Editor's choice

Editor's choice: About children . . . and more
Rajendra Kale
BMJ 2007;334, doi:10.1136/bmj.39237.605150.47

US editor's choice: Morals and ethics and medicine
Douglas Kamerow
BMJ 2007;334, doi:10.1136/bmj.39239.430613.3A

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BMJ 2007;334:1173, doi:10.1136/bmj.39225.414537.80

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BMJ 2007;334:1174, doi:10.1136/bmj.39218.422650.80

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Control of methamphetamine misuse
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Clinical trial registration
Christine Laine, Richard Horton, Catherine D DeAngelis, Jeffrey M Drazen, Frank A Frizelle, Fiona Godlee, Charlotte Haug, Paul C Hébert, Sheldon Kotzin, Ana Marusic, Peush Sahni, Torben V Schroeder, Harold C Sox, Martin B Van Der Weyden, Freek W A Verheugt
(published 4 June 2007)

Letters

This week's letters

Presumed consent: First address informed consent in organ donation
Michael Potts
BMJ 2007;334:1179, doi:10.1136/bmj.39234.422361.3A
Presumed consent: Is prognosis key in donation?  
Richard Bartley  
BMJ 2007;334:1179, doi:10.1136/bmj.39234.443646.3A

Presumed consent: Tell public about brain death  
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Presumed consent: Add carrying a card to QOF  
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Cosmetic genitoplasty: Surgical solution is becoming acceptable, as for birth  
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MTAS: Lessons from the disaster  
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Reed Elsevier to stop hosting arms exhibitions  
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Indian doctor arrested under antiterrorism law
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BMJ 2007;334:1184-1185, doi:10.1136/bmj.39237.523206.4E

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Researcher accused of breaching research ethics faces GMC
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Doctors advise women not to drink any alcohol during pregnancy
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Website gives survival rates for congenital heart disease centres
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UK development secretary sets out strategy to tackle global health crisis
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More women over 40 seek fertility treatment
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Shortcuts from other journals: World Trade Center dust blamed for respiratory illnesses

BMJ 2007;334:1188, doi:10.1136/bmj.334.7605.1188-a
Shortcuts from other journals: Surgery for sciatica should be optional
BMJ 2007;334:1188, doi:10.1136/bmj.334.7605.1188-b

Shortcuts from other journals: Switching flu vaccination to schoolchildren could be disastrous for older people
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Shortcuts from BMJPG journals: BMJ press release led to increase in mumps notification
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Shortcuts from BMJPG journals: Long term results of epilepsy surgery are encouraging
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Shortcuts from BMJPG journals: No need to double antibiotic dose in children with non-severe pneumonia
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Shortcuts from BMJPG journals: The fisherman's tale
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Head to head: Should genetic information be disclosed to insurers? No
Richard Ashcroft
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Formula estimation of glomerular filtration rate: have we gone wrong?
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At what age can schoolchildren provide effective chest compressions? An observational study from the Heartstart UK schools training programme
Ian Jones, Richard Whitfield, Michael Colquhoun, Douglas Chamberlain, Norman Vetter, Robert Newcombe

Interventions to promote walking: systematic review
David Ogilvie, Charles E Foster, Helen Rothnie, Nick Cavill, Val Hamilton, Claire F Fitzsimons, Nanette Mutrie, on behalf of the Scottish Physical Activity Research Collaboration (SPARColl)

Side effects of phenobarbital and carbamazepine in childhood epilepsy: randomised controlled trial
Selina H Banu, Moshrat Jahan, Umme Kulsum Koli, Saadia Ferdousi, Naila Z Khan, Brian Neville

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Clinical review: Herpes zoster
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10-minute consultation: Tiredness
George Moncrieff, John Fletcher
BMJ 2007;334:1221, doi:10.1136/bmj.39182.615405.94
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**From the frontline:** Wanted: stress monkeys  
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**Drug tales and other stories:** All together now  
Ike Iheanacho  
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**Between the lines:** Murder he wrote  
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## Obituaries

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Boleslav Lichterman  
BMJ 2007;334:1226, doi:10.1136/bmj.39224.617106.BE

**Nicholas Bennett-Jones**  
Edgar Parry  
BMJ 2007;334:1227, doi:10.1136/bmj.39232.634861.BE

**David Bartlett Bower**  
Beresford Crook, Maureen Sands, J Richard Smith  
BMJ 2007;334:1227, doi:10.1136/bmj.39232.666377.BE

**Charles Edward Daniel Hearn**  
Philip Allen  
BMJ 2007;334:1228, doi:10.1136/bmj.39232.814977.BE

**Kenneth Anthony ("Tony") Kalanyi Kebba**  
Frances Gotch  
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**David Mendel**  
David Thompson  
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**Kieran O'Driscoll**  
Dermot Mac Donald, Declan Meagher  
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Minerva

Minerva

BMJ  2007;334:1228, doi:10.1136/bmj.39233.459699.BD1

Minerva
Richard Singleton, Sheelagh Little
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Question time
R A Joske
BMJ  2007;334:1203, doi:10.1136/bmj.39218.437836.DE

Call for papers for BMJ theme issue on diabetes

BMJ  2007;334:1217, doi:10.1136/bmj.39225.633438.DE

BMJ updates: Mild renal impairment increases cardiovascular risk

BMJ  2007;334:1220, doi:10.1136/bmj.39161.576447.BE

Career focus

Read this week's articles on
Evidence that physical activity improves health is convincing, but we lack knowledge about how to increase physical activity in individuals and populations. Taking part in sport may improve health, but sport is only taken up by a small proportion of the adult population, and mainly by the better educated.

In this week's BMJ, a systematic review by Ogilvie and colleagues assesses the effect of interventions to improve walking on how much people walk, physical activity, fitness, disease risk factors, and wellbeing.

It found that interventions tailored to people's needs, which targeted the most sedentary or those motivated to change, can increase walking by up to 30-60 minutes each week. Few studies included in the review assessed clinical benefits from the increased walking, and this remains to be shown in randomised controlled trials.

So what is the evidence so far on the effects of interventions on other types of physical activity? A recent Cochrane review of randomised controlled trials found that trials promoting physical activity in general significantly increased self-reported physical activity (standardised mean increase of 0.31, 95% confidence interval 0.12 to 0.50), and fitness (0.40, 0.0.9 to 0.70).

The review by Ogilvie and colleagues also included non-randomised studies, which, although considered weaker forms of evidence, are necessary to assess the effect of population level interventions such as bike lanes, walking paths, and recreational areas.

One non-randomised community intervention in Odense, Denmark, promoted bicycling through many initiatives and increased the number of bicycle trips by more than 20% over five years. At the same time, the number of accidents involving cyclists was 20% lower than in the rest of the country.

