<table>
<thead>
<tr>
<th></th>
<th>Probiotic (n=69)</th>
<th>Control (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>39 (57)</td>
<td>34 (52)</td>
</tr>
<tr>
<td>White European</td>
<td>61 (88)</td>
<td>59 (89)</td>
</tr>
<tr>
<td>Mean (SD) age (years)</td>
<td>73.7 (11.1)</td>
<td>73.9 (10.5)</td>
</tr>
<tr>
<td>Median (IQR) BMI</td>
<td>25.5 (20.6-31.5)</td>
<td>23.7 (19.7-30.5)</td>
</tr>
<tr>
<td>Mean (SD) albumin (g/l)</td>
<td>33.2 (5.3)</td>
<td>32.7 (6.1)</td>
</tr>
<tr>
<td>Median (IQR) white cell count (1/l)</td>
<td>9.0 (6.8-13.3)</td>
<td>9.5 (7.0-13.1)</td>
</tr>
<tr>
<td>Median (IQR) plasma sodium (mmol/l)</td>
<td>138.0 (135-140)</td>
<td>137.0 (135-139)</td>
</tr>
<tr>
<td>Median (IQR) C reactive protein (mg/l)</td>
<td>37.0 (30.0-118.0)</td>
<td>46.0 (15.8-140.0)</td>
</tr>
<tr>
<td>Median (IQR) thyroid stimulating hormone (mU/l)</td>
<td>1.17 (0.56-2.09)</td>
<td>0.9 (0.6-1.74)</td>
</tr>
<tr>
<td>Median (IQR) thyroxine (pmol/l)</td>
<td>15.5 (14.0-17.2)</td>
<td>15.3 (13.0-16.7)</td>
</tr>
<tr>
<td>Median (IQR) length of stay (days):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before randomisation</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>After randomisation</td>
<td>9.0 (5.0-16.0)</td>
<td>8.0 (4.5-14.0)</td>
</tr>
<tr>
<td>Alcohol drinkers</td>
<td>34 (49)</td>
<td>33 (50)</td>
</tr>
<tr>
<td>Median (IQR) alcohol units/week in drinkers</td>
<td>6 (2-12)</td>
<td>9 (3-21)</td>
</tr>
<tr>
<td>Smokers</td>
<td>19 (28)</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Mean (SD) No of cigarettes/week in smokers</td>
<td>82 (64)</td>
<td>102 (87)</td>
</tr>
</tbody>
</table>

| No of antibiotics prescribed: | | |
| 1 | 40 (58) | 34 (52) |
| 2 | 26 (38) | 29 (44) |
| 3 | 3 (4) | 3 (5) |

| Risk of antibiotic causing diarrhoea*: | | |
| Low | 0 (0) | 1 (1.5) |
| Medium | 26 (38) | 19 (29) |
| High | 43 (62) | 46 (70) |

| Indication for antibiotics: | | |
| Respiratory tract infection | 33 (48) | 33 (50) |
| Prophylaxis before/after surgery | 17 (25) | 17 (26) |
| Urinary tract infection | 10 (15) | 10 (15) |
| Other† | 7 (10) | 5 (8) |
| Missing | 2 (3) | 1 (2) |

*IQR=interquartile range; BMI=body mass index. 
*Low risk=metronidazole and parenteral aminoglycosides (gentamicin); medium risk=tetracyclines (oxytetracycline), sulphonamides (trimethoprim), macrolides (azithromycin, clarithromycin, erythromycin), quinolones (ciprofloxacin); high risk=aminopenicillin (amoxicillin, benzylpenicillin, co-amoxiclav, flucloxacillin), cephalosporins (cefalexin, cefazidime, cefuroxime).†

treat was 5 (3 to 15). For *C difficile* associated diarrhoea the figures were 17% (7% to 27%) and 6 (4 to 14).

Tables 3 shows the result of logistic regression of antibiotic associated diarrhoea as the dependent variable with treatment group, age, sex, indication for antibiotics, number of antibiotics, smoking, alcohol consumption, body mass index, serum albumin, thyroxine, white cell count, C reactive protein, and plasma concentrations of creatinine, potassium, and sodium as covariates. Every 1 g/l increase in albumin concentration was associated with an 18% reduction in the odds of diarrhoea, and every 1 mmol/l increase in sodium concentration was associated with a 16% reduction. After adjustment for these variables the probiotic treatment reduced the odds of diarrhoea by 75%. The small number of cases of *C difficile* associated diarrhoea made logistic analysis inappropriate.

Additional information is available on bmj.com.

**DISCUSSION**

Twice daily intake of a probiotic drink containing *L casei*, *L bulgaricus*, and *S thermophilus* for one week longer than the duration of antibiotic treatment can prevent diarrhoea associated with antibiotic use and that caused by *C difficile*. There were no adverse events and the drink was well accepted. This is a major advance on previous meta-analyses, which called for further definitive trials and expressed considerable doubt as to the efficacy in preventing *C difficile* associated diarrhoea.6–8

**Strengths and weaknesses**

This study was adequately powered for the large treatment effect in antibiotic associated diarrhoea and used a probiotic freely available in the UK. Additionally, we were able to show the bacterial content of the product, included a four week absence of antibiotic use before enrolment, and tested for *C difficile* toxin in all patients with diarrhoea.

In vitro studies have shown that different bacterial strains work differently,12 and previous trials have produced conflicting results13–19; thus other strains may not produce the same beneficial effect as the strains tested here. We could not establish which bacteria species are effective from the three strains in this probiotic drink; the three species may be working synergistically to prevent diarrhoea or alternatively one species may be more effective than another. Therefore, our results cannot be extrapolated to other probiotic products, which must be tested in similar trials.20

An obvious methodological weakness is the possibility of unblinding of the researchers and patients. We did, however, take precautions to avoid unblinding and, most importantly, several people confirmed the presence of diarrhoea. The loss to follow-up of 16% of the study population is also a weakness, though the numbers lost in each group were similar (12 in the probiotic group and 10 in the control group) and should not significantly alter the results.

The figure illustrates the difficulties in recruitment for this study; of 1760 patients screened only 135 took part. This raises questions about whether the results are generalisable. Some patients were excluded to prevent inclusion of diarrhoea from other causes and some patients were excluded because of a lack of informed consent; these factors are irrelevant in routine use and amounted to 79% of exclusions in this trial. Others were excluded to ensure safety, and 21% were excluded on these grounds. Infections such as endocarditis or bacteraemia are rare, and recent safety reviews have questioned whether probiotics were actually the cause of infection in some documented cases.5 Nevertheless, we were cautious when recruiting for this study. Such strict criteria, however, may not be needed in practice. The high refusal rate (148) is unsurprising as we were approaching mainly elderly patients early in their hospital stay. The need for extensive data collection, monitoring, and collection of stool samples will certainly have discouraged some patients. Should probiotics become routinely used in hospitals patients are far more likely to accept it as an established rather than a trial treatment. Thus, we think the results can be generalised to any older patients in hospital, taking into account safety concerns for specific patients.

**Costs**

Using the numbers needed to treat (5 for antibiotic associated diarrhoea, 6 for *C difficile* associated diarrhoea) we calculated the cost to prevent one case of antibiotic associated diarrhoea. The estimated average cost of the probiotic was £10 (€14.8; $20) per patient (assuming an average antibiotic course of 10 days plus a further seven days of probiotics, and using current retail prices for Actimel, about £0.30 (€0.44; $0.60) each). The cost to prevent one case would therefore be £50 (€74; $100) for antibiotic associated diarrhoea
Consumption of a readily available probiotic drink containing Lactobacillus casei, L. bulgaricus, and Streptococcus thermophilus, twice a day during a course of antibiotics and for one week afterwards, reduces the incidence of diarrhoea associated with antibiotic use and C difficile.

WHAT THIS STUDY ADDS

Compliance with the probiotic drink was good

The cost to prevent one case of diarrhoea was £50 (£74; $100) and £60 (£87.5; $120) to prevent one case of C difficile.

and £60 (£89; $120) for C difficile associated diarrhoea, excluding dispensing and nursing costs. Evidence suggests that additional treatment costs per patient for C difficile associated diarrhoea are on average £3669 (£1835; £2738) in the United States21 and £4000 (£5920; £8000) in the United Kingdom22, mainly because of increased length of stay in hospital but also because of the use of vancomycin. Clearly substantial savings could be made by the routine use of probiotics.

We thank Winston Banya for statistical advice and conducting the randomisation. Sheila Bacon, Paula Brown, and Linda Wedlake for assistance with data collection. Edward Pawley, Lucy O'Driscoll, Regina Storch, kulip Dehal, and the pharmacy departments at each hospital for management and dispensing of the study drinks; the nursing staff on all the wards involved for help with keeping stool charts, monitoring patients, and collecting stool samples; Manfred Almeida and the staff in the division of microbiology, Hammersmith Hospitals Trust, for help with lactobacilli counts and C difficile toxin tests; and Ruth Peters for organising data entry.

Contributors: ALD'S, MH, CJB, CR, and TRR were all involved in the preparation of the protocol, ALD'S, CJB, and MH obtained ethical approval, ALD'S, CJB, CR, and TRR obtained funding, MH, NM, and ALD'S recruited patients and collected data; MH managed the running of the trial; TRR set up and SW undertook the microbiological investigations; MH and ALD'S undertook data cleaning and analysis with the assistance of CR and CB; all authors assisted in the production of the manuscript and interpretation of the results and all approved the final version. MH is guarantor.

Funding: Healthcare Foundation and Hammersmith Hospital Trustees research committee and Danone Vitapole (Paris, France). The Healthcare Foundation made initial comments on the design of the study. Once funding was agreed none of the funding sources had any role in the data collection, analysis, interpretation of data, writing of the report, or the decision to submit the paper for publication.

Competing interests: CR, MH, and ALD'S have received funding from Danone to attend Danone International Conferences on Probiotics. CJB is a member of Danone UK advisory group.

Ethical approval: London multicentre research ethics committee.


Accepted: 11 May 2007
Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial

Manjit S Gohel, specialist registrar,1 Jamie R Barwell, consultant vascular and transplant surgeon,2 Maxine Taylor, leg ulcer nurse specialist,1 Terry Chant, vascular nurse specialist,3 Chris Foy, medical statistician,4 Jonothan J Earnshaw, consultant surgeon,5 Brian P Heather, consultant surgeon,5 David C Mitchell, consultant surgeon,3 Mark R Whyman, consultant surgeon,1 Keith R Poskitt consultant surgeon1

ABSTRACT
Objective To determine whether recurrence of leg ulcers may be prevented by surgical correction of superficial venous reflux in addition to compression.

Design Randomised controlled trial.

Setting Specialist nurse led leg ulcer clinics in three UK vascular centres.

Participants 500 patients (500 legs) with open or recently healed leg ulcers and superficial venous reflux.

Interventions Compression alone or compression plus saphenous surgery.

Main outcome measures Primary outcomes were ulcer healing and ulcer recurrence. The secondary outcome was ulcer free time.

Results Ulcer healing rates at three years were 89% for the compression group and 93% for the compression plus surgery group (P=0.73, log rank test). Rates of ulcer recurrence at four years were 56% for the compression group and 31% for the compression plus surgery group (P<0.01). For patients with isolated superficial reflux, recurrence rates at four years were 51% for the compression group and 27% for the compression plus surgery group (P=0.33). Patients who had superficial with segmental deep reflux, recurrence rates at three years were 52% for the compression group and 24% for the compression plus surgery group (P=0.04). For patients with superficial and total deep reflux, recurrence rates at three years were 46% for the compression group and 32% for the compression plus surgery group (P=0.33). Patients in the compression plus surgery group experienced a greater proportion of ulcer free time after three years compared with patients in the compression group (78% v 71%; P=0.007, Mann-Whitney U test).

Conclusion Surgical correction of superficial venous reflux in addition to compression bandaging does not improve ulcer healing but reduces the recurrence of ulcers at four years and results in a greater proportion of ulcer free time.

Trial registration Current Controlled Trials ISRCTN07549334.

INTRODUCTION
In recent years the importance of the effect of venous leg ulceration on healthcare expenses and patients’ quality of life has been recognised.1-4 European studies have reported a prevalence of 1% in the adult population, increasing dramatically in those aged more than 80.5-7 The precise pathophysiological mechanisms causing ulceration remain debatable, although chronic venous hypertension (usually as a result of venous reflux) is generally accepted to play a major part.5-9

Chronic venous hypertension may be countered by high elevation of the leg and multilayered compression bandaging, applied by trained staff within the setting of a specialist leg ulcer service. Excellent healing rates have been reported with this approach.9-11 Strategies to prevent ulcer recurrence include patient education and class 2 elastic compression stockings.12 Stockings are often difficult to put on and uncomfortable, however, resulting in poor patient compliance.13 Moreover, conservative approaches do little to correct the underlying problem of chronic venous hypertension.

Anatomical studies using colour venous duplex ultrasonography have shown that incompetence in superficial veins (long or short saphenous) is present in most legs with chronic ulceration, sometimes in combination with deep venous reflux.14-16 Isolated reflux in deep or perforating veins is uncommon.12-16 Several surgical strategies to correct the underlying venous anatomical abnormalities have been attempted. Deep venous procedures may be associated with high complication rates, and studies have shown little clear benefit.17 However, several studies have suggested that corrective surgery for superficial venous reflux may have clinical benefits for ulcer healing and recurrence.18-20

The effect of surgery and compression on healing and recurrence (ESCHAR) study aimed to assess these outcomes in patients with chronic venous leg ulceration. The early results have been published and suggested that compression along with superficial venous surgery may reduce recurrence rates.21 We present the long term findings.
METHODS
The ESCHAR study started recruitment in January 1999 at three centres in southwest England, serving a population of about 200,000. Since 1995 at two of the centres (Cheltenham General Hospital, Gloucestershire Royal Hospital) the management of leg ulcers has been directed by a specialist nurse-led leg ulcer service. No such service existed at the third centre (Southmead Hospital), but the Gloucestershire model of leg ulcer care was extended to Southmead for the duration of this trial for recruited patients.