Another study found that children who cycled to school were 8% more fit than children who used other modes of transport including walking. It concluded that a 10-15 minute session of cycling twice a day would be enough to increase aerobic fitness in children.

Observational studies have consistently shown that children who walk or cycle to school engage in more physical activity (other than the travel activity) than those who travel by other means. This extra activity may reflect selection (children who are generally more active choose active transport) or it may be that children who are encouraged to take up active transport go on to engage in other activities. However, because of the lack of cycle lanes in many countries it may be difficult to promote increased cycling for safety reasons.

A weakness in many of the trials of walking interventions is the lack of assessment of health gains; however, epidemiological studies suggest that health benefits of active transport are substantial. The nurses' health study found that women who increased both walking distance and speed had a lower risk of cardiovascular disease, type 2 diabetes, and all cause mortality. The risk in the upper quintile of walking was around half that seen in the sedentary group. Similarly, another study found a 30% lower mortality rate in participants who cycled to work than in non-cyclists after adjusting for general physical activity level, socioeconomic background, and smoking.

Ogilvie and colleagues' study shows that interventions can increase the amount of walking. It has not yet been proved that the lower rates of disease and mortality seen in people who walk is caused by walking itself, but even this low intensity type of exercise probably improves metabolic control and other health parameters. The challenge now is to make politicians work for an environment that promotes walking, and to call on doctors to encourage patients to walk, especially those with disorders such as hypertension, metabolic syndrome, or raised fasting insulin.

Teaching children basic life support skills
Improve outcomes but implementation needs to be earlier and more widespread

Basic life support performed by bystanders improves outcomes in cardiorespiratory collapse, yet less than 1% of the general population can perform it effectively. It has been estimated that if 15-20% of the population could perform basic life support, out of hospital mortality could be significantly reduced.1 The most effective way of achieving this is to teach this technique in schools, making it a “life skill.”

In this week’s BMJ, a study by Jones and colleagues assesses the effect of a basic life support programme on the ability of children to administer effective chest compressions on a manikin.2 Of the three age groups compared (9-10, 11-12, 13-14 years), only children aged over 13 years could perform chest compressions to the recommended depth of 38-51 mm as effectively as adults. However, younger children could place their hands in the correct position on the chest to perform basic life support. The authors suggest that younger children could use this knowledge to instruct an adult on the appropriate technique, despite not being able to do it themselves. Also, young children could be taught how to assess the need for basic life support and activate the emergency medical services. These conclusions support the teaching of basic life support to children.

Structured courses such as the “Injury minimisation programme for schools” (www.impsweb.co.uk), which started in 1994, have integrated the teaching of basic life support into the school curriculum (with the support of local hospitals) and have trained more than 114,000 children in the United Kingdom.

Courses are also taught by the British Red Cross, St John’s Ambulance Service, St Andrew’s Ambulance Service, Heartstart, and Opportunities for Resuscitation and Citizen Safety (ORCS). In Northern Ireland, the “ABC for life” programme was set up in 2005 by the Queen’s University Belfast, with the aim of teaching 25,000 primary schoolchildren each year. Most of these courses focus on teaching children aged 10 years and older. At this age children are more likely to be developing “abstract thinking” and may be physically capable of performing chest compression.

Basic life support courses can change children’s attitudes and behaviour. A large study comparing children who received such training with those who did not showed that after five months the trained children were more willing to undertake emergency life saving procedures and conducted resuscitation significantly better.4

Despite these promising results some caveats exist. In both adults and children the skills decline over time, so refresher courses are needed. A study that repeated the training after six months in school aged children found that knowledge was maintained and that the children’s resuscitation skills improved.1

“Hands-on” practice is needed to maintain the motor skills required to perform basic life support. Although additional teaching aids such as online resuscitation training may help with the child’s knowledge, they do not improve the child’s skills.5

Effective skills can only be attained through high quality training.6 Poor performance arises from inadequate instruction and not allowing sufficient time for the child to learn the technique. This includes time for the method to be demonstrated and for the child to practise the technique under adequate supervision.

High quality teaching can only improve outcomes if uptake is adequate. In countries where teaching basic life support in schools is optional, the uptake of training is low. Barriers include funding and time constraints in the “overfull” school curriculum.7 8 Compulsory training is probably necessary to obtain the levels of skill required to improve outcomes.

The final barrier to implementing basic life support training is lack of resources. Head teachers in Barcelona, sampled in a questionnaire survey, thought that school was the most appropriate setting for teaching these skills, and that such training would increase children’s self esteem and could potentially save lives. However, they identified funding as a potential problem, estimating that the cost would be between £5 (€6.80; $8.20) and €10 per child—although this seems a small price to pay for improving survival.9

Out of hospital survival from cardiorespiratory collapse could be improved if basic life support was routinely taught to all schoolchildren. Introducing it as early as possible in the school curriculum, perhaps in story and online learning formats, would be non-threatening to young children, who are usually keen to learn and able to absorb new information. Once they are physically able, the transition from theoretical knowledge to practical skills should be relatively easy.

Treatement of epilepsy in developing countries
Cheap and effective drugs exist but are not accessible to most patients

Of the 35 million people with epilepsy who live in developing countries, around 85% receive no treatment at all.1 2 As a consequence, they experience morbidity related to seizures and the psychosocial consequences of stigma and discrimination. Regrettably, most of these people—many of whom are children—could have their seizures completely controlled and they could return to a normal life by taking a single daily dose of a drug that costs less than $3 (£1.50; €2.20) each year.3 In this week’s BMJ, a randomised controlled trial conducted in Bangladesh by Banu and colleagues compares the effects of carbamazepine and phenobarbital on seizure control and behavioural side effects in 108 children with epilepsy.4

The World Health Organization recommends phenobarbital as the treatment of choice for partial and tonic clonic seizures in resource restricted countries,5 but this policy has been questioned because phenobarbital is thought to be less well tolerated than other antiepileptic drugs.6 Concerns apply particularly to children, who are especially vulnerable to this drug’s adverse cognitive and behavioural effects.7 Differences in tolerability between phenobarbital and other anticonvulsants are probably less prominent than generally thought, however, and they were detected mostly in trials where the assessment of outcomes may have been affected by doctor or patient bias.2 8 Importantly, most studies in developing countries did not show excess neuropsychological toxicity of phenobarbital compared with other anticonvulsants,9 11 possibly because dosages in these studies tended to be lower than those used in developed countries, or because lack of options make people less willing to report side effects.

The study by Banu and colleagues found no significant difference in behavioural problems such as restlessness and hyperactivity between phenobarbital and carbamazepine (7% v 11%), and no significant difference in psychological and behavioural assessments after one year.11 Of those children who completed a 12 month follow-up, 47.5% of those on phenobarbital and 60% of those on carbamazepine were seizure-free for the last six months.

Conducting clinical trials in resource restricted countries is difficult. As with previous similar studies, the trial by Banu and colleagues has limitations, including an open label design and low power to detect potentially important differences in seizure outcome and behavioural test scores. More children were lost to follow-up in the phenobarbital group (22%) than in the carbamazepine group (9%). Therefore, on an intention to treat basis, the proportion of children who were seizure free in the last six months was considerably higher in the carbamazepine group than in the phenobarbital group (50% v 33%), which raises questions about potentially lower compliance in children assigned to phenobarbital. Drug concentrations were not reported. The two groups were not well balanced for some characteristics; girls were under-represented in the phenobarbital group, a potentially important factor because behavioural problems were more frequent in girls than in boys.

Despite these limitations, the study shows that most children tolerated phenobarbital well and behaviour even improved in many. This supports other findings in similar settings. In a randomised study of 302 children and adults with epilepsy in rural Kenya, side effects were reported more frequently with phenobarbital than with carbamazepine, but the number of patients with side effects did not differ significantly between drugs; 3% of patients on phenobarbital were withdrawn for adverse effects and 5% on carbamazepine.9 When 73 children with newly diagnosed epilepsy were randomised to phenobarbital, carbamazepine, or valproate in Taiwan, no significant differences in psychometric scores were found between groups.10 Similarly, no treatment related differences in behaviour rating scores were found in 94 children with epilepsy randomised to phenobarbital or phenytoin in rural India.11 Observational studies support the conclusion that phenobarbital is relatively well tolerated in developing countries.2 Apart from its low cost, phenobarbital has other merits such as efficacy against all seizures other than absences, seizure freedom rates comparable to those associated with modern drugs, a starting dose within the effective range, a low risk of life threatening adverse effects, linear pharmacokinetics, once daily dosing, and availability of a parenteral formulation.8

Most controlled trials of phenobarbital in epilepsy have methodological shortcomings, including an open label design, small sample size, and, at times, questionable choice of dosing regimens.7 Although larger double blind randomised studies are needed for a better assessment of the role of phenobarbital in the treatment of epilepsy,8 Banu and colleagues deserve praise for providing more evidence supporting its use in resource restricted settings.

The burden of untreated epilepsy in terms of human suffering and social costs is enormous. Governments and non-governmental organisations in developing countries need to ensure that effective treatment is available for all. Even in these settings, drug choice should be tailored to the individual, and phenobarbital will not be the best option for all. In fact, the price of drugs is a small part of the cost of ensuring a minimum standard of epilepsy care. Dispensing facilities are often unavailable in remote rural areas, and even when available they often fail to provide a continuous supply of drugs,12 which has potentially serious consequences. Seven children in Banu’s study discontinued treatment for more than seven days for various

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Emilio Perucca
Professor
Clinical Pharmacology Unit,
Institute of Neurology,
University of Pavia, I-27100 Pavia,
Italy
perucca@unipv.it

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EDITORIALS
Control of methamphetamine misuse
Policy should target substance misuse as a whole, rather than single substances

Methamphetamine is a highly addictive substance that has caused serious public health problems globally. As it is relatively easy to manufacture from precursor substances, regulation of precursors has taken centre stage in global strategies for drug control. Recently, the UK Medicines and Healthcare Products Regulatory Agency announced that the precursors pseudoephedrine and ephedrine, also used in flu remedies sold over the counter, may in future be available on prescription only.

Methamphetamine was first synthesised in Japan in 1919 and has been manufactured legally in the United States since the 1950s. Use declined during the 1970s when the public became aware of the harms of amphetamines and practitioners were inhibited from prescribing them by the Controlled Substance Act (1970). However, when methamphetamine re-emerged in the 1980s, it had been transformed into “ice,” a smoked form of high purity that produces sustained into intoxication. As it exists today, illicit methamphetamine is manufactured in many forms and may be used in many ways (inhaled, ingested, smoked, or injected).

Many definitions of which substances are included in the class of synthetic stimulants or amphetamine-type substances exist, but generally the class includes amphetamine, methamphetamine, and 3,4 methylenedioxyamphetamine (MDMA or ecstasy). They cause increased energy, decreased appetite, and a heightened sense of wellbeing. The onset and duration of action vary by specific compound, dose, purity, and route of administration. Complications of use vary greatly and include cardiovascular, neurological, and psychiatric effects. Other possible complications include risk taking behaviour during intoxication and heavy metal exposure as a result of mercuric chloride and lead acetate used in the illicit production of methamphetamine.5 5

According to the World Drug Report issued in 2006 by the United Nations Office of Drugs and Crime, around 200 million people used illicit drugs. Amphetamine-type substances ranked second, after cannabis, with an estimated 35 million users. Of these, 25 million used amphetamines (including methamphetamine) while the remaining 10 million used ecstasy. When all indicators of amphetamine production and use were combined, the overall global trend was towards a stable to mildly increasing amphetamine market after years of annual increases. However, the results of specific market indicators were mixed, and trends for specific geographical regions varied.

The report also found that seizures of substances diverted for manufacturing amphetamine-type substances reached record levels and exceeded seizures of the end product in 2005. The main methamphetamine precursors seized were pseudoephedrine and ephedrine. The main amphetamine precursors seized were phenyl-2-propanone and phenylacetic acid. Although the rate of dismantling laboratories that produce amphetamines has increased, dismantling of large volume international laboratories (so called superlabs) has not.

The relation between the regulation of precursor substances and outcomes in drug users, such as hospital admissions and arrests, has been reported by two studies in the US. They concluded that regulations limiting access to bulk powder and single ingredient ephedrine and pseudoephedrine products reduced hospital admissions and arrests. However, regulations targeting mixed agent cold remedies used by small scale manufacturers did not result in similar decreases.

So what is the most effective strategy to reduce harm from amphetamine-type substances? Although the manufacture and misuse of synthetic stimulants contribute greatly to morbidity and mortality in substance users worldwide, the global disease burden of this class of substances is much lower than that of tobacco, alcohol, and marijuana.6 9 10 Also, most people who use amphetamine-type substances take multiple substances.11

Even if the pattern of drug use is stable over time, drug markets are dynamic. Efforts to prevent the manufacture and use of amphetamine-type substances should therefore be integrated into a rational scheme to reduce overall substance use that is designed to tackle existing and emerging drug threats. Over-investing resources in the control of one drug, or one precursor, carries with it the risk of failing to appreciate emerging threats. For instance, many people fear the “meth crisis,” but fewer seem aware of the recent warnings issued by the UN Office of Drugs and Crime about the resurgence of cocaine in Western Europe.12

Responses to this crisis should include limiting supply and distribution,13 educating the public about harms, screening for early use, and aggressively treating addiction in an integrated approach that tackles addiction in its many forms.