Referrals were received from community nursing teams, general practitioners, and other hospital medical specialists. Patients underwent a standardised leg ulcer assessment, consisting of medical history and clinical examination, assessment of ankle brachial pressure index, and colour venous duplex scanning. Routinely insonated segments included femoral vein, above and below knee popliteal vein, long and short saphenous veins, and calf perforating veins. We defined disease as being present if retrograde flow was more than one second after calf compression. Duplex scanning was carried out by trained vascular scientists. We assessed consecutive patients referred to the vascular services in the three centres and recruited those with open or recently healed leg ulceration (within six months) between knee and malleoli of greater than four weeks’ duration, an ankle brachial pressure index of 0.85 or greater, and superficial or deep venous reflux on duplex scanning. We excluded patients in whom duplex scanning was not possible or multilayer compression therapy not practical, those who were unable or unwilling to give informed consent, those with deep venous occlusion, those unfit for surgery (even under local anaesthetic), and those with malignant ulceration. For the purposes of this study we classed patients without deep reflux as having isolated superficial reflux. Patients with reflux in some, but not all, deep veins were described as having superficial and segmental deep reflux, whereas patients with reflux throughout the deep system were described as having superficial and total deep reflux. The diagnosis of superficial venous reflux was made purely on findings from duplex scans rather than the presence of visible varicosities.

If patients had ulceration of both legs, we studied the clinically worse leg, as decided by the patient. Treatment was the same for both legs. Written informed consent was obtained from the patients.

Randomisation and treatments
Patients were randomly allocated to treatment with multilayer compression therapy alone or compression plus superficial venous surgery. Computer generated random numbers were sealed in sequentially numbered envelopes and group allocation was independent of time, place, and person delivering the treatment.

Compression therapy
Patients with open ulceration were treated weekly with multilayered compression bandaging (Smith & Nephew, Hull) aiming for 40 mm Hg of pressure at the ankle graduated to 17-20 mm Hg at the upper calf. Patients with healed legs were prescribed class 2 elastic stockings (MEDI, Hereford) and advised to wear these during the day. All patients were given standard written and verbal advice to elevate the affected leg and to exercise.

Surgical treatments
Patients randomised to compression plus surgery were offered superficial venous surgery guided by findings on duplex scans. Patients with reflux at the saphenofemoral junction or long saphenous vein were offered saphenofemoral junction disconnection, stripping of the long saphenous vein to below the knee, and calf varicosity avulsions. Venous reflux in the short saphenous vein was treated with saphenopopliteal junction disconnection and calf varicosity avulsions. We treated patients who were considered unfit for general anaesthesia with saphenofemoral or saphenopopliteal junction disconnections, or both, under local anaesthetic.

Follow-up and outcome measures
Patients with open ulceration were reviewed monthly in the clinics until ulceration had healed, or more often if clinically necessary. After healing, patients were reviewed at one month then every three months for

![Chart](chart.png)
one year and every six months thereafter. Patients were given instructions to contact the service immediately for possible ulcer recurrence. After recurrence, intensive follow-up was continued to three years in two of the centres (Cheltenham and Gloucester) when details of further episodes of ulcer healing and recurrence were recorded.

Primary outcome measures were ulcer healing and ulcer recurrence. Ulcer free time was assessed as a secondary outcome measure. Ulcer healing was defined as complete re-epithelialisation of the leg. We classified any breakdown of epithelium between knee and malleoli after ulcer healing as ulcer recurrence. Ulcer free time was defined as the total time with a healed leg and was calculated to three years.

Statistical analysis
We calculated the sample size using previous non-randomised study data for ulcer recurrence rates at 12 months. Details have been published previously.21 Allowing a wide margin for mortality, losses to follow-up, protocol violations, non-healing ulcers, and extended follow-up, we estimated a recruitment target of 500 patients. Analyses were carried out on an intention to treat basis with no per protocol analyses planned. We calculated ulcer healing and recurrence using Kaplan-Meier survival analysis with log rank comparisons. For the purposes of the Kaplan-Meier analysis we took time zero as the date of recruitment for patients with healed legs and date of healing for patients recruited with open ulceration. We planned subgroup analyses for patients with isolated superficial reflux, superficial with segmental deep reflux, and superficial with total deep reflux. Tests for interaction were carried out using Cox regression analysis. All analyses were carried out using SPSS for windows version 13.0.1, with P values less than 0.05 considered as significant.

RESULTS
Between January 1999 and August 2002, 1418 consecutive patients with open or recently healed leg ulcers and superficial venous reflux were screened for inclusion in the study, of whom 500 consented (fig 1). A total of 258 patients were randomly allocated to compression alone and 242 to compression plus surgery. Fifty four patients were lost to follow-up or withdrew from the trial (27 compression, 27 compression plus surgery) and were censored from Kaplan-Meier analyses. Forty seven patients randomised to compression plus surgery did not attend for surgery and three randomised to compression requested surgery.

The groups were well matched for age, sex, ulcer chronicity, and ulcer size (table 1). Of the 500 patients, 300 had isolated superficial reflux, 126 had superficial with segmental deep reflux, and 74 had superficial with total deep reflux. Overall mortality was 17% at three years, with the groups showing similar mortality (19% compression, 16% compression plus surgery; P=0.245, log rank test). No deaths occurred within 30 days of surgery or as a direct result of surgery.

Of 242 patients randomised to compression plus surgery, 195 (81%) attended for their operation; surgery was carried out to the long saphenous vein in 141 (72%), the short saphenous vein in 27 (14%), and both the long and the short saphenous veins in 21 (11%). Six patients (3%) underwent calf perforator surgery only. Surgical complications were seen in eight patients, as reported previously.21 Temporary hospital admission was necessary in two cases.

Ulcer healing
Overall ulcer healing rates at three years were 89% in the compression group and 93% in the compression plus surgery group (P=0.737, log rank test; fig 2). Numbers were too small to calculate healing rates at three years for the subgroups stratified by venous reflux pattern. Analysis for interaction showed that the effect of surgery on healing did not differ between the subgroups stratified by venous reflux pattern (P=0.053, hazard ratio 0.756, 95% confidence interval 0.513 to 1.004).

Ulcer recurrence
Ulcer recurrence rates at four years were significantly lower in the compression plus surgery group.
compared with the compression group (31% v 56%; P<0.001, log rank test; fig 3). For patients with isolated superficial reflux, recurrence rates at four years were 27% in the compression group and 51% in the compression plus surgery group (P<0.001; fig 4). For patients with superficial plus segmental deep reflux, recurrence rates at three years were 24% in the compression plus surgery group and 52% in the compression group (P=0.044; fig 4). For patients with superficial plus total deep reflux, recurrence rates at three years were 24% in the compression plus surgery group and 46% in the compression group, although this was not a statistically significant finding (P=0.23; fig 4). Cox regression analysis confirmed that randomisation to surgery significantly reduced ulcer recurrence (P<0.001, hazard ratio 2.926, 95% confidence interval 1.723 to 4.133), although the influence of surgery on recurrence was not shown to differ between the subgroups with differing patterns of venous reflux (P=0.227, hazard ratio 0.833, 95% confidence interval 0.479 to 1.191).

Ulcer free time
Ulcer free time was assessed to three years in 365 of the 500 (73%) patients. Patients randomised to compression plus surgery experienced significantly longer absolute (100 v 85 weeks, P=0.013) and proportional (78% v 71%, P=0.007) ulcer free time up to three years than those randomised to compression. A total of 122 episodes of recurrent ulceration occurred during the study; 81 in the compression group compared with 41 in the compression plus surgery group (P=0.001, Mann-Whitney U test).

DISCUSSION
Superficial venous surgery in addition to compression therapy for chronic venous leg ulceration reduced ulcer recurrence and improved ulcer free time when compared with compression alone. In accordance with previous, smaller studies, the clinical benefit seemed greatest for patients with isolated superficial reflux but was also present for patients with coexistent segmental deep reflux. For patients with isolated superficial reflux, four would need to undergo surgery to prevent one episode of ulceration in four years. Although the improvement in ulcer recurrence rates was less impressive in the groups with segmental and total deep reflux, the subgroups were smaller and the actual benefit of surgery may have been underestimated. Other authors have reported reversal of venous reflux in deep and perforating veins after superficial venous surgery, and postoperative duplex scans of patients in our study showed a similar effect. Therefore deep venous reflux should not be considered an absolute contraindication to superficial venous surgery as patients may experience significant haemodynamic and clinical benefits. Ulcer healing was not improved by superficial venous surgery possibly because the haemodynamic benefit of multilayer
Compression bandaging was not significantly improved by the addition of surgery.27,28

Strengths and weaknesses of the study

Our study was set within an established leg ulcer service across three vascular centres, and we considered consecutive patients. Inclusion criteria were deliberately open and surgery was carried out by competent surgeons of varying grades consistent with standard patient care. The study was designed to emulate standard clinical practice to ensure that results could be widely applicable to the patient population with leg ulceration. Our choice of surgery and patient stratification were based solely on findings from colour venous duplex scanning. Other studies have suggested that non-invasive assessment of venous refill time using photoplethysmography may help predict success after surgery.29 Further refinement of the selection process could improve the identification of patients most likely to derive a clinical benefit from the addition of venous surgery.

Poor compliance with surgical treatment for patients with leg ulceration has been reported.10 In our study 24% of patients randomised to surgery refused to attend for their operation despite extensive counselling before recruitment. Moreover, patients waited a median of seven weeks for their operation and therefore may not have received an immediate benefit. Despite these factors we carried out all analyses on an intention to treat basis, suggesting that the benefits of surgery may have been underestimated. In recent years several less invasive procedures for the treatment of superficial venous reflux have been forwarded, including foam sclerotherapy,31 radiofrequency ablation,32 and endovenous laser.33 These techniques, often carried out under local anaesthetic, may have a role for patients reluctant to undergo traditional surgery, although long term durability remains unproved.

Class 2 stockings have been shown to reduce ulcer recurrence and we prescribed them for all patients after ulcer healing.12 We did not formally assess compliance with stocking use, although patients were given similar written and verbal advice. Other authors have reported poor compliance with stocking use,13 which may partly explain the high incidence of recurrent ulceration without surgery (56% at four years in this study). Of the patients randomised to compression plus surgery, 31% had recurrent ulceration within four years. Some did not attend for their operation and others underwent surgery under local anaesthetic without stripping of the long saphenous vein. Factors other than venous reflux, such as coexisting medical problems or ankle stiffness causing poor calf muscle function,34 may have contributed to recurrent ulceration in individual cases. Whether these patients experienced more ulcer free time after surgery as a result of less frequent or shorter episodes of recurrent ulceration remains unproved. Nevertheless, residual venous reflux and neovascularisation are common after superficial venous procedures, and stripping of the long saphenous vein to the knee is preferable.35

Future research

The recent introduction of novel, endovenous techniques for the correction of venous incompetence may provide a more acceptable treatment option for elderly patient groups with chronic venous ulceration.21,33 Further studies are needed to ascertain the haemodynamic benefits, durability, and clinical efficacy of these techniques compared with traditional venous surgery. Further work is also needed to help identify those patients who would benefit most from correction of venous incompetence and to determine why some patients experience recurrence despite the abolition of reflux.

Conclusions

Chronic leg ulceration is common and distressing for patients and an important financial burden for healthcare providers. These long term findings support the early results from the effect of surgery and compression on healing and recurrence study and present a cogent argument for the widespread provision of colour duplex scanning and superficial venous surgery for patients with chronic venous leg ulcers.

We thank for their support and assistance CE Davies, G Turton, G Woolfrey, J Waldron (Gloucestershire Leg Ulcer Service); C Wakely, J Minor, K Harvey, A Sassano (vascular scientists); and B Whitman (research assistant).

Contributors: MG was involved with data acquisition, management and analysis, and wrote this report. JB, JE, MW, and KP were involved with study concept and design, performed surgery, and critically revised this report. BH and DM performed surgery, were involved with data acquisition, and critically revised this report. MT, TC were involved with data acquisition, and critically reviewed this report. CF provided statistical guidance and critically reviewed this report.

Funding: NHS Executive South and West Research and Development Directorate, Southmead Hospital Research Foundation, and Medical Research Council. The funding sources had no financial or other interest in study outcome and had no role in study design, data control or reporting.

Competing interests: None declared.

Ethical approval: Gloucestershire and Southmead research ethics committees.