Christine Laine and Richard Horton on behalf of the ICMJE working group
laine@mail.acponline.org

See bmj.com for full details of the ICMJE working group

Competing interests: Employment: FG was previously editorial director of Current Controlled Trials, which owned the ISRCTN (International Standard Randomised Controlled Trial Number) trials register. SK is employed by the National Library of Medicine, which produces ClinicalTrials.gov, but he is not responsible for activities or policies regarding ClinicalTrials.gov. Expert testimony: FG. Other RH is co-chair and JMD and HCS are members of the WHO ICTRP scientific advisory group. MBVDW is a member of the government advisory committee for the Australian and New Zealand Clinical Trials Registry. PS’s affiliation as a representative and past president of the World Association of Medical Editors (WAME) does not imply endorsement by WAME member journals that are not part of the ICMJE

Clinical trial registration

Looking back and moving ahead

In 2005, the International Committee of Medical Journal Editors (ICMJE) initiated a policy requiring investigators to deposit information about trial design into an accepted clinical trials registry before the onset of patient enrolment.1 This policy aimed to ensure that information about the existence and design of clinically directive trials was publicly available, an ideal that leaders in evidence based medicine have advocated for decades.2 The policy precipitated much angst among research investigators and sponsors, who feared that registration would be burdensome and would stifle competition. Yet, the response to this policy has been overwhelming. The ICMJE promised to re-evaluate the policy two years after implementation. Here, we summarise that re-evaluation, specifically commenting on registries that meet the policy requirements, the types of studies that require registration, and the registration of trial results. As is always the case, the ICMJE establishes policy only for the 12 member journals (a detailed description of the ICMJE and its purpose is available at www.icmje.org), but many other journals have adopted our initial trial registration recommendations, and we hope that they will also adopt the modifications discussed in this update.

The research community has embraced trial registration. Before the ICMJE policy, ClinicalTrials.gov, the largest trial registry at the time, contained 13 153 trials; this number climbed to 22 714 one month after the policy came into effect.2 In April 2007, the registry contained over 40 000 trials, with more than 200 new trial registrations occurring weekly (D Zarin, personal communication). The four other registries that meet the ICMJE criteria have also grown as scores of journals have adopted the ICMJE clinical trials registration policy. In response to burgeoning registration, many investigators, sponsors, and government agencies have asked the ICMJE to recognise their local registries as databases that meet the policy. Fortunately, the World Health Organization’s (WHO) International Clinical Trials Registry Platform (ICTRP), which was nascent when the ICMJE began to require trial registration, has matured rapidly and provides options for those who desire a wider array of registries. The ICTRP has taken the first steps towards developing a network of primary and partner registers that meet WHO specified criteria.3 Primary registers are WHO selected registers managed by not-for-profit entities that will accept registrations for any interventional trials, delete duplicate entries from their own register, and provide data directly to WHO. Partner registers, which will be more numerous, will include registers that submit data to primary registers but limit their own register to trials
**Summary**

- In addition to accepting registration in any of the five existing registries, the International Committee of Medical Journal Editors (ICMJE) will accept registration of clinical trials in any of the primary registers that participate in WHO’s International Clinical Trials Registry Platform (ICTRP). Registration in a partner register only is insufficient.
- The ICMJE will begin to implement the WHO definition of clinical trials for all trials that begin enrollment on or after 1 July 2008. This definition states that a clinical trial is “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.”
- The ICMJE will not consider results posted in the same clinical trials registry in which the primary registration resides to be a previous publication if the results are presented in the form of a brief, structured (<500 words) abstract or table.

The ICMJE strongly supports WHO’s efforts, through the ICTRP, to develop a coordinated process for identifying, gathering, deduplicating, and searching trials from registries around the world, thus eventually providing a one stop search portal for those seeking information about clinical trials. In addition to the five existing registries, the ICMJE will now also accept registration in any of the primary registers that participate in WHO ICTRP. Because it is crucial that trial registries are independent of-for-profit interests, the ICMJE policy requires registration in a WHO primary register rather than solely in a partner register, since for-profit entities manage some partner registers. As previously, trial registration with missing or uninformative fields for the minimum data elements is inadequate.

Initially, the ICMJE required registration of all clinically directive trials, which it defined as “any research project that prospectively assigns human participants to intervention or comparison groups to study the cause and effect relationship between a medical intervention and a health outcome.” In May 2005, the ICMJE clarified this definition to exclude preliminary trials designed to study pharmacokinetics or major unknown toxicity (phase I trials). However, the ICMJE recognises the potential benefit of having information about preliminary trials in the public domain, because these studies can guide future research or signal safety concerns. Consequently, the ICMJE is expanding the definition of the types of trials that must be registered to include these preliminary trials and adopts WHO’s definition of a clinical trial, “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.” Health related interventions include any intervention used to modify a biomedical or health related outcome (for example, drugs, surgical procedures, devices, behavioural treatments, dietary interventions, and process of care changes). Health outcomes include any biomedical or health related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. As previously, purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) will not require registration. The ICMJE member journals will start to implement the expanded definition of clinically directive trials for all trials that begin enrollment on or after 1 July 2008. Those who are uncertain whether their trial meets the expanded ICMJE definition should err on the side of registration if they wish to seek publication in an ICMJE journal.

Over the time during which registration of trial methods has become common practice, several forces have begun advocating for registration of trial results. We recognise that the climate for results registration will probably change dramatically and unpredictably over coming years. For the present, the ICMJE will not consider results posted in the same primary clinical trials register in which the initial registration resides as previous publications if the results are presented in the form of a brief, structured (<500 words) abstract or table. The ICMJE favours a standard abstract format for results reporting, and the CONSORT (Consolidated Standards for the Reporting of Trials) group’s forthcoming guidelines for abstracts related to trials may be one such option. The ICMJE believes that parties interested in results registration should consider requiring the deposition of such an abstract in the registry 24 months after closure of data collection if results are not published in a peer reviewed venue by that time. The registered abstract should either cite any related full, peer reviewed publications or include a statement that indicates that the report has not yet been published in a peer reviewed journal. Researchers should be aware that editors may consider more detailed deposition of trial results in publicly available registries to be prior publication. When submitting a paper, authors should fully disclose to editors all posting in registries of results of the same or closely related work.