Effects of treatments for symptoms of painful diabetic neuropathy: systematic review

Man-chun Wong, pain management nurse,1 Joanne W Y Chung, professor,2 Thomas K S Wong, chair professor2

ABSTRACT

Objective To evaluate the effects of treatments for the symptoms of painful diabetic neuropathy.
Design Systematic review.
Data sources Articles (English and full text) on double blind randomised trials found by searching with the key words anticonvulsant, antidepressant, non-steroidal anti-inflammatory drugs, tramadol, opioid, ion channel blocker, diabetic neuropathy, diabetic peripheral neuropathy, peripheral neuropathy, and neuropathy. The search included Medline, Embase, EMB reviews-AP Journal club, and the Cochrane central register of controlled trials.
Study selection Randomised controlled trials comparing topically applied and orally administered drugs with a placebo in adults with painful diabetic neuropathy.
Data extraction Data were extracted to examine quality of methods, characteristics of studies and patients, efficacy, and side effects. The primary outcome was dichotomous information for 50% or moderate reduction of pain. Secondary outcomes were 30% reduction of pain and withdrawals related to adverse events.
Results Odds ratios were calculated for achievement of 30%, 50%, or moderate pain relief and for withdrawals related to adverse effects. Twenty five reports were included and seven were excluded. The 25 included reports compared anticonvulsants (n=1270), antidepressants (94), opioids (329), ion channel blockers (173), N-methyl-D-aspartate antagonist (14), duloxetine (805), capsaicin (277), and isosorbide dinitrate spray (22) with placebo. The odds ratios in terms of 50% pain relief were 5.33 (95% confidence interval 1.77 to 16.02) for traditional anticonvulsants, 3.25 (2.27 to 4.66) for newer generation anticonvulsants, and 22.24 (5.83 to 84.75) for tricyclic antidepressants. The odds ratios in terms of withdrawals related to adverse events were 1.51 (0.33 to 6.96) for traditional anticonvulsants, 2.98 (1.75 to 5.07) for newer generation anticonvulsants, and 2.32 (0.59 to 9.69) for tricyclic antidepressants. Insufficient dichotomous data were available to calculate the odds ratios for ion channel blockers.
Conclusion Anticonvulsants and antidepressants are still the most commonly used options to manage diabetic neuropathy. Oral tricyclic antidepressants and traditional anticonvulsants are better for short term pain relief than newer generation anticonvulsants. Evidence of the long term effects of oral antidepressants and anticonvulsants is still lacking. Further studies are needed on opioids, N-methyl-D-aspartate antagonists, and ion channel blockers.

INTRODUCTION

Diabetic neuropathy is a common complication of diabetes. It usually progresses gradually and involves small and large sensory fibres. The symptoms, such as loss of ability to sense pain, loss of temperature sensation, and developing neuropathic pain, follow a “glove and stocking” distribution, beginning in the lower limbs, first affecting the toes, and then progressing upward.1 The primary cause of diabetic neuropathy is thought to be hyperglycaemia.2

Diabetic neuropathy represents a major health problem worldwide. An Australian population based survey of 2436 patients with known or newly diagnosed diabetes showed that 13.1% of them had peripheral neuropathy.3 Another multicentre study in the United Kingdom showed that 22-32% of 6363 diabetic patients had peripheral neuropathy.4 Similar results have been reported by an Italian multicentre study, which showed that 32.3% of 8757 diabetic patients had neuropathy.5

Symptoms of neuropathic pain are commonly reported in patients with diabetic neuropathy. Partanen and colleagues found that among 132 patients, 7-13% had pain and paraesthesias when they were diagnosed as having type 2 diabetes mellitus.6 The prevalences of pain and of paraesthesia were 20% and 33% 10 years after diagnosis.5 Sorensen and colleagues identified neuropathic pain in 11.7% of those who had insensate neuropathy and in 2.3% of those with sensitive neuropathy among 2610 patients with type 2 diabetes.7

Tight glycaemic control has been shown to be effective in slowing the progression of diabetic neuropathy.8-11 The diabetes control and complications trial in 1441 patients with type 1 diabetes showed that tight glycaemic control can delay the onset and slow the progression of neuropathy, as measured by clinical examination, autonomic testing, and nerve conduction studies.10,11 Apart from glycaemic control, antidepressants and anticonvulsants are commonly used to reduce the intensity of pain in patients with painful diabetic neuropathy.
In the clinical setting, despite the use of various analgesics to manage the neuropathic pain of diabetic neuropathy, the problem persists. We did a systematic review to explore the effectiveness of analgesics in managing diabetic neuropathy.

**METHODS**

**Search strategy to identify studies**

We used several methods to identify the studies to be included. We identified randomised trials that studied analgesics used to treat diabetic neuropathy by using Medline(R) without revision from 1966 to October 2006, Embase from 1980 to October 2006, EMB reviews-AP Journal club from 1991 to September/October 2006, and the third quarter 2006 of the Cochrane central register of controlled trials. We identified additional reports from the reference lists of the retrieved papers.

The key words used in the search were anticonvulsant, non-steroidal anti-inflammatory drugs, ion channel blocker and neuropathy, antiepileptic/anticonvulsant and neuropathy, antidepressant or ant depresive agents and neuropathy, tramadol and neuropathy, opioid and neuropathy, pregabalin and neuropathy, duloxetine and neuropathy, capsaicin and neuropathy, antidepressant or antide pressive agents and diabetic neuropathies or diabetic peripheral neuropathy, antidepressant or antidepressive agents and peripheral neuropathy.

**Selection criteria**

Participants in the studies were adults aged 18 years and above with diabetic neuropathy. The interventions involved the administration of oral or topical analgesics. The classes of drugs included paracetamol, antidepressants, opioids, non-steroidal anti-inflammatory drugs, N-methyl-D-aspartate antagonists, tramadol, capsaicin, and anticonvulsants. The comparator was a placebo. We excluded studies comparing different classes of analgesics, such as anticonvulsants versus antidepressants. The primary and secondary outcomes of the studies had to include subjective reports of pain relief or pain intensity. We included randomised controlled trials that investigated the analgesic effects of pain relieving drugs for patients with diabetic neuropathy. We excluded reports that were non-randomised, case reports, clinical observations, or studies of intravenous analgesics, intramuscular analgesics,
or Chinese herbal medicine. We included full text reports published in English.

Quality assessment
We used a three item, 1-5 quality scale to score each report that met the inclusion criteria. We excluded studies without randomisation and blinding and trials with a quality score of 2 or less. We also assessed use of concealment and intention to treat analysis. Lastly, we did not consider trials with a sample size under 10. Two of the three reviewers made quality assessments, and disputes were settled by consensus.

Data extraction
We selected studies for retrieval from the library by reviewing the information from the title and abstract against our inclusion criteria. On the basis of their titles, we retrieved studies identified from the reference list of the available articles. We compared full reports of the studies with the inclusion criteria to determine their relevance to the systematic review. Two reviewers extracted data independently to examine characteristics of studies and patients, efficacy, and side effects.

We sent 25 letters to authors for further information on their published reports, including method of randomisation, concealment, double blinding, outcome measures, and reason for dropouts. Two of them replied.

Outcome
We defined clinical success as about a 50% reduction in pain. This was the number of patients with a "moderate," "good," or "notable" improvement in global assessment of treatment or at least moderate pain relief on a suitable categorical scale. Secondary outcomes were 30% reduction in pain and the number of patients who withdrew as a result of adverse events.

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Anticonvulsant (n/N)</th>
<th>Placebo (n/N)</th>
<th>Odds ratio (random) (95% CI)</th>
<th>Weight (%)</th>
<th>Odds ratio (random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>50% reduction of pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dogra 2005⁶⁸</td>
<td>24/69</td>
<td>14/77</td>
<td>22.35 (2.40 to 5.14)</td>
<td>2.40</td>
<td>3.00 (1.55 to 5.78)</td>
</tr>
<tr>
<td>Rosenstock 2004⁷⁵⁵</td>
<td>30/75</td>
<td>10/69</td>
<td>19.59 (3.93 to 8.88)</td>
<td>3.93</td>
<td>2.83 (1.74 to 4.68)</td>
</tr>
<tr>
<td>Lesser 2004⁷¹²</td>
<td>37/81</td>
<td>17/97</td>
<td>27.61 (3.96 to 77.83)</td>
<td>3.96</td>
<td>3.00 (2.00 to 7.83)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>225</td>
<td>243</td>
<td>69.86 (3.00 to 77.83)</td>
<td>3.00</td>
<td>3.00 (3.00 to 7.83)</td>
</tr>
<tr>
<td>Total events: 91</td>
<td>41 (treatment), 41 (control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2=1.11$, df=2, P=0.57, $I^2=0$

Test for overall effect: $z=5.52$, P=0.0001

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment (n/N)</th>
<th>Control (n/N)</th>
<th>Odds ratio (random) (95% CI)</th>
<th>Weight (%)</th>
<th>Odds ratio (random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderately improved in patient global impression of change</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Backonja 1998⁶⁶</td>
<td>47/79</td>
<td>25/76</td>
<td>30.14 (3.00 to 5.78)</td>
<td>3.00</td>
<td>3.00 (1.55 to 5.78)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>79</td>
<td>76</td>
<td>30.14 (3.00 to 5.78)</td>
<td>3.00</td>
<td>3.00 (1.55 to 5.78)</td>
</tr>
</tbody>
</table>

Total events: 47 (treatment), 25 (control)

Test for heterogeneous: not applicable

Test for overall effect: $z=3.28$, P=0.001

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Anticonvulsant (n/N)</th>
<th>Placebo (n/N)</th>
<th>Odds ratio (random) (95% CI)</th>
<th>Weight (%)</th>
<th>Odds ratio (random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>304</td>
<td>319</td>
<td>100.00 (3.25 to 4.66)</td>
<td>3.25</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2=1.12$, df=3, P=0.75, $I^2=0$

Test for overall effect: $z=6.41$, P=0.0001

Fig 3 | Withdrawals related to adverse events for traditional anticonvulsants versus placebo

Fig 4 | Treatment efficacy of newer generation anticonvulsants versus placebo
Data analysis
We combined the results and expressed them as odds ratios with 95% confidence intervals, using a random effect model, for the studies with sufficient data. We used Review Manager 4.2 for all statistical calculations. We assessed homogeneity with the $I^2$ statistic for studies with sufficient data, and for the studies without sufficient data we assessed homogeneity visually. We based a subgroup analysis on different classes of drugs.

RESULTS
Description of the studies
We screened 1231 citations for eligibility; we identified no eligible study on non-steroidal anti-inflammatory drugs. We retrieved 32 full text articles published in

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Trial</th>
<th>Active drug</th>
<th>Daily dose (mg)</th>
<th>No</th>
<th>Age (mean)</th>
<th>Design</th>
<th>Jadad score</th>
<th>Concealment</th>
<th>ITT*</th>
<th>Treatment period</th>
<th>Follow-up (efficacy of treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical treatment</td>
<td>Capsaicin cream</td>
<td>Capsaicin group 1991</td>
<td>0.075% capsaicin</td>
<td>Apply four times daily</td>
<td>277</td>
<td>60</td>
<td>Parallel</td>
<td>4</td>
<td>NM</td>
<td>Yes (for PGE)</td>
<td>8 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral treatment</td>
<td>Rull 1969*5</td>
<td>Carbamazepine</td>
<td>200-600</td>
<td>30</td>
<td>54.2</td>
<td>Crossover, no washout</td>
<td>4</td>
<td>NM</td>
<td>No</td>
<td>2 weeks</td>
<td>Completion of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Backonja 1998*6</td>
<td>Gabapentin</td>
<td>3600</td>
<td>165</td>
<td>53</td>
<td>Parallel</td>
<td>5</td>
<td>NM</td>
<td>Yes</td>
<td>8 weeks</td>
<td>Completion of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eisenberg 2001*7</td>
<td>Lamotrigine</td>
<td>25-400</td>
<td>59</td>
<td>55</td>
<td>Parallel</td>
<td>3</td>
<td>NM</td>
<td>No</td>
<td>8 weeks</td>
<td>Completion of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dogra 2003*8</td>
<td>Oxcarbazepine</td>
<td>1443 (mean)</td>
<td>146</td>
<td>60</td>
<td>Parallel</td>
<td>4</td>
<td>NM</td>
<td>No</td>
<td>4 weeks</td>
<td>Completion of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Beydoun 2006*9</td>
<td>Oxcarbazepine</td>
<td>600/1200/1800</td>
<td>347</td>
<td>60</td>
<td>Parallel</td>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>16 weeks</td>
<td>Completion of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rosenstock 2004*10</td>
<td>Pregabalin</td>
<td>300</td>
<td>146</td>
<td>59.7</td>
<td>Parallel</td>
<td>5</td>
<td>Yes</td>
<td>No</td>
<td>8 weeks</td>
<td>Completion of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Richter 2005*11</td>
<td>Pregabalin</td>
<td>150/600</td>
<td>246</td>
<td>57</td>
<td>Parallel</td>
<td>5</td>
<td>NM</td>
<td>Yes</td>
<td>6 weeks</td>
<td>Completion of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lesser 2004*12</td>
<td>Pregabalin</td>
<td>75/300/600</td>
<td>337</td>
<td>59.9</td>
<td>Parallel</td>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>5 weeks</td>
<td>Five weeks for double blind period</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kochar 2002*13</td>
<td>Sodium valproate</td>
<td>1200</td>
<td>57</td>
<td>56</td>
<td>Parallel</td>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>4 weeks</td>
<td>Completion of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kochar 2004*14</td>
<td>Sodium valproate</td>
<td>1000</td>
<td>43</td>
<td>55</td>
<td>Parallel</td>
<td>5</td>
<td>NM</td>
<td>No</td>
<td>3 months</td>
<td>Completion of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressant:</td>
<td>TCA</td>
<td>Max 1987*15</td>
<td>Amitriptyline</td>
<td>25-100</td>
<td>37</td>
<td>57 (median)</td>
<td>Crossover, no washout</td>
<td>4</td>
<td>NM</td>
<td>No</td>
<td>6 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Max 1991*16</td>
<td>Desipramine</td>
<td>201 (mean)</td>
<td>24</td>
<td>62 (median)</td>
<td>Crossover, no washout</td>
<td>4</td>
<td>NM</td>
<td>No</td>
<td>6 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kvinesdal 1984*17</td>
<td>Imipramine</td>
<td>100</td>
<td>15</td>
<td>54</td>
<td>Crossover, no washout</td>
<td>4</td>
<td>NM</td>
<td>No</td>
<td>5 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRI</td>
<td>Sindrup 1992*18</td>
<td>Citalopram</td>
<td>40</td>
<td>18</td>
<td>56 (median)</td>
<td>Crossover, one week washout</td>
<td>4</td>
<td>NM</td>
<td>No</td>
<td>3 weeks</td>
<td>Completion of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNRI</td>
<td>Goldstein 2005*19</td>
<td>Duloxetine</td>
<td>20/60/120</td>
<td>457</td>
<td>60</td>
<td>Parallel</td>
<td>4</td>
<td>Yes</td>
<td>Yes</td>
<td>12 weeks</td>
<td>Completion of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Raskin 2005*19</td>
<td>Duloxetine</td>
<td>60/120</td>
<td>348</td>
<td>58.8</td>
<td>Parallel</td>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>12 weeks</td>
<td>Completion of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ion channel blocker</td>
<td>Dejgard 1988*20</td>
<td>Mexiletine</td>
<td>10 mg/kg</td>
<td>16</td>
<td>50 (median)</td>
<td>Crossover, four week washout</td>
<td>3</td>
<td>NM</td>
<td>No</td>
<td>10 weeks</td>
<td>Completion of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oskarsson 1997*21</td>
<td>Mexiletine</td>
<td>225/450/675</td>
<td>126</td>
<td>53.5</td>
<td>Parallel</td>
<td>3</td>
<td>NM</td>
<td>No</td>
<td>3 weeks</td>
<td>Completion of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wright 1997*22</td>
<td>Mexiletine</td>
<td>600</td>
<td>31</td>
<td>50</td>
<td>Parallel</td>
<td>3</td>
<td>NM</td>
<td>Yes</td>
<td>3 weeks</td>
<td>Upon completing treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMDA antagonist</td>
<td>Nelson 1997*23</td>
<td>Dextromethorphan</td>
<td>381 (mean)</td>
<td>14</td>
<td>54 (median)</td>
<td>Crossover, one week washout</td>
<td>5</td>
<td>NM</td>
<td>No</td>
<td>6 weeks</td>
<td>Completion of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid</td>
<td>Gimbel 2003*24</td>
<td>Controlled release oxycodone</td>
<td>10-120</td>
<td>159</td>
<td>59</td>
<td>Parallel</td>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>42 days</td>
<td>Completion of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Watson 2003*25</td>
<td>Controlled release oxycodone</td>
<td>10-80</td>
<td>45</td>
<td>63</td>
<td>Crossover, one week washout</td>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>4 weeks</td>
<td>Completion of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Harati 1999*26</td>
<td>Tramadol</td>
<td>200-400</td>
<td>125</td>
<td>59</td>
<td>Parallel</td>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>42 days</td>
<td>Completion of treatment</td>
</tr>
</tbody>
</table>