Three years ago, trial registration was the exception; now it is the rule. Registration facilitates the dissemination of information among clinicians, researchers, and patients, and it helps to assure trial participants that the information that accrues as a result of their altruism will become part of the public record. WHO’s global efforts towards comprehensive trial registration and the ICMJE’s requirements for registration aim to increase public trust in medical science.

Is prognosis key in donation?

Potts (previous letter) highlights an often misunderstood aspect of organ donation: that death is not always what it seems, especially to relatives.1 However, I wonder whether his concerns are predominantly motivated by theological considerations?

I suspect the key word is prognosis, as accepted by a wide consensus of peers. The heart may still be beating, but if the prognosis is bleak why not let someone else have a chance of a longer life?

Richard Bartley physiotherapist
Denbigh Infirmary, Denbigh, Clwyd LL16 3ES
monty.python@mac.com
Competing interests: None declared.

Tell public about brain death

Until fairly recently, the definition of death was cardiopulmonary death, not brain death.1 There is a vast suspicion that doctors will take organs from those who are not “really dead”—this suspicion will seem to be confirmed if the heart is still beating and there seems to be undue haste to harvest the organs.

The public needs to be educated on what “brain dead” means, the difference between brain death and a coma, the need for speed in removal of the organs, and, most importantly, the criteria that must be met to confirm that someone is indeed “dead” before organs will be removed.

Joan McClusky medical writer
New York, NY 10003, USA joanmnewyork@aol.com

Competing interests: None declared.

Add carrying a card to QOF

Why not make possession of a donor card a QOF (quality and outcomes framework) target?1

A question about possession of a donor card is fairly simple but if the practice was required to discuss donation, and obtain informed consent, this would require more resources.

The information could be available on the NHS spine, although I share concerns about awareness of contraindications to donation.

Anne Holmes general practitioner
Tithes Barn Medical Centre, Stockton on Tees TS19 8RH
anne.holmes@ntlworld.com

Competing interests: None declared.

1 English V. Is presumed consent the answer to organ shortages? Yes. BMJ 2007;334:1088. (26 May.)

Surgical solution is becoming acceptable, as for birth

Liao and Creighton refer to idiosyncratic decisions about cosmetic genitoplasty in the absence of local and national guidelines.1 Having worked as a clinical psychologist in women’s health for several years, I have seen patients at various stages on the labial surgery pathway, and the reasons for referral to me have been varied.

Some women have had labial surgery and request further interventions, thus causing concern to their surgeons. Satisfaction with surgery has been professed, but it has not changed how they feel about their bodies. These women are faced either with the prospect of more surgery or the stark reality that such a solution may not offer everything they had hoped. Other referrals are to “cover all bases,” check that the patient is in “sound mind,” and rarely can a serious psychiatric diagnosis be invoked. Unfortunately, some of these patients have already been given a date for their surgery and think that it can proceed unless the psychologist says otherwise. Thus they are unlikely to embrace a psychological rather than a surgical solution.

My surgical colleagues seem to be reluctant to provide such interventions, but they respond to psychological distress and can be disempowered by the general rhetoric of “patient choice.” Surgical solutions for various concerns about the body may be what patients seem to want, but increasing the availability of surgery can inhibit the visibility of other choices.
Some clinicians may believe that laparoscopy is on the fringes of obstetrics and gynaecology. But history repeats itself. We have all seen the rise in caesarean section rates in the United Kingdom. This is reported to have happened because of concerns about litigation, but another process may be in operation—the sanitisation of a surgical solution to giving birth. This comes from the widespread availability of a surgical solution. Do we not already have a snapshot of how things will develop if we do not debate this issue now?

Competing interests: None declared.

Jacqueline Doyle clinical psychologist, Department of Clinical Psychology, Hillingdon Hospital, Uxbridge, Middlesex UB8 3NN jacqueline.doyle@thnhs.uk


PHARMACISTS IN PRIMARY CARE

Study shows wrong people, wrong skills, wrong tools …

Salter et al identify some deficiencies in a small sample of pharmacist consultations.1 Their results say more about the need for consultation training and the context of the pharmacists and patients involved in this study than they do about the concept of pharmacist medication review.

The pharmacists involved in this study were the wrong people because they had no connection with the patient, the general practitioner, the local pharmacy, or the hospital department and therefore lacked credibility. They had the wrong skills because they scrupulously avoided exploring patients’ ideas and beliefs and persisted in a predetermined agenda that patients did not identify with. They had the wrong tools because they did not have the medical records or any indication for the medicines. They were doing the wrong job because people who have just had their medicines reviewed are not likely to benefit from a further review. And the timing was wrong because older people just discharged from the turmoil of hospital need some time to settle and reflect before someone intervenes again.

This study says little about pharmacists’ ability to conduct medication reviews. The HOMER study was not a realistic model for pharmacist medication review.2 The discharge note must be reviewed in context of the clinical record and in discussion with the general practitioner. Only then should the patient be visited. Their paper is therefore a lesson in the need to construct a useful intervention before setting out to test it. It is also reminds us of the need to learn Osler’s century old lesson “Listen to the patient, he’s telling you the diagnosis.”

Duncan R Petty lecturer practitioner Arnold Zermansky University of Leeds, Leeds LS2 9JT d.petty@leeds.ac.uk

Competing interests: None declared.

Study shows wrong people, wrong skills, wrong tools …

1 Salter C, Holland R, Harvey R, Henwood K. “I haven’t even phoned my doctor yet.” The advice giving role of the pharmacist during consultations for medication review with patients aged 80 or more: qualitative discourse analysis. BMJ 2007;334:1101-4. (26 May)


ANAEMIA IN DEVELOPING COUNTRIES

Mass iron treatment is cheaper than routine deworming

Gulani et al say that routine administration of intestinal anthelmintic agents results in a marginal increase in haemoglobin (1.71 g/l).3 What needs to be considered is whether this approach of mass anthelmintic therapy is actually economically feasible, especially in third world countries where iron deficiency anaemia is a major health issue.2 This needs special consideration, given the fact that the primary cause of anaemia in third world countries is dietary malnutrition rather than intestinal infestation with helminths.3

A better and more economically feasible approach to thwart the “epidemic” of anaemia might be mass supplementation with iron supplements such as oral ferrous sulphate.4 The average cost of mebendazole treatment (100 mg three times a day for three days) is £1.5. According to Gulani et al, this regimen increases haemoglobin by 1.7 g/l. On the other hand, ferrous sulphate at a dose of 325 mg three times a day will increase haemoglobin by the same amount in about two weeks and cost £1.5.