ITT=intention to treat analysis; NM=not mentioned; NMDA=N-methyl-D-aspartate; PGE=physician’s global evaluation; SNRI=serotonin noradrenaline reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant.
English. Three studies used mixed patient groups,14-16 two studies did not use randomisation,17 18 and the Jadad score was \( \leq 2 \) in two studies19 20; we excluded all these studies. Finally, we included 25 articles that met the inclusion criteria, w1-w25 and 17 of them were included in the meta-analysis of treatment efficacy (fig 1). The table shows the characteristics and methodological quality of the included studies.

### Anticonvulsants

Ten trials, with a total of 1576 patients, investigated traditional and newer generation anticonvulsants, including sodium valproate, w13 w14 gabapentin,w6 lamotrigine,w7 carbamazepine,w5 pregabalin,w10-w12 and oxcarbazepine.w8 w9 The carbamazepine trial used a crossover design. Two of the pregabalin studies and one of the oxcarbazepine studies were dose response trials.w9 w11 w12 The treatment period varied from two weeks to three months. We extracted no efficacy data from one of the studies on sodium valproate.w14 We extracted data on 300 mg pregabalin, 1200 mg oxcarbazepine, and the first treatment period in the carbamazepine trial for meta-analysis.w5 w9 w10 w12 We analysed data on 600 mg pregabalin separately.w11 w12

The odds ratios in terms of 50% pain relief with pregabalin 600 mg daily and pregabalin 300 mg daily were from one of the studies on sodium valproate.w14 We extracted data on 300 mg pregabalin, 1200 mg oxcarbazepine, and the first treatment period in the carbamazepine trial for meta-analysis.w5 w6 w10 w12 We analysed data on 600 mg pregabalin separately.w11 w12 We categorised anticonvulsants into two groups—traditional anticonvulsants and newer generation anticonvulsants.

The pooled odds ratio of treatment efficacy with traditional anticonvulsants was 5.33 (95% confidence interval 1.77 to 16.02) (fig 2). The pooled odds ratio for withdrawal related to adverse events with traditional anticonvulsants was 1.51 (0.33 to 6.96) (fig 3).

The pooled odds ratio of treatment efficacy with newer generation anticonvulsants was 3.25 (2.27 to 4.66) (fig 4). The pooled odds ratio for withdrawal related to adverse events with newer generation anticonvulsants was 2.98 (1.75 to 5.07) (fig 5).
The odds ratios in terms of withdrawal related to adverse effects were 2.81 (1.13 to 7.04) for pregabalin 600 mg daily and 2.23 (0.68 to 7.26) for pregabalin 300 mg daily. The odds ratios in terms of 30% pain relief with pregabalin 300 mg and 600 mg daily were 3.28 and 3.84. The odds ratio in terms of 30% pain relief with oxcarbazepine 1445 mg was 2.04.

The common side effects from use of anti-convulsants were somnolence and dizziness, and the major adverse reaction was liver derangement. Two participants withdrew from studies because of liver derangement.\textsuperscript{13,14}

Antidepressants

Four trials with a total of 94 patients investigated the tricyclic antidepressants desipramine,\textsuperscript{15} imipramine,\textsuperscript{17} and amitriptyline\textsuperscript{15} and the selective serotonin reuptake inhibitor citalopram.\textsuperscript{21} All of them were crossover studies with treatment periods between three and six weeks. Only one study had a one week washout period: we extracted the data from both treatment periods of this study.\textsuperscript{21} Although we could extract no data from the published report on citalopram, this study used published data from a previous study.\textsuperscript{21} The odds ratio in terms of 50% pain relief with citalopram was 3.5 (0.3 to 38.2), and the odds ratio for withdrawal related to adverse events was 5.6 (0.3 to 125.5). The pooled odds ratio for treatment efficacy of tricyclic antidepressants was 22.24 (5.83 to 84.75) (fig 6). The pooled odds ratio for adverse effect related withdrawal from tricyclic antidepressants was 2.32 (0.59 to 9.69) (fig 7). The most common adverse effect related to withdrawal was dry mouth and sedation.
Serotonin noradrenaline reuptake inhibitor

Two trials with a total of 805 patients investigated duloxetine.\textsuperscript{18,19} Both trials used a 12 week parallel group design, and both of them were dose response trials. The pooled odds ratio in terms for 50% pain relief with duloxetine 60 mg was 2.55 (1.73 to 3.77) (fig 8), and the odds ratio for withdrawal related to adverse events was 2.36 (1.05 to 5.35) (fig 9). For duloxetine 120 mg, the odds ratios were 2.10 (1.03 to 4.27) for 50% pain relief (fig 10) and 4.65 (2.18 to 9.94) for withdrawal related to adverse events (fig 11). The most frequently reported adverse events were nausea, somnolence, dizziness, and constipation.

Ion channel blockers

Three trials investigated mexiletine in a total of 173 patients. One trial used a crossover design,\textsuperscript{20} and another was a dose response study.\textsuperscript{21} The pooled weighted mean difference of the mean score on a visual analogue scale for pain intensity for mexiletine 600 mg and 720 mg versus placebo was $-1.87$ (−2.64 to −1.11) (fig 12). One study reported no statistical differences between mexiletine 600-675 mg and a placebo with a three week treatment period.\textsuperscript{22}

The pooled odds ratio for adverse effect related withdrawal from mexiletine was 1.08 (0.13 to 8.80) (fig 13). The adverse effects related to withdrawal were itching, pain, headache, nausea, and vomiting.\textsuperscript{22}

\textit{N-methyl-D-aspartate antagonists}

Only one trial, with a total of 14 patients, investigated dextromethorphan.\textsuperscript{23} This trial used a crossover design, with a six week treatment period and a one week washout. We could not extract the data for the first treatment period, so we based the calculation on the data for the whole treatment period. The odds ratio
in terms of 50% pain relief with a mean daily dose of 381 mg dextromethorphan was 31.2 (1.5 to 633.1). No extractable dichotomous data on adverse events related to withdrawal have been published.

Opioids
Three trials with a total of 329 patients investigated controlled release oxycodone and tramadol. One of the controlled release oxycodone trials used a crossover design. In another trial, a 37 mg average daily dose of controlled release oxycodone reportedly had a superior analgesic effect compared with placebo.

Although we could extract no data from the published report on tramadol, this study used and published data from a previous study. The odds ratio of 50% pain relief was 3.8 (1.8 to 8.0) for tramadol at an average daily dose of 210 mg. The pooled odds ratio for treatment efficacy of opioids was 4.25 (2.33 to 7.77) (fig 14).

The pooled odds ratio for withdrawal from opioids related to adverse events was 4.06 (1.16 to 14.21) (fig 15). The most common adverse events related to use of controlled release oxycodone were constipation, somnolence, and nausea. The withdrawal related adverse events for tramadol were dyspepsia and nausea. Common adverse events related to use of tramadol were nausea, constipation, headache, and somnolence.

Topical agents
One trial with a total of 22 patients investigated isosorbide dinitrate spray. This trial used a crossover design, with a four week treatment period and a two week washout. However, we could extract no
Oral tricyclic antidepressants and traditional anticonvulsants are better for short term pain relief than newer generation anticonvulsants, traditional anticonvulsants, and opioids. Next generation anticonvulsants, a selective serotonin reuptake inhibitor, and a serotonin noradrenaline reuptake inhibitor for relieving the pain of diabetic neuropathy. Most trials of application, coughing or sneezing, accidental irritation to other body parts, and rashes.

**DISCUSSION**

Our systematic review shows that tricyclic antidepressants, traditional anticonvulsants, and opioids have better efficacy than newer generation anticonvulsants, a selective serotonin reuptake inhibitor, and a serotonin noradrenaline reuptake inhibitor for relieving the pain of diabetic neuropathy. Most trials were of good methodological quality, although sample size was small and some of the trials used a crossover design without a washout period.

Some of the trials included in this review used the crossover method; only four of them mentioned using a washout period. In a study with no washout period, the carryover effect may not be eliminated from the first period of the treatment effect; we therefore used only the data from the first period to calculate the efficacy of the drugs (if we could extract the data). However, this may lead to selection bias, resulting in an underestimation of the effect of the drug. In Rull’s study, the odds ratio was 33 when calculated for the first treatment period and 18.31 when calculated for the whole treatment period. Therefore, interpretation of systematic review results should be cautious when both crossover and parallel studies are included.

A single study investigated N-methyl-D-aspartate antagonists, and estimating the effect of the drug on the basis of only one study is difficult. For ion channel blockers, three trials reported contradictory results, so we could not calculate the efficacy of this treatment. Although the odds ratio of 50% pain relief for tramadol was 3.8, that for withdrawal related to adverse events was greater for tramadol than for other treatments, which may reduce the generalisability of the findings for this drug. For anticonvulsants, the odds ratio for 50% pain relief was greater with traditional anticonvulsants than with newer generation anticonvulsants. In contrast, the odds ratio for withdrawals related to adverse events was greater for newer generation anticonvulsants than for traditional anticonvulsants. This may be related to the use of different inclusion criteria and treatment periods. Finally, the treatment period was less then six months in all of the studies, so the long term effect of these drugs cannot be judged.

Painful symptoms reported by patients with diabetic neuropathy have been frequently documented. Neuropathic pain symptoms are reported in 3-20% of patients with diabetic neuropathy. Pain paroxysms, deep aching pain, and hot or burning pain have often been described. In the clinical setting, management focuses on two aspects: disease modifying treatment such as glycaemic control and the use of various kinds of analgesics to reduce the intensity of the pain. Although pain intensity may not be sufficient to reflect the outcome of treatment, it is a common outcome measure in clinical research. Few studies reported treatment efficacy for different qualities of pain such as allodynia and burning pain. The efficacy of drug treatment may be underestimated, especially for particular painful symptoms.

**Conclusions**

Although an increasing number of trials have investigated different kinds of drugs to manage neuropathic pain, anticonvulsants and antidepressants are still the options most commonly used for painful diabetic neuropathy. Long term studies of the efficacy and adverse effects of anticonvulsants and antidepressants are needed, as these drugs are commonly used in clinical setting. Further studies are needed on ion channel blockers, N-methyl-D-aspartate antagonists, and opioids, as well as non-pharmacological strategies. In addition, their treatment efficacy for common painful symptoms needs to be explored. Finally, we propose a treatment algorithm based on the available data (fig 16).

![Proposed treatment algorithm for painful diabetic neuropathy](image-url)
Contributors: M-cW planned the review, searched the literature, selected articles, extracted and analysed the data, and drafted and revised the manuscript. JWYC initiated the review, selected articles, and extracted and analysed the data. TKSW supervised the review. All authors approved the final version. M-cW is the guarantor.

Funding: None.

Ethical approval: Not needed.

Competing interests: None declared.


Accepted: 13 April 2007
Schizophrenia

Marco M Picchioni, Robin M Murray

Schizophrenia is one of the most serious and frightening of all mental illnesses. No other disorder arouses as much anxiety in the general public, the media, and doctors. Effective treatments are available, yet patients and their families often find it hard to access good care. In the United Kingdom, as in many parts of the world, this is often due to poor service provision, but sometimes it is simply down to misinformation. In this review, we clarify the causes and presentation of schizophrenia, summarise the treatments that are available, and try to clear up a few myths.

Methods

We searched the online electronic databases Web of Knowledge, the Cochrane Library, and the current National Institute for Health and Clinical Excellence (NICE) guidelines for suitable evidence based material.

What is schizophrenia?

The name schizophrenia derives from the early observation that the illness is typified by “the disconnection or splitting of the psychic functions.” Unfortunately, this has led to the misconception that the illness is characterised by a “split personality,” which it is not. Box 1 lists the common symptoms of schizophrenia.

People with schizophrenia typically hear voices (auditory hallucinations), which often criticise or abuse them. The voices may speak directly to the patient, comment on the patient’s actions, or discuss the patient among themselves. Not surprisingly, people who hear voices often try to make some sense of these hallucinations, and this can lead to the development of strange beliefs or delusions.

Many patients also have thought disorder and negative symptoms. While negative symptoms may be less troubling to the patient, they can be very distressing to relatives.

While we often think of schizophrenia as a major departure from normal health, mild symptoms can occur in healthy people and are not associated with illness. This has led to the conclusion that schizophrenia reflects a quantitative rather than qualitative deviation from normality, rather like hypertension or diabetes.

How common is schizophrenia?

Systematic reviews show that despite its relatively low incidence (15.2/100 000), the prevalence of schizophrenia (7.2/1000) is relatively high, because it often starts in early adult life and becomes chronic. The incidence of schizophrenia varies; at present it is rising in some populations (such as South London) but falling in others.

A comprehensive global survey concluded that schizophrenia accounts for 1.1% of the total disability adjusted life years worldwide and 2.8% of the years lived with disability worldwide.

Who gets schizophrenia?

Schizophrenia typically presents in early adulthood or late adolescence. Men have an earlier age of onset than women, and also tend to experience a more serious form of the illness with more negative symptoms, less chance of a full recovery, and a generally worse outcome. Systematic reviews show that it is more common in men than women (risk ratio 1.4:1) and is more frequent in people born in cities—the larger the city and the longer the person has lived there the greater the risk. It is more common in migrants. A large and comprehensive study showed that rates of schizophrenia in African-Caribbean people living in the UK are six to eight times higher than those of the native white population. Rates remain high in the children of migrants, but this is not reflected in increased rates in their home country. Environmental and social factors have been implicated in this increased risk, and intriguingly the risk of schizophrenia in migrants is greatest when they form a small proportion of their local community.

What causes schizophrenia?

Are genes important?

Schizophrenia is a multifactorial disorder, and the greatest risk factor is a positive family history. While the lifetime risk in the general population in just below 1%, it is 6.5% in first degree relatives of patients, and it rises to more than 40% in monozygotic twins of affected people. Extended family, adoption, and twin studies show that this risk reflects the genetic proximity between relative and proband.

It seems likely that many risk genes exist—each of small effect and each relatively common in the general population. Patients probably inherit several risk genes, which interact with each other and the environment to cause schizophrenia once a critical threshold is crossed.

What environmental factors are important?

A meta-analysis has shown that patients with schizophrenia are more likely to have experienced obstetric
manifests as distorted or illogical speech

Thought disorder

A fixedly held false belief that is not shared by others from the patient’s community

Delusions can occur in any sense—touch, smell, taste, or vision—but auditory hallucinations are the most common (usually "hearing voices").

Thought disorder

A failure to use language in a logical and coherent way

Typified by “knight’s move” thinking—thoughts proceed in one direction but suddenly go off at right angles, like the knight in chess, with no logical chain of thought

Negative symptoms

These include social withdrawal, self neglect, loss of motivation and initiative, emotional blunting, and paucity of speech

Box 2 | Most common positive symptoms of schizophrenia

- Lack of insight (97%)
- Auditory hallucinations (74%)
- Ideas of reference (70%)
- Delusions of reference (67%)
- Suspiciousness (66%)
- Flatness of affect (66%)
- Delusional mood (64%)
- Delusions of persecution (64%)
- Thought alienation (52%)
- Thoughts spoken aloud (50%)

Can drug abuse cause schizophrenia?

We know that stimulants like cocaine and amphetamines can induce a picture clinically identical to paranoid schizophrenia, and recent reports have also implicated cannabis. The evidence that patients with established schizophrenia smoke more cannabis than the general population is overwhelming. Well conducted and comprehensive cohort studies, like that from Dunedin in New Zealand,12 show that early cannabis use—long before psychotic symptoms appear—increases the future risk of schizophrenia fourfold, while a meta-analysis of prospective studies reported a doubling of the risk.13 This effect is robust, even after controlling for any effect of self medication,13 undermining the suggestion that early cannabis use is an attempt to alleviate distress caused by the developing illness. Only a small proportion of people who use cannabis develop schizophrenia, just as only a few of those who misuse alcohol develop cirrhosis. This probably reflects a genetically determined vulnerability to the environmental stressor, a gene-environment interaction. Indeed, variations in the dopamine metabolising COMT (catechol-O-methyltransferase) gene affect the propensity to develop psychosis in people who use cannabis.14

Early diagnosis and management in primary care

Box 2 lists the most common positive symptoms of schizophrenia, and box 3 shows the ICD-10 (international classification of diseases, 10th revision) diagnostic criteria. However, few patients initially present with such florid symptoms. Patients are more likely to have more nebulous symptoms such as anxiety and depression, social problems, or changes in behaviour, particularly difficulties in concentrating or becoming withdrawn from their normal social life. Box 4 outlines useful screening questions for patients presenting in this manner.

If the onset of psychosis is suspected, the patient should be rapidly referred to secondary care. This will be the local early intervention or home treatment team in many parts of the UK, or the generic catchment area community mental health team. The risk that patients pose to themselves and others must be assessed at this
first assessment and this information included in the referral. If the presence of psychotic symptoms is confirmed by a psychiatrist, then after discussion it may be appropriate for the general practitioner to prescribe an antipsychotic. Current NICE guidelines recommend considering and offering an oral atypical antipsychotic such as amisulpride, risperidone, quetiapine, or olanzapine in low doses. The need for hospital admission and even the use of the Mental Health Act will depend mainly on the patient’s presentation, the risk assessment, and the availability of good community support. General practitioners can contribute greatly to this decision because of their long term relationship with the patient and family.

Is early recognition important?
Most general practitioners with a couple of thousand patients on their list will see one or two new cases of psychosis each year. The mean duration of untreated psychosis—the time between full symptoms emerging and starting continuous antipsychotic treatment—is currently around one to two years in the UK. A systematic review and meta-analysis have shown that the longer this period, the worse the outcome. The idea that reducing the duration of untreated psychosis will be reflected in improved outcome has led to a recent expansion in first episode services in the UK and other countries. Whether or not this proves to be the case, patients with psychotic symptoms should be identified and treated as quickly as possible.

Long term management in primary care
An average general practitioner in the UK will look after about 12 patients with schizophrenia and exclusively manage the care of about six. Once a patient has recovered from an acute episode of schizophrenia, current NICE guidelines recommend that they remain on prophylactic doses of antipsychotic for one to two years and continue to be supervised by specialist services. After that time, if they are well and symptom free, the drug dose can gradually be reduced and the patient carefully monitored to detect any signs of relapse; if such signs occur, then the dose must be increased until they disappear. Such a programme of careful monitoring may best be achieved by collaboration between primary and secondary care.

General practitioners are central to ensuring that patients with schizophrenia receive good quality physical health care (fig 1). Current NICE guidelines encourage all practices to establish a mental health register and offer regular physical health checks tailored to the needs of the patient. Special attention should be paid to screening for endocrine disorders; hyperglycaemia and hyperprolactinaemia; cardiovascular risk factors such as smoking, hypertension, and hyperlipidaemia; and side effects of medication, particularly neurological, cardiovascular, and sexual ones (box 5).

Some patients will inevitably need to be referred back to secondary care. Guideline criteria for this decision include:
- Poor treatment compliance
- Poor treatment response
- Ongoing substance misuse
- Increase in risk profile.

**What treatment can a patient expect in secondary care?**

**Pharmacological**
The first line drug for a patient with a first episode of psychosis is an oral atypical antipsychotic, such as risperidone or olanzapine (fig 2). Drug companies have emphasised the superior side effect profile of these drugs, but in reality the atypicals have different side effects from typical antipsychotics, and they can be just as debilitating. Well conducted randomised controlled trials have shown that, except for clozapine, they are no more effective than the older typical drugs. Thus, patients with established illness who already take...
a typical antipsychotic, who are clinically well, and who
have no troublesome side effects should not change to an
atypical.15 Clinicians should consider changing patients
who take typical antipsychotics and have extra-
pyramidal side effects to an atypical drug. Intermittent
dosing regimens and drug holidays to reduce side effects
are not recommended because of the increased risk of
relapse. Depot preparations are usually offered to pre-
vent covert non-concordance with treatment and to facil-
itate dosing regimens. The lowest effective dose of
antipsychotic should be used, and the concurrent use
of two or more antipsychotics should be limited to spe-
cialist services. Anticholinergic drugs should not be rou-
tinely prescribed to prevent side effects because of their
adverse effects on cognition and memory.

Meta-analysis has shown that clozapine is the best
drug for 20-30% of patients who are resistant to
treatment.22 Treatment resistance is defined as failure
to respond to two or more antipsychotics (one of which
should be an atypical) when given at an adequate dose
for at least six to eight weeks, and once confounding
factors such as concordance failure or substance mis-
use have been excluded. To prevent agranulocytosis,
which occurs in less than 1% of patients taking cloza-
pine, a full blood count must be done regularly. Cloza-
pine is the only antipsychotic that can reduce positive
and negative symptoms in patients with treatment
resistance, and it should be prescribed as soon as treat-
ment resistance is confirmed.

Psychological
Several psychological treatments can help ameliorate
symptoms, improve functioning, and prevent relapse,
although their availability is often limited by a lack of
trained therapists. Systematic reviews show that cog-
nitive behaviour therapy can reduce persistent symptoms
and improve insight18,21; NICE guidelines recommend
that it should be provided for at least 10 sessions over
three months. Family therapy provides support and

<table>
<thead>
<tr>
<th>Common side effects of antipsychotic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First generation antipsychotics</strong></td>
</tr>
<tr>
<td>Extrapyramidal effects:</td>
</tr>
<tr>
<td>- Dystonia</td>
</tr>
<tr>
<td>- Pseudoparkinsonism</td>
</tr>
<tr>
<td>- Akathisia</td>
</tr>
<tr>
<td>- Tardive dyskinesia</td>
</tr>
<tr>
<td>Sedation</td>
</tr>
<tr>
<td>Hyperprolactinaemia</td>
</tr>
<tr>
<td>Reduced seizure threshold</td>
</tr>
<tr>
<td>Postural hypotension</td>
</tr>
<tr>
<td>Anticholinergic effects:</td>
</tr>
<tr>
<td>- Blurred vision</td>
</tr>
<tr>
<td>- Dry mouth</td>
</tr>
<tr>
<td>- Urinary retention</td>
</tr>
<tr>
<td>Neuroleptic malignant syndrome</td>
</tr>
<tr>
<td>Weight gain</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
</tr>
<tr>
<td>Cardiotoxicity (including prolonged QTc)</td>
</tr>
<tr>
<td><strong>Second generation antipsychotics</strong></td>
</tr>
<tr>
<td>Olanzapine:</td>
</tr>
<tr>
<td>- Weight gain</td>
</tr>
<tr>
<td>- Sedation</td>
</tr>
<tr>
<td>- Glucose intolerance and frank diabetes mellitus</td>
</tr>
<tr>
<td>- Hypotension</td>
</tr>
<tr>
<td>Risperidone:</td>
</tr>
<tr>
<td>- Hyperprolactinaemia</td>
</tr>
<tr>
<td>- Hypotension</td>
</tr>
<tr>
<td>- Extrapyramidal side effects at higher doses</td>
</tr>
<tr>
<td>- Sexual dysfunction</td>
</tr>
<tr>
<td>Amisulpiride:</td>
</tr>
<tr>
<td>- Hyperprolactinaemia</td>
</tr>
<tr>
<td>- Insomnia</td>
</tr>
<tr>
<td>- Extrapyramidal effects</td>
</tr>
<tr>
<td>Quetiapine:</td>
</tr>
<tr>
<td>- Hypotension</td>
</tr>
<tr>
<td>- Dyspepsia</td>
</tr>
<tr>
<td>- Drowsiness</td>
</tr>
<tr>
<td><strong>Clozapine</strong></td>
</tr>
<tr>
<td>Sedation</td>
</tr>
<tr>
<td>Hypersalivation</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Reduced seizure threshold</td>
</tr>
<tr>
<td>Hypotension and hypertension</td>
</tr>
<tr>
<td>Tachycardia</td>
</tr>
<tr>
<td>Pyrexia</td>
</tr>
<tr>
<td>Weight gain</td>
</tr>
<tr>
<td>Glucose intolerance and diabetes mellitus</td>
</tr>
<tr>
<td>Nocturnal enuresis</td>
</tr>
<tr>
<td>Rare serious side effects:</td>
</tr>
<tr>
<td>- Neutropenia (93%)</td>
</tr>
<tr>
<td>- Agranulocytosis (0.8%)</td>
</tr>
<tr>
<td>- Thromboembolism</td>
</tr>
<tr>
<td>- Cardiomyopathy</td>
</tr>
<tr>
<td>- Myocarditis</td>
</tr>
<tr>
<td>- Aspiration pneumonia</td>
</tr>
</tbody>
</table>

Ongoing research questions
Might there be better ways to define schizophrenia than by the presence of
hallucinations and delusions?
What are the biological underpinnings of schizophrenia? Can we gain a better
understanding of the site of any pathophysiological lesions and their impact on
cerebral function?
What other factors in the environment increase vulnerability to schizophrenia?
How does early substance misuse increase vulnerability to schizophrenia?
Can we tailor treatment—especially drug treatment—to individual patients, to improve
outcome and reduce the risk of side effects?