Shailendra Kapoor resident physician University of Illinois at Chicago, Chicago, Schaumburg, IL, 60195, USA shailendrakapoor@yahoo.com

Competing interests: None declared.


MTAS

Lessons from the disaster

Some lessons must be swiftly learnt from the Medical Training Application Service (MTAS) experience.3 The BMA and the Academy of Medical Royal Colleges have been made to look feeble and ineffectual after entering into “partnership” roles with the Department of Health. The postgraduate deans have been notably silent and have behaved as willing accomplices in the promotion of MTAS. The deans have declined as an independent force in medical training and are struggling to fulfil their correct role in providing quality educational leadership because of over-dependence on political approval linked to their funding mechanism. The reputation of UK medical training has taken a damaging hit.

The royal colleges, threatened by loss of power and influence and undermined by the emergence of the Postgraduate Medical Education and Training Board (PMETB), seem to have been all too easily lured into partnership agreements, using a set of desirable motherhood and apple pie objectives that were seductively easy to sign up to. The trap was then sprung and the poorly drafted and unworkable operational details released deliberately late in the process. The timetable of the action plan became a higher priority than the quality of the project itself. Website design and selection procedures were unfinished, and consultation on details was token or non-existent. Bullying tactics created an unstoppable momentum for MTAS implementation, regardless of the obvious problems piling up and the well based objections of a majority of consultants. The colleges are protesting that they have been misrepresented, although manipulated would be more accurate with junior doctors feeling disconnected and unsupported until it was too late. The government, anxious to displace blame elsewhere, insists they were fully on board.

These “partnership” arrangements have become a damaging form of pseudo collaboration. The end result has been a major system crash between the Department of Health and the profession, which is now much deeper than the single catastrophe of MTAS.

John Turner consultant physician, University Hospital Aintree, Liverpool, L9 7TU. jythe.turner@aintree.nhs.uk

Competing interests: IT is a consultant and educational supervisor.

Nigeria files criminal charges against Pfizer

Jeannie Lenzer

Officials in Nigeria have filed criminal and civil charges against Pfizer for its role in the deaths and disabilities of children who were treated with an experimental drug during a meningitis outbreak in Kano in 1996.

The charges, filed by government prosecutors in Nigeria, follow three attempts by families of the children to sue in US courts. All three attempts were denied after Pfizer successfully argued that the US courts were not an appropriate forum.

Four separate legal actions have been filed in Nigeria, including 31 criminal counts against 10 people, according to the Washington Post (www.washingtonpost.com). 2 Jun, “Pfizer faces new charges over Nigerian drug test”). The plaintiffs also seek a total of $9bn (£4.5bn; €7bn) in civil suits.

The charges stem from Pfizer’s test of its unlicensed drug, trovafloxacin (Trovan) to treat 100 children with meningitis. A comparator group of 100 children were treated with a low dose of ceftriaxone. Suits on appeal in US courts charge Pfizer with causing harm to the children in both arms of the trial, alleging that a number of the children either died or were left deaf, mute, or brain damaged.

The families allege that the company failed to tell them that their children were being enrolled in an experimental drug trial and that free, effective treatment was available from Médecins Sans Frontières at the same hospital. Five children in the trovafloxacin arm and six in the ceftriaxone arm died, according to Pfizer.

Pfizer issued a statement in response to the charges, saying “Pfizer continues to emphasise—in the strongest terms—that the 1996 Trovan clinical study was conducted with the full knowledge of the Nigerian government and in a responsible and ethical way consistent with the company’s abiding commitment to patient safety.

“Any allegations in these lawsuits to the contrary are simply untrue.”

Drugs “refund” scheme proposed by NICE

Susan Mayor

The drugs advisory body for England and Wales has recommended a “refund” scheme in which the manufacturer of bortezomib (Velcade) would reimburse the NHS for the cost of the drug in patients who do not respond to treatment.

The refund scheme, proposed by the National Institute for Health and Clinical Excellence (NICE), could signal a way for the NHS to cope with funding the rapidly growing range of new and expensive drugs. It was suggested by the company making bortezomib, Janssen-Cilag, as part of its appeal against NICE’s previous recommendation that the drug was not cost effective.

NICE’s independent advisory committee agreed and recommended in draft guidance published this week that all suitable patients with progressive multiple myeloma should be offered bortezomib. Patients who show a full or partial response should continue treatment, with the costs of treatment being met by the NHS. Patients showing a minimal or no response after four cycles should stop treatment, and the manufacturer will refund the costs of the drug to the NHS.

Andrew Dillon, chief executive of NICE, said, “We are aware of the challenge that the NHS faces in ensuring that patients can access expensive but potentially effective treatments for life threatening conditions such as cancer.” Bortezomib costs about £9000 (€13 000; $18 000) for a course of three cycles of treatment per patient, with eight cycles costing about £25 000.

“If the drug’s manufacturer accepts the proposals we are consulting on, it will mean that when the drug works well the NHS pays, but when it doesn’t the manufacturer should bear the cost. All patients suitable for treatment will get the chance to see if the drug works well for them,” said Mr Dillon.

The draft guidance recommends bortezomib as an option for people with progressive myeloma who have received at least one previous treatment and who have had, or are unsuitable for, bone marrow transplantation. The response to bortezomib must be measured using serum M protein (a protein produced in vast excess in multiple myeloma) after a maximum of four cycles of treatment.

The draft guidance is at www.nice.org.uk.
Questions over HPV vaccine in the US and Australia

Janice Hopkins Tanne NEW YORK

Questions have emerged in the United States and Australia about the possible side effects of Gardasil, the vaccine for human papillomavirus.

In the US, three deaths closely time related to immunisation with the vaccine were among 1637 adverse reactions reported by Judicial Watch, a public interest watchdog. Judicial Watch obtained the reports from the Food and Drug Administration using the Freedom of Information Act. The reports were filed through the FDA’s vaccine adverse event reporting system.

In Australia, 25 girls at a Catholic high school in Melbourne who had just received their first injection of the vaccine on 22 May experienced headache, nausea, and dizziness, the Age reported. Four were sent to hospital and two were admitted overnight. All were discharged.

One expert called it mass hysteria. Shares of the vaccine’s Australian developer, CSL, fell after news reports of the incident www.theguardian.com.au 25 May, “Why are we experimenting with drugs on girls?”.

The FDA approved the vaccine in June 2006, and an advisory committee of the Centers for Disease Control and Prevention unanimously voted to recommend it for girls aged 11 and 12 years. It is effective against human papillomavirus types 6, 11, 16, and 18, which cause most cervical cancers and genital warts.

The vaccine has been controversial because some parents objected to state mandates to give it to young girls, preferring to encourage their daughters to abstain from sexual activity until marriage (BMJ 2007;334:721-3).

Judicial Watch reported on 23 May that the three deaths included one poorly documented death from a blood clot three hours after receiving the vaccine and two deaths in young women with existing heart or clotting problems.

See: Fainting schoolgirls wipe $A 1bn off the market value of Gardasil producer, p 1195

Reed Elsevier to stop hosting arms exhibitions after wide protests

Nayanah Siva LONDON

Reed Elsevier, the global publisher that owns the Lancet, has announced that it will no longer take part in arms fairs.

For more than three years Reed Elsevier has owned the company Spearhead Exhibitions, which has hosted some of the largest international defence exhibitions. This connection has angered some members of the medical and scientific community.

Sir Crispin Davis, chief executive officer of the company, said last week, “Our defence shows are quality businesses which have performed well in recent years. None the less, it has become increasingly clear that growing numbers of important customers and authors have very real concerns about our involvement in the defence exhibitions business. “We have listened closely to these concerns and this has led us to conclude that the defence shows are no longer compatible with Reed Elsevier’s position as a leading publisher of scientific, medical, legal, and business content.”

Reed Elsevier’s involvement has been severely criticised by numerous journals, even including its own Lancet. Staff at the journal, which was founded in 1823, were unaware of their owner’s connection with the arms trade until 2005, when they expressed their concerns in an editorial (Lancet 2005;366:868).

“We reject completely any perceived connection between the journal and the arms trade, no matter how tangential it might be . . . We respectfully ask Reed Elsevier to divest itself of all business interests that threaten human, and especially civilian, health and well being,” the editorial said.

An editorial in the BMJ in March called for medical societies to look elsewhere for publishers, for journal editors to express their disgust, and for researchers to refuse to submit their high profile randomised controlled trials to Reed Elsevier (BMJ 2007;334:547-8, 17 March)

More opposition to Elsevier’s participation in arms exhibitions was expressed in a letter to the Times newspaper in March signed by several literary authors, including Ian McEwan, Will Self, and Nick Hornby. “We call upon Reed Elsevier to end its involvement in a dirty and damaging business,” the letter said www.timesonline.co.uk 1 Mar, “The London book fair, democracy in action, shoot first”).

Peter Hall, chairman of Doctors for Human Rights, criticised Reed Elsevier for refusing to take any action earlier, in the face of two years of criticism.
System for detecting side effects can beat regulatory agency

Bob Roehr  WASHINGTON, DC

A new approach to pharmacovigilance developed by doctors in Chicago can identify adverse drug reactions up to six years before the Food and Drug Administration or monitoring programmes run by the drug industry, researchers say (Archives of Internal Medicine 2007;167:1041-9).

The scheme, the research on adverse drug events and reports (RADAR) project, was developed by Charles Bennett and colleagues at the Northwestern University Feinberg School of Medicine, in Chicago, and launched in 1998.

Dr Bennett told the BMJ that other pharmacovigilance programmes are based on epidemiology and databases. The RADAR approach is based on considering whether there is a theoretical reason why a drug might have an adverse side effect, and looking at that, he said.

The project has started 80 investigations and issued 30 reports. It focuses on incidents such as those requiring major surgery or organ transplant, and deaths. “We work actively, we are not waiting passively for all of these reports to show up in databases, we’re calling people on the phone. We have a strategy to look to see if it is interesting or not and make an early decision” in terms of a full investigation.

Dr Bennett cites the example of the antiplatelet drug clopidogrel. “We were able to get that [evidence about its adverse effects] out to the FDA and into the public’s hands within six months of the drug receiving approval.” Clopidogrel was approved in 1997 and the adverse reaction that the RADAR system identified was thrombotic thrombocytopenia.

“That side effect occurred at the rate of four per one million, so it is not common, though it is fatal. That would take seven years with the FDA.” Clopidogrel has a chemical structure similar to another drug with the same side effect, which allowed the doctors to form and test the risk hypothesis.

Emphasis is on the quality rather than quantity of data, with gathering and analysis carried out by a group that does not have a stake in the outcome. “We’ve shown with this project that people who have a basic science background and who are interested from a scientific standpoint can add a lot to the field by working with very complete reports, and a collaborative network.”

Dr Bennett says that one weakness of the FDA reporting system is that because much of it is voluntary the data are shallow and incomplete. “I think you get what you pay for,” he says. He describes it as “essentially a bunch of statisticians waiting for the data to generate a signal.”

Raymond Woosley is president of the Critical Path Institute, based at the University of Arizona. It is a non-profit making partnership with the FDA that advances modernisation of the drug development and monitoring process.

He says that when electronic medical records are completely implemented, and that will take years, they will help the identification of adverse events from approved drugs.

Chinese court sentences former drug chief to death

Jane Parry  HONG KONG

A court in Beijing has handed down a death sentence on Zheng Xiaoyu, the former head of the Chinese State Food and Drug Administration. He was found guilty of taking ¥6.5m (£0.4m; €0.6m; $0.9m) in bribes and gifts and of dereliction of duty for failing to ensure the safety of drugs and devices that were approved during his tenure.

Court documents quoted by China’s state news agency, Xinhua, say that Mr Zheng pleaded guilty to charges that he “sought benefits” from eight domestic drug companies in exchange for approval of drugs and medical devices between June 1997 and December 2006. In addition, six drugs granted approval on the basis of false documents between 2001 and 2003 were found to be fake.

“[Mr Zheng’s acts] greatly undermined the integrity of an official post and the efficiency of China’s drug monitoring and supervision, endangering public life and health, and had a very negative social impact,” a court statement said.

Mr Zheng was director of the regulatory agency since its formation in May 2003 until mid-2005. Before that he was head of the State Pharmaceutical Administration from 1994 to 1998 and head of the State Drug Administration from 1998 to 2003.

Until 2002 all drugs distributed in China required approval from the State Drug Administration and then from its successor, the State Food and Drug Administration. He was investigated by the Communist Party of China’s Central Commission for Discipline Inspection in December 2006 and was expelled from the Communist Party in March this year.

Zheng Xiaoyu faces a death sentence
Bush’s nominee for surgeon general opposed

Bob Roehr WASHINGTON, DC

The nomination of James Holsinger to be surgeon general of the United States is drawing mounting opposition from AIDS and gay groups. That may lead to particularly contentious confirmation hearings because the leading Democratic candidates Hillary Clinton and Barack Obama sit on the Senate health committee that will review the nomination.