Box 5 | Common side effects of antipsychotic drugs
---
| **First generation antipsychotics** |
| Extrapyramidal effects: |
| - Dystonia |
| - Pseudoparkinsonism |
| - Akathisia |
| - Tardive dyskinesia |
| Sedation |
| Hyperprolactinaemia |
| Reduced seizure threshold |
| Postural hypotension |
| Anticholinergic effects: |
| - Blurred vision |
| - Dry mouth |
| - Urinary retention |
| Neuroleptic malignant syndrome |
| Weight gain |
| Sexual dysfunction |
| Cardiotoxicity (including prolonged QTc) |
| **Second generation antipsychotics** |
| Olanzapine: |
| - Weight gain |
| - Sedation |
| - Glucose intolerance and frank diabetes mellitus |
| - Hypotension |
| Risperidone: |
| - Hyperprolactinaemia |
| - Hypotension |
| - Extrapyramidal side effects at higher doses |
| - Sexual dysfunction |
| Amisulpiride: |
| - Hyperprolactinaemia |
| - Insomnia |
| - Extrapyramidal effects |
| Quetiapine: |
| - Hypotension |
| - Dyspepsia |
| - Drowsiness |
| **Clozapine** |
| Sedation |
| Hypersalivation |
| Constipation |
| Reduced seizure threshold |
| Hypotension and hypertension |
| Tachycardia |
| Pyrexia |
| Weight gain |
| Glucose intolerance and diabetes mellitus |
| Nocturnal enuresis |
| Rare serious side effects: |
| - Neutropenia (93%) |
| - Agranulocytosis (0.8%) |
| - Thromboembolism |
| - Cardiomyopathy |
| - Myocarditis |
| - Aspiration pneumonia |

Box 4 | Suggested screening questions for patient presenting with possible psychosis
---
- Do you hear voices when no one is around? What do they say?
- Do you ever think that people are talking or gossiping about you, maybe even
thinking about trying to get you?
- Do you ever think that somehow people can pick up on what you are thinking or can
manipulate what you are thinking?
SUMMARY POINTS

Schizophrenia usually starts in late adolescence or early adulthood
Genetic risk and environmental factors interact to cause the disorder
The most common symptoms are lack of insight, auditory hallucinations, and delusions
Clinicians should suspect the disorder in a young adult presenting with unusual symptoms and altered behaviour
Treatments can alleviate symptoms, reduce distress, and improve functioning
Delayed treatment worsens the prognosis

What is the prognosis?
The common perception that schizophrenia has a poor prognosis is not true. More than 80% of patients with their first episode of psychosis will recover, although less than 20% will never have another episode. While many patients with schizophrenia have a lifelong vulnerability to recurrent episodes of illness, a large proportion will have few relapses and make a good functional recovery. Poor premorbid adjustment, a slow insidious onset, and a long duration of untreated psychosis—tied with prominent negative symptoms—tend to be associated with a worse prognosis. An acute onset, an obvious psychosocial precipitant, and good premorbid adjustment all improve the prognosis.

Thanks to Paul Tabraham and Penny Collins for help preparing this manuscript.

eduction for families. It aims to improve communication between family members, raise awareness in all people involved, and reduce distress. It can help reduce relapse rates, admission rates, symptoms, and the burden on carers, as well as improve compliance with treatment. Systematic reviews have shown that psychoeducation can reduce relapse and readmission rates and is potentially cost efficient. Other treatments with less robustly established evidence include cognitive remediation therapy and social skills training. Psychodynamic psychotherapy may increase the risk of relapse.14-15

What is the prognosis?
The common perception that schizophrenia has a poor prognosis is not true. More than 80% of patients with their first episode of psychosis will recover, although less than 20% will never have another episode.24 While many patients with schizophrenia have a lifelong vulnerability to recurrent episodes of illness, a large proportion will have few relapses and make a good functional recovery. Poor premorbid adjustment, a slow insidious onset, and a long duration of untreated psychosis—tied together with prominent negative symptoms—tend to be associated with a worse prognosis.16 An acute onset, an obvious psychosocial precipitant, and good premorbid adjustment all improve the prognosis.

Additional educational resources

Information for healthcare professionals
Mental Health Care (www.mentalhealthcare.org.uk/)—A collaboration between the Institute of Psychiatry and Rethink providing clinical and up to the minute research evidence on a wide range of mental health matters
EPPIC (www.eppic.org.au/index.asp)—Website produced by the EPPIC service in Melbourne with helpful advice and information sheets about the nature of first episode psychosis

Information for patients and carers
Mental Health Care (www.mentalhealthcare.org.uk/)—A collaboration between the Institute of Psychiatry and Rethink providing clinical and up to the minute research evidence on a wide range of mental health matters
Rethink (www.rethink.org)—One of the major UK mental health charities that focus on psychotic illnesses
Royal College of Psychiatrists (www.rcpsych.ac.uk/mentalhealthinformation.aspx)—A series of articles aimed at professionals, carers, and patients that provides comprehensive information on a variety of mental health problems

Contributors: Both authors contributed to the conception, planning, drafting and critical revision of the article and approved the final version. MJP is guarantor.
Competing interests: MMP has received travel awards from Pfizer, Janssen-Cq, and Eli Lilly. RMM has received honorariums for speaking at meetings organised by most major producers of antipsychotic drugs, and his research group has received funding from Eli Lilly and Astra Zeneca.
Provenance and peer review: Commissioned, externally peer reviewed.

Subgroup analyses: how to avoid being misled

John Fletcher

Three simple examples from recent BMJ papers illustrate how to understand subgroup analyses and why they may be misleading.

Subgroup analyses are regarded with some suspicion because they can be misleading and less reliable than analyses based on all the people included in the research design. This is a wise precaution when the comparison was not planned at the outset. But when subgroup analyses are described in the protocol of the trial or review along with a stated hypothesis, these secondary analyses may be used to show true differences in effect or to illustrate applicability across patient subgroups. Three recently published BMJ papers, including one in this issue, provide examples of each of these types of subgroup analysis.

Cautious interpretation

In a trial that set out to examine the effect on birth weight of reduced caffeine intake during pregnancy, the overall analysis found little effect. The difference in birth weight between the women who had drunk caffeinated coffee and those who had drunk decaffeinated coffee was 16 g (95% confidence interval −40 g to 73 g).

However, a clinically important difference in birth weight of 263 g (97 g to 430 g) between the two groups was seen in women who smoked more than 10 cigarettes a day. This poses a problem for readers who need to judge whether babies born to women who both smoke and drink caffeinated coffee will have lower birth weight.

During a clinical trial it is usual to collect detailed information on patient characteristics as well as the specific outcome measures for the trial. This gives rise to the possibility of researchers performing many separate analyses in the hope that “something will turn up” that has a P value lower than 0.05. This approach to analysis is similar to the sharpshooter who fires at a barn and then paints a target around the bullet hole. A target shows how accurate the shot was only if it was in place before the shooting. In the same way, statistical tests applied to unusual looking results may give the false impression of a “bull’s eye.”

Journal editors need to play their part by checking that reported analyses are those specified in the original research protocol. If the protocol had specified that the researchers expected that the effect of caffeine reduction would vary depending on whether people smoked, then this subgroup analysis would provide strong evidence of an effect. But the smoking subgroup analysis was not planned in the protocol. Therefore, even though it makes clinical sense and the P value is very small, the finding carries less weight and should not be taken as reliable without confirmation in other studies.

Showing differences

In a systematic review of strategies to prevent pneumonia in ventilated patients, the authors expected the quality of the trials to make a difference to the results. In the introduction to the review they stated that they believed that oral decontamination might be shown to be less effective in preventing pneumonia in the higher quality trials than in the lower quality trials. They thought that blinding of treatment allocation would be important, as well as three other measures of trial quality.

The table (partially reproduced from table 3 in the review) shows the comparison of results from the five well blinded and the two poorly blinded trials of antiseptic decontamination versus no prophylaxis showed a relative risk of pneumonia of 0.66; the two poorly blinded trials showed a relative risk of 0.28.

These results represent a reduction in cases of pneumonia of a third versus three quarters. Most
Kaplan-Meier survival curves showing ulcer recurrence stratified for venous reflux pattern

<table>
<thead>
<tr>
<th>Venous Reflux Pattern</th>
<th>Time (years)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated superficial reflux</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Superficial with segmental deep reflux</td>
<td>0.044</td>
<td></td>
</tr>
<tr>
<td>Superficial with total deep reflux</td>
<td>0.331</td>
<td></td>
</tr>
</tbody>
</table>

**Numbers at risk**
- Compression plus surgery: 133, 107, 83, 46, 18, 54, 38, 27, 13, 29, 21, 14, 9
- Compression alone: 140, 90, 63, 27, 3, 56, 32, 25, 11, 30, 17, 10, 7

Clinicians would judge this, if real, to be an important difference.

To judge whether this difference is larger than would be expected by chance, the last column of the table presents a comparison. The two risks are divided to give a ratio of relative risks of 2.36, and the P value for this difference is 0.03. This suggests that there probably is a real difference in the results between well blinded and poorly blinded studies. The more modest reduction in pneumonia seen in the better trials is probably nearer the truth. What strengthens this conclusion is that the researchers specified in their research protocol that they expected to see this difference and have shown it.

**Illustrating applicability**

A randomised controlled trial of compression therapy with and without venous surgery provides an example of a subgroup analysis that shows applicability of the overall findings to several groups of patients. All patients had compression bandaging, but half were randomised to receive varicose vein surgery in addition. The main results from this trial showed a similar rate of initial healing of leg ulcers with and without surgery but a recurrence of ulcers after four years of 31% in patients receiving surgery versus 50% in those not receiving surgery. This difference is clinically important and statistically significant P<0.01.

The surgeons were interested in whether the degree of reflux in the varicose veins had a bearing on the effects of surgery. They decided at the outset of the trial to compare treatment effects in three subgroups of patients: those with superficial reflux alone, those with additional segmental deep reflux, and those with total deep reflux. The figure (figure 4 in the published trial) shows the results. The curves show the ulcer recurrence rate for the three subgroups. To the eye, these curves look quite similar, and it would be difficult to argue that these show an important difference in recurrence of ulcers.

The statistical test that the authors used is reported in the text of the results as a test for interaction with a P value of 0.23. The test for interaction is used to detect a difference in effect between the subgroups. A low P value would suggest that the curves are different and that ulcer recurrence rates were different for each type of venous reflux. Here, though, the P value is large. This is partly because there is very little difference in ulcer recurrence and partly because of the smaller size of each subgroup. Nevertheless, the comparison and the P value do not give any reason to suppose there is an important difference between the subgroups in ulcer recurrence.

The curves in the figure also report P values for each curve, and these refer to the comparison between surgery and compression, and compression alone in each type of venous reflux category. These P values are potentially misleading as they suggest a statistically significant advantage in terms of ulcer recurrence for surgery and compression in isolated superficial reflux, but marginally significant or non-significant results in the two classes of deep reflux. However, just because the result is statistically significant in one group and not in the other two does not mean that there is a real difference between the groups. The important comparison to make is of effects between the subgroups (as shown above) and not the effect within each subgroup as here. The reason for the difference in P values is the difference in sizes of the subgroups: the size of the first is much larger (more than 130 participants per arm) than the other two (about 50 and 30 per arm).

**How to approach subgroup analyses**

When interpreting the results of subgroup analyses, a good working assumption is that the main result probably applies to everyone unless good evidence exists to the contrary. There may be groups for whom the results are different, but this can be shown reliably only if the researchers set out in their protocol their plan to show these differences. Showing applicability across subgroups is less exact as it relies on “non-significant” P values and a clinical judgment of similarity.

**Questions to consider when reading a subgroup analysis**

- Was the subgroup analysis planned before the data were collected? If not, treat the results with caution until confirmed elsewhere
- What was the result (for example, relative risk) in each subgroup? Use your judgment to decide if the results are similar or different
- Is there a statistical test of the difference between subgroups? The words to look for are “effect modification,” “interaction,” or “difference in effect”


**FURTHER READING**

Health for London: are we now on the right route?

PERSONAL VIEW Stephen Thornton

This week sees the publication of Healthcare for London: A Framework for Action, a review of London’s health service by Ara Darzi, chairman of surgery at Imperial College London and now a junior health minister (see News, p 61).

How refreshing it is to read a policy document that focuses on real health problems and makes practical suggestions about how to solve them. Not for Professor Darzi a theoretical exposition of system reform or a set of proposals for organisational change that seem remote from the delivery of health care at the coalface; instead he gives us a vision of future health care in London that simply makes sense. His work, too, heralds the welcome return of service planning—much derided by governments over the past 20 years but necessary even where providers operate in a competitive market environment, giving clear signals of long term intent to attract potential investors.

Many of London’s healthcare problems have been well known for generations. They include gross health inequalities, inadequate primary care, and an outdated pattern of secondary and tertiary hospital provision. What Professor Darzi brings to this afresh is an evidence base that will engage clinicians in the need for change. His work also brings into sharp relief one of the hidden scandals of health care in the United Kingdom: our collective failure to treat stroke effectively.

Stroke remains the third biggest cause of death in England. In people aged under 75, mortality from stroke fell by 44% in men and by 43% in women between 1993 and 2005 in England. But this improvement must be seen in the light of international trends in stroke mortality, which show the UK with higher mortality than similar countries (www.health.org.uk/qquir). Similarly, mortality from cerebrovascular disease in the UK has been falling steadily, yet again the UK has a high mortality in comparison with similar countries.

The Royal College of Physicians’ national clinical guidelines for stroke recommend that thrombolytic treatment be given within three hours of onset of symptoms after an ischaemic stroke. Yet the college’s sentinel stroke audit shows that, in 2006, only 12% of hospitals had arrangements with local ambulance services for emergency transfer to hospital for acute stroke, over and above the regular system, and that only 18% of hospitals offered a thrombolysis service (www.rcplondon.ac.uk/pubs/books/strokeaudit/index.asp). Notably, over 12 months no patients underwent thrombolysis in 10 of the 40 sites offering the treatment, and only 218 patients in total (0.2%) underwent it. This is a tiny proportion of the patients who could potentially benefit.

The Darzi plan has the potential to transform London’s stroke services and place them among the best in the world. Where London leads the rest of England might follow. But will these and the other radical changes he proposes ever be implemented? The history of reports into London’s flawed health services is not a good one. Neither the 1992 Tomlinson report nor the Turnberg one of 1998 were ever fully carried out.

In the past, institutional vested interest—dressed up as protecting local services for local people—has prevented the emergence of a rational pattern of secondary and tertiary hospital services. Perhaps now it has been realised that to compete effectively in the global economy of medical research there really is only scope for two academic health science centres and that collaboration between the players to create such institutions is the only means of survival. Perhaps, with the Department of Health’s current policy to make NHS finances more transparent, and the emergence of foundation trusts that need to be fleet of foot in adapting to commissioners’ new requirements to protect their income, there is no longer anywhere for institutions to hide while mounting their campaigns to resist change.

The reaction of the medical profession will be important. When the new health secretary, Alan Johnson, spoke recently in the Health Service Journal about the need to re-engage clinicians (www.hsj.co.uk 5 Jul, “Johnson and Darzi lead Brown’s campaign to woo back voters”), many in the profession will have interpreted this as a willingness of the government to slow the pace of change. Many health professionals, not least those in general practice, will view Professor Darzi’s recommendations as being far from this, as the implications for primary care are potentially the most radical aspect of his plan. They spell the end of general practice as we know it. Not only would single handed practitioners disappear, but GPs in group practices would have to collaborate in the delivery of the comprehensive multidisciplinary care envisaged for the “polyclinic.”

Just one word of warning. With the Darzi report’s focus being inevitably on the overall pattern of services needed in London, the danger is that the service may spend a great deal of energy putting old wine into new bottles. As care is transferred into new settings it must become safer and more reliable for patients. This process will require detailed redesign, different delineation of roles, and a cultural shift. If we provide clinical leaders with the training, capacity, and authority to lead this process we stand a fair chance of carrying the public with us.

Stephen Thornton is chief executive, The Health Foundation, London. Stephen.thornton@health.org.uk

Competing interests: ST is a non-executive director of Monitor, the independent regulator for NHS foundation trusts.
How to restructure-proof your health service

PERSONAL VIEW Jeffrey Braithwaite

Politicians are often criticised for saying one thing and doing another. Is the announcement last week by prime minister Gordon Brown and new health secretary Alan Johnson a further example? They are sponsoring a major review of the NHS while pledging to stop giving top-down instructions and ceasing centrally dictated restructuring.

What do major reviews produce, other than more instructions and new rounds of restructuring? This is especially contradictory given that Mr Brown and Mr Johnson, in making their announcement, argued that the NHS “cannot stand still,” and the review’s terms of reference stipulated that the way forward for the NHS is to be “clinically driven, patient centred, and responsive to local communities.”

This review will surely try to reorganise from the top the way predecessor reviews did—principally, through above-down measures. In politicians, the strong desire to be seen to be in charge invariably wins over the weak desire to be at arm’s length or encourage bottom-up measures, especially from something that determines votes as much as the NHS does. Something Mr Brown said in announcing the review confirms this suspicion: “No institution touches the lives of the British people like the NHS. It is part of what makes Britain the place it is.” What prime minister would resist wanting to make a personal mark on something so integral to society’s fabric?

We would do well to remember that restructuring health services is a prevalent international activity which the NHS, over almost six decades, has taken to a high art form. It comes in many versions, involving fitting pieces of the health systems jigsaw together in novel configurations. Revamping boxes on the organisational chart is popular. Merging NHS trusts and combining and recombining services that to a greater or lesser extent are perceived to mesh well (into clinical directorates, for example) are some of the most frequent.

The evidence indicates that top-down measures and restructuring can cause disarray. Rather than accelerating organisational progress, merging can put trusts back by 18 months or more, Fulop et al found (BMJ 2002;325:246-9). Clinical staff need a strategy to counterbalance any disruptive effects from this review, so while it is under way, do this: talk to colleagues, and together call the staff to a meeting. You will undoubtedly need a series of meetings. Involve everyone, including the junior and ancillary staff, and make sure the opinion leaders come. Invite your immediate manager, and even the next one up the line, if he or she is enlightened and responsive to bottom-up initiatives. Secure some input from patients—this is not just trendy, it is an intelligent thing to do. Experienced patients know a lot about what they need and what you should do. They can be your best advocates.

Resist the temptation to call your gathering the “Restructure-Proofing Meeting,” at least within the chief executive’s earshot, but that is what it is. The “Strengthening Our Services Meeting” label works well.

Get to work and design a range of enhancements that will build the service and its teams. Try out ways to make your service more streamlined and patient centred. Secure baseline and subsequent data on the changes to patient outcomes, patient satisfaction, and staff morale that result from your initiatives.

These strategies recognise something that clinicians know and politicians don’t: deep in the genetic make-up of effective health services lie people, professionalism, and relationships—not reviews, structures, and imposed targets. It will take a year to get your lines of defence sorted, but this corresponds to the timeline for the completion of the government’s review, reporting at the 60th anniversary of the NHS in summer 2008. If you develop your services in a positive direction you will be likely to take the review’s findings, whatever they are, in your stride. While other services are buffeted you can maintain your game plan, because your staff and colleagues are committed to the partnership ideal and they have bonded, especially if they have shared a journey towards making genuine improvements.

Another benefit is that, although you intended to restructure-proof your service, you will find you have remodelled it in the process. There is a delicious irony here. You have data to show you have achieved the gains, without restructuring under external pressure. The political solution, if it comes in the form of fresh instructions or a new structure, has been neatly finessed. You are likely to find that your services are more “clinically driven, patient centred, and responsive to local communities.” That’s restructuring-proofing with a vengeance.

Jeffrey Braithwaite is professor and director, Centre for Clinical Governance Research, Faculty of Medicine, University of New South Wales, Sydney, Australia j.braithwaite@unsw.edu.au

A longer version with full references is available on bmj.com
LIVE FROM LONDON
Deborah Cohen

My brilliant career as health minister

If newly appointed health secretary Alan Johnson is finding his ministerial portfolio daunting, he might want to try his hand at health policy planning on Fantasy Health Minister (www.policyforum.co.uk/game) before he makes any bold decisions. Devised by the odd coupling of the New Statesman and Pfizer, this game gives you four sessions in office to make a difference to the health of the nation, while trying to balance your budget and improve your political standing. Popularity is rated by doctors, nurses, the media, your party, the opposition, patients, the private sector, and unions.

I decide to take the tack commentators suspect Alan Johnson will take—subtly continue with market reforms while trying to appease a disenfranchised workforce and guarantee patients’ access to services. Rumours are also rife that given he’s sponsored by Unison he is more likely to pay lip service to nurses’ demands. So that’s exactly what I do—I hire more nurses. This not only reduces the waiting time for patients, and reduces the stress and workload of staff, it puts a smile on the faces of the unions, nurses and the voters—patients.

I also decide to fight hospital acquired infections—although at a cost of £3.5bn rather than Johnson’s earmarked £50m. Hospitals are cleaner; recorded MRSA outbreaks decrease dramatically; and the Daily Mail will have to find a different axe to grind. It’s not cheap, though, and those nurses have to be trained somehow, so I would have to find a different axe to grind. It’s not cheap, though, and those nurses have to be trained somehow, so in line with NHS reforms, I employ the private sector to take over the training of some staff. Surprisingly, smiles all round except on the faces of the opposition.

This is only the first step. Pundits are also conjecturing that prime minister Gordon Brown will continue with Blairite reforms. Because I’m road testing NHS policy for Johnson, I decide to see what would happen if I fully privatise the NHS—from the New Statesman’s perspective at least. The privatisation is messy and expensive, and not entirely successful. Though my running costs are greatly reduced, the process is expensive. Nurses and doctors dislike the new system, but are better paid. Some patients get quicker, better treatment while others fall through the cracks. But the private sector is extremely happy. The prime minister calls to tell me: “Due to the privatisation of the NHS, the healthcare budget will be much smaller during your next session in office. We can use the money you’ve saved to reduce taxes and fund other departments. Your fellow cabinet ministers I’m sure will join me in hearty congratulations.”

This leaves the opposition short of ideas, forcing the shadow health minister to rail: “Don’t re-elect the government that privatised your healthcare system. Give us your vote, and we’ll return to a public system.”

If this game is anything to go by, the recipe for a lengthy tenure as health secretary is to charm the media and the unions, cosy up to the medical workforce and gradually involve the private sector. If speculation is correct, Alan Johnson might have it about right.

See also p 71

OUTSIDE THE BOX
Trisha Greenhalgh

Lecturing by remote

I recently suggested that conference organisers should stop using so-called “international experts” (anyone who arrives on a business class flight with a PowerPoint presentation and is incapable of locating their hotel unaided) as the pull to get bums on seats locally.

Soon after that, an important sounding gathering in California wanted me to speak, and was up for the creative use of new technology. The chair sent me a detailed brief, and I prepared my presentation, along with notes, several weeks in advance (this in itself was progress—I usually do it on the plane).

We planned a dress rehearsal, at which I was to sit in my study at home and the chair and technicians were to gather in the lecture theatre where my talk was scheduled. All this was technically unnecessary since everyone knows it’s possible to get a phone connection from London to California. But it highlighted another problem: if the speaker has not been physically transported to the conference, she might forget the occasion altogether. Instead of the anticipated “First slide please . . .”, the audience got my teenagers shouting, “Muuuuuu, some American dude for you . . .” and then (rather sheepishly), “We think she’s probably at the gym.”

I programmed the definitive event into every timepiece I had, and I barricaded myself in behind a wall of “do not disturb” signs. The connection worked. I gave my talk with dual projection—one showing my slides and the other a picture of me standing at a lectern in a flash suit. Apart from the fact that the line was silent when I was speaking (I had to resist the temptation to ask “Are you guys still there?”), it was no different from lecturing to a darkened hall under strong lights.

While I was taking questions, a friend in the audience emailed me from his Blackberry to say, “You’re coming through loud and clear.” I wanted to email back, “Has anyone guessed that I’m in my pyjamas?”

There’s a research study to be done here, for which the null hypothesis is that it is necessary for academics to congregate face to face in a tropical venue in order to exchange meaningful ideas. Does anyone feel like being randomised? Trisha Greenhalgh is professor of primary health care, University College London p.greenhalgh@pcps.ucl.ac.uk

p.greenhalgh@pcps.ucl.ac.uk

100
Walking with kings

Why is so much of the commentariat—the monstrous regiment of newspaper columnists and television presenters—so hostile to our great and wholly beneficent profession?

There are two reasons, I think. The first is that we like those who have higher ethical standards than our own no more than we like those who have lower ethical standards. The second is that many critics of our profession wanted to be doctors but didn’t quite make it.

But not every frustrated doctor turns against the profession. Rudyard Kipling, for example, wanted to be a doctor but always held the profession in the highest regard, despite never having entered it himself. Some of his best friends were doctors, including William Gowers and John Bland-Sutton (no mean writer himself).

The poem If was inspired by “Dr Jim,” Leander Starr Jameson, of the famous (or infamous) Jameson raid against the Boers.

In 1908 Kipling addressed the students of the Middlesex Hospital. His address was published in a little booklet called Doctors, and perhaps it will not surprise you to learn that even in those halcyon days hospital managers were verbose—the introductory remarks of Reginald Lucas, member of the board of management, being at least twice as long as those of Kipling himself. In the course of his rambling introductory address Mr Lucas managed to pour scorn on the idea that “amongst provocative causes of cancer, the habit of smoking tobacco and the profession of sweeping chimneys were most frequent.” This idea he put on a par with a belief in the curative powers of Wiltsire Holt water, “which came from a spring near Bradford-on-Avon.”

Luckily, a house surgeon, running out of the special water, filled a bottle with ordinary tap water and found it had the same effect. Since then “the composition of all medicines must be disclosed to the Cancer Investigation Committee,” a kind of proto-NICE.

Unlike the rambling Mr Lucas, Kipling was concise. He said that people could be divided into two classes: patients and doctors. Doctors were in constant struggle with a senior practitioner called Death, who always won in the end but whose victories could be postponed.