President George Bush nominated Dr Holsinger (below) on 24 May. His paper credentials make him eminently suitable for the position of chief public health officer—a medical degree from Duke University; a masters degree in hospital financial management from the University of South Carolina; a 25 year career with the Veterans Health Administration, rising to a senior management position; and subsequent work for the University of Kentucky and the state healthcare system.

He also strongly identifies as a Christian, and it is his actions as a Christian that are proving controversial in the United States. Dr Holsinger served as the head of the nine member Judicial Council of the United Methodist Church, which in June 2004 defrocked Beth Stroud, a lesbian minister in Philadelphia.

The council claimed that she might serve had she remained celibate, but sex outside of marriage is not allowed, and gay people are not allowed to marry. So, Reverend Stroud’s long term relationship with her partner was considered to be immoral.

The pressure group AIDS Action has taken the strongest position of any organisation to date, opposing the nomination. Its deputy director, Ronald Johnson, told the BMJ that the group will write to senator Ted Kennedy, Senate health committee chairman, and to Mike Enzi, the most senior member of the opposition party on the committee, spelling out its opposition to the nomination, which must be confirmed by the entire US Senate.

“We feel this is another distressing signal and message that this administration—this president—does not either understand or take seriously the domestic epidemic.”

Indian doctor held under controversial antiterrorism law

Owen Dyer LONDON

Demonstrators in six Indian cities last week called for the release of a paediatrician arrested under controversial antiterrorism laws in the central Indian state of Chhattisgarh.

Binayak Sen, a noted civil rights activist, was arrested on 14 May accused of using prison visits to pass a message between two prisoners accused of involvement in local Maoist rebel groups.

Chhattisgarh is one of several Indian states troubled by a longstanding insurgency led by disparate Maoist guerrilla groups, known as Naxalites, after the town of Naxal where the movement originated. The Naxalites have support among local indigenous communities in remote areas of the state.

Chhattisgarh’s state government has encouraged the growth of an armed civilian militia to counter these groups, known as the salwa judum in the Gondi language—or “peace mission.” About 45,000 people have been swept out of their forest villages into guarded camps since the militia was created in June 2005. Reports of serious human rights abuses by both sides are commonplace.

Dr Sen worked on behalf of indigenous communities for 30 years. He helped to found a cooperative hospital for mine workers, the Shaheed hospital, and played a big part in evolving a statewide programme of training community health workers.

He also became active in monitoring human rights violations, and in the past two years has reported numerous abuses by civilian militia and state police. Dr Sen is the general secretary of the Chhattisgarh unit of the People’s Union for Civil Liberties, one of India’s leading human rights organisations.

The police allege that Dr Sen passed a letter from one inmate of Raipur jail to another while visiting prisoners in his capacity as a human rights observer. He was detained under the provisions of the Chhattisgarh Special Public Security Act, 2005, which allows detention without charge for up to seven years, without judicial remedy, bail, or appeal, of anyone suspected by police of aiding the Maoist insurgency.

Amnesty International has taken up his case, demanding that he be freed or charged with a recognised criminal offence. On 25 May, he was charged under the Indian penal code with criminal conspiracy, conspiracy to wage war against the state, and sedition.

Ramesh Gopalakrishnan, of Amnesty International, told the BMJ that the Organisation is still calling for his release. “These offences allow sweeping interpretations of criminal intent. Activists in India are arrested

Germany may tighten laws on sports medicine after doping incidents

Annette Tuffs HEIDELBERG

Doctors and politicians in Germany are demanding stricter laws for sports medicine after three doctors were discovered to have given performance enhancing drugs to professional cyclists.

Two of the three doctors, from Freiburg University Hospital, were suspended last week by the university when they admitted doping professional cyclists. In separate statements, Lothar Heinrich and Andreas Schmid said that they gave the blood cell stimulating hormone erythropoietin to the cycling team of the German telephone company Deutsche Telekom, now T-Mobile.

The confessions were made after several cyclists had recently publicly admitted to taking drugs for performance and accused the doctors of involvement.

“I admit that I supported doping individual cycling professionals from the mid-1990s,” Dr Schmid said in a statement released by his attorney. Previously, he and his colleague had denied any wrongdoing.

Freiburg prosecutors are investigating and the university has also promised a full independent investigation into the past 20 years of its participation in sports medicine.

The incident had spread to amateur ranks a few days later when another doctor from the Freiburg
all the time on such charges, which give wide, arbitrary powers to police,” he said.

Joel Almeida, a friend of Dr Sen who recently organised a small protest outside the Indian High Commission in London, said, “Dr Sen is a champion of peace and fair play and an internationally respected medical doctor who has devoted his whole life to peaceful service of the poorest people. He should be released immediately.”

Dr Sen is currently being held at Raipur jail, where supporters report he is reasonably comfortable.

Researchers accused of breaching research ethics faces GMC

Owen Dyer LONDON

A former senior lecturer at the UK Institute of Psychiatry repeatedly breached research ethics guidelines and lied to study sponsors while building an international reputation as a leading researcher, according to charges laid by the General Medical Council.

The GMC’s fitness to practise committee heard that Tonmoy Sharma, who left the Institute of Psychiatry as a clinical senior lecturer in 2001, falsely claimed to have sought and received approval from ethics committees for several studies.

He is also accused of recruiting patients by telephone without informing their carers; offering financial inducements to research subjects; breaching agreed research protocols; lying in a job application; posing as a professor; and threatening a patient with withdrawal of treatment if she left a study.

Joanna Glynn, counsel for the GMC, told the hearing that Dr Sharma “was a man who paid little more than lip service to ethical rules in research.”

In four studies, he claimed that his research had ethical permission from the Bethlem and Maudsley Ethical Committee, when none had been given, the charges allege. In another case he is alleged to have falsely told the Alzheimer’s Society that he had ethics clearance from the Institute of Psychiatry. On another occasion, he allegedly told Novartis that the Alzheimer’s Society was sponsoring his research when it was not.

Dr Sharma is accused of telling both Novartis and Sanofi-Synthelab that studies he was carrying out on their behalf were being carried out at the Institute of Psychiatry with ethics committee approval, when in fact they were carried out at private facilities. He is also accused of using proprietary Novartis data in another study.

In 1999 Dr Sharma was offered the chair in psychiatry at the department of psychiatry and behavioural sciences at University College, London, subject to completion of his doctorate thesis. He allegedly told superiors for two years that he was handing in chapters, when he had never done so.

He described himself as “Tonmoy Sharma MD PhD” on the website of his company, Psychmed, despite having never obtained a doctorate degree. In 2002 he was invited to speak as a “visiting professor” at Pittsburgh University. From this point he styled himself Professor Sharma, contrary to British academic convention, the GMC alleges.

Dr Sharma