Doctors were highly privileged. “You and kings,” said Kipling, “are about the only people whose explanations the police will accept if you exceed the legal limit in your car.”

There was more: “On presentation of your visiting card you can pass through the most turbulent crowd unmolested; even with applause . . . If you choose to fly a Red Cross flag over a desert you can turn it into a centre of population towards which men will crawl on their hands and knees . . . You can order houses, streets, whole quarters of a city to be pulled down or burnt up, and you can count on the cooperation of the nearest armed troops, to see that your prescriptions are properly carried out.”

Really! I must try it some time (I’d lay waste to two thirds of Britain in a trice). But of course, with powers came responsibilities: “In all times of flood, fire, famine, plague, pestilence, battle, murder, or sudden death, it will be required of you that you remain on duty until your strength fails you . . . Have you heard of any Bill for an eight hours’ day for doctors?” Well, yes, actually I have, although admittedly a century later. “But that,” as Mrs Hawksbee of Plain Tales from the Hills would say, “is another story.”

Theodore Dalrymple is a writer and retired doctor.
A prime time series uses computer generated images to illustrate what happens to patients at times of medical crisis—but is it worth the effort, asks Craig Gerrand

“Right from the start, we all have one overwhelming instinct.” So say the makers of Fight for Life, a documentary series examining how the instinct for survival makes the body resilient against “incredible” odds. Each episode looks at a different stage in life—birth, childhood, teenage years, prime, middle age, and old age—and the challenges to survival during each. The series tells the stories of people during medical crises, punctuating them with computer generated images, which mean that we see the story from the inside: City Hospital meets The Matrix. Episode one sees Gabriel facing “incredible” danger before birth—meconium is seeping into his lungs—and there it is, black and tarry, squelching blob-like down the bronchi. The dramatic tension is raised. Gabriel’s chances of survival are 30%. There is an emergency ambulance transfer. A priest is called; the newborn infant baptised. Without giving too much away, there is ECMO (extracorporeal membrane oxygenation), the risk of intracerebral bleeding, excursions up the nose and into the lungs—and there are tears. The star of this tale is Gabriel’s 19 year old mother, Fay, who supports all those around her. Here is a role model for teenage parents.

Among the other stories is that of Arnav, whose medical parents find themselves on the receiving end of care. Arnav is breech and for good measure is being strangled by his umbilical cord. It seems to take an age (try holding your breath) to deliver him by caesarean section. We meet Elijah, in Baltimore, with a sacrococcygeal teratoma, and Lily. Thankfully Lily is delivered fit and well, but even here the narrator doesn’t let us off the hook, emphasising that if she gets stuck en route, both baby and mother could die.

The second programme brings us children with asthma, a head injury, and, in the most compelling tale, 9 year old James, who undergoes a heart transplant. The computer generated images partly enlighten the viewer but are primarily designed to entertain. They are of high quality, and the distinction between real footage and the images is often blurred. Some are more successful than others; the animation of a neonatal head passing through the pelvis is excellent. But to a medical eye, the dividing cells of a tumour and the phagocytes devouring meconium are more comic book than pathology book. The footage of heart transplantation surgery is so graphic that computer images add little. Fight for Life is hospital based and it is heartening to see health professionals portrayed as caring, highly skilled individuals. Doctors talk to their patients and are empathetic and compassionate. This footage is real, not computer generated. Some medical staff are heroes. The high drama of the heart transplant requires surgeons to take the high stakes decision to remove the heart before the donated organ arrives in the hospital. Although not exclusively shot in the NHS, the programme is a great advertisement for it. Champions of change take note: we should take care to preserve an environment that allows clinical excellence of this kind to flourish. Viewers who become patients will expect it of us.

The dramatic tone of the narrative is intended to parallel the visual excitement. The dangers lurking at every step are emphasised; every case is potentially a worst case scenario. Given the subject matter, this approach is often unnecessary and occasionally irritating. The players speak for themselves.

So why do people at times of crisis agree to take part in these programmes? Could they be harmed? An uncertainty principle applies: observation by camera crew inevitably changes that which is being observed. The camera is at best a distraction. The crying patient or parent is the documentary maker’s money shot. Programmes like these are at worst voyeuristic and harmful, but at best can be uplifting, educational, and a force for good. For example, seeing a child in the throes of an asthma attack is better than reading about it in any book. Although Fight for Life strikes a reasonable balance, its potential as a force for good is not completely realised. More could have been made of the need for organ donors. No mention is made of how appropriate action might save the life of a head injured child before the ambulance arrives.

On balance, these are enjoyable programmes, although not for medics who are looking for escapism after a day on the front line. For doctors the appeal will be in seeing how others perceive us, and whether you see anyone you know. Further programmes include stabbings, cancer, trauma, and an aneurysm. I for one will be watching.

Craig Gerrand is consultant orthopaedic surgeon, Newcastle upon Tyne Hospitals NHS Trust. Craig.Gerrand@nuth.nhs.uk

Seeing a child in the throes of an asthma attack is better than reading about it in any book
Arthur Thomas Marshall and Mary Louise Marshall (née Neville)

Arthur Thomas Marshall, former consultant obstetrician Worcester (b 1913; q Birmingham 1938; FRCS, FRCOG), d 8 May 2007. Mary Louise Marshall (née Neville), former consultant obstetrician Selly Oak Hospital, Birmingham (b 1916; q Cork 1940; FRCOG), d 11 May 2007. Arthur Marshall narrowly avoided joining the Kenyan police force by winning a scholarship to medical school. He volunteered for the Royal Navy in 1939 and served on destroyers in Portsmouth and Scapa Flow before spending time in north Africa, Burma, and India. He was demobbed in 1945 as surgeon lieutenant-commander. After the war he specialised in obstetrics and gynaecology and was a consultant from 1955 to 1978. He was an enthusiastic golfer and trout fisherman and a freemason for 50 years.

After qualifying Mary Neville completed her training in obstetrics and gynaecology in Selly Oak Hospital. She was appointed consultant in 1949—one of only two female consultants in the specialty at the time. She met Arthur when he returned to the hospital after the war, and they were married in 1950. After her retirement in 1980 Mary joined the staff of St Mary’s Hospice, Birmingham, and later became chairman of the women’s refuge in Droitwich. She undertook a bereavement counselling course aged 78 and became chairman of Worcestershire Cruse.

Mary died from pneumonia three days after Arthur, whom she had cared for in his last years. They leave three children and nine grandchildren.

Tom Marshall

James Wilson Harkess

Former Korsair professor of orthopaedics Louisville Medical School, Kentucky (b 1925; q Edinburgh 1948), died after being hit by a car on 31 October 2006. James Wilson Harkess sought experience in orthopaedics outside the United Kingdom at the Albany Hospital, Albany, New York, and was asked to stay on the surgical programme. In 1958 he joined the staff at the Medical College of Georgia in Augusta, where he rapidly became a full professor and assistant chief of orthopaedics. In 1967 he accepted the newly created chair of Korsair professor of orthopaedics in Louisville, guiding and leading the department to national recognition until 1981, when he retired to private practice. He continued as clinical professor until 2002. He was honoured by the state of Kentucky and served in several consultant capacities. He leaves a wife, Janice, and three children.

Philip Kennedy

Tessa Louise Whitton

Consultant in anaesthesia and pain management Frenchay Hospital, Bristol (b 1966; q Southampton 1989; FRCA), died from gastric cancer on 24 February 2007. Tessa trained in anaesthetics throughout the southwest region and followed this by a year as an assistant professor in Seattle. Her passion for pain management was a reflection of her warm and sympathetic nature, which always encouraged patients to have confidence in her. Tessa was an avid traveller and accomplished linguist. In Mexico she carried out voluntary medical work with Zapataista villagers and also learnt to speak and sing in fluent Spanish. With characteristic spirit, Tessa researched her illness thoroughly and pursued all avenues of treatment. She spent her last days at home, looked after by family and friends.

Stephen Hill

Joseph Patrick Booth

Former general practitioner South Norwood (b 1926; q King’s College Hospital, London, 1955; DOBstRCOG), died from the complications of atherosclerosis on 6 November 2006. After an education much disrupted by the second world war, Joe Booth left school early to volunteer for the army. On demobilisation he went to Regent Street Polytechnic as an ex-service student from where he obtained a place at King’s. A growing family encouraged him to switch from his early interest in surgery to general practice. When his wife, Cynthia, died of breast cancer in 1971, he moved into a group practice. He was a much loved general practitioner, his patients continuing to write to him even 20 years after he had retired. He was also an accomplished potter, childminder, and raconteur. He leaves five children and five grandchildren.

Sara Booth, Brian Bartley

Peter Kenneth Robinson

Former consultant neurologist Wessex Regional Hospital Board, Hampshire (b 1920; q Cambridge/St Bartholomew’s Hospital 1945; MA, MD, FRCP), died from chronic heart failure on 25 May 2007. Peter trained at the National Hospital and later at Johns Hopkins Hospital, where he held a Nuffield Foundation fellowship. On appointment in 1956 he was one of two neurologists in the then Wessex region who, with others, formed the regional neuroscience centre in Southampton in 1965. His prodigious workload meant that he was known throughout the region. In spite of this he found time to sit on various committees, not least the Association of British Neurologists, which elected him president in 1983. Outside medicine Peter was an accomplished painter and ornithologist. He had longstanding links with his local church, and in retirement was a guide at Winchester Cathedral. Predeceased by his wife, Barbara, he leaves three daughters and nine grandchildren.

Philip Kennedy

For the full versions of articles in this section see bmj.com
MINERVA

Giving very sick patients nicotine replacement therapy may not be entirely safe, although it is sometimes given to smokers in the intensive care unit (ICU) to prevent withdrawal. A retrospective case-control analysis of this treatment in ICU patients found that it is associated with increased in-hospital mortality—20% in smokers who took the treatment versus 7% in those who did not. Treatment remained independently associated with increased mortality when severity of illness and invasive mechanical ventilation were adjusted for (Critical Care Medicine 2007;35:1517-21).

Delays in surgery for hip fracture have a significant effect on short and longer term outcome. An Israeli multicentre survey conducted over four years found that people who had surgery within two days of fracture had lower mortality while in hospital, and at one month and one year, than did those who waited for more than four days for surgery. Large variations were seen between hospitals, and the authors call for a prompt review of quality improvement (International Journal for Quality in Health Care 2007;19:170-6).

Elderly European patients with cancer fare worse than younger ones. Of the 16 different cancers investigated, people over 65 years did worse than those aged 55-64. Most of the variation was in the first five years, and it was especially wide within the first year, but after that many cancers had similar survival rates in both age groups. The excess relative variation was in the first five years, and it did worse than those aged 55-64. Most of the cancers investigated, people over 65 years of age had lower mortality while in hospital, and at one month and one year, than did those who waited for more than four days for surgery. Large variations were seen between hospitals, and the authors call for a prompt review of quality improvement (International Journal for Quality in Health Care 2007;19:170-6).

An 11 month old infant presented with a four week history of reluctance to sit or stand. He had no fever, tenderness, or abnormalities on examination, including that of the lower limbs, hips, and spine. Investigations revealed normal full blood count, inflammatory markers, and blood culture. Radiological investigations included a normal radiograph and ultrasound scan of the hips. A magnetic resonance imaging scan of the lower limbs and pelvis performed under general anaesthetic was normal, and that of the spine confirmed a diagnosis of lumbar discitis. Identifying the aetiological agent in discitis is difficult as blood cultures are usually negative, but *Staphylococcus aureus* is reportedly the most common causative organism. Serological investigations in this child were negative.

English children are more physically active during the week than they are at weekends, according to data taken from sealed pedometers during three school terms. Boys took more steps each day than girls. Nearly half the girls met or exceeded the body mass index cut off points for health, while 29% of boys did the same. It seems that it is home life that needs to change (Preventive Medicine 2007;44:416-20).

Female office workers experience high amounts of neck pain (Pain 2007;129:311-20). Interestingly, 61% of the 333 women who completed the questionnaire reported mild neck symptoms lasting longer than eight days in the past 12 months, and the single psychosocial risk factor identified on multivariate logistic regression analysis was low support from supervisors. Lower support from supervisors was also the factor most strongly associated with severity of pain.

Minerva is always disappointed when an editor returns her work because she hasn’t conveyed her intended message sufficiently well. But even public health leaflets designed for lay people can miss the point and leave their readers mystified. The English breast screening programme’s information leaflet was tested on a random sample of 100 women. Although the leaflet improved their knowledge, some simple messages were still not understood by everyone (Journal of Public Health 2007;29:173-7).

Setting up organ donor registers is a hugely expensive task and the benefits are often slim because the chance that the organs of registered people will be suitable for donation is very low. If donor families have the right of refusal, the value of a register falls greatly. The alternative is to “piggy back” on existing registers such as those for drivers’ licences (Medical Decision Making 2007;27:243-9).

Can dermatologists distinguish between atopic dermatitis and plaque psoriasis by feel alone? A study of 16 patients and a “blinded” dermatologist found that the correct diagnosis was made in 14 of 16 cases. The study’s aim was to confirm a concept about dissociated sensory modalities, and it doesn’t prove that palpation adds value to a visual diagnosis. That said, in real life the visual component of an examination is probably more instantly diagnostic than the palpable component (Journal of the American Academy of Dermatology 2007;56:949-51).

Medical students perform many functions, and this time it’s their feet that have been put to good use. A team in India investigated the association between foot length and stature in 250 medical students. They found that length of the right foot, sex, and age predicted 77% of the variations in stature (Journal of Forensic and Legal Medicine 2007;14:279-83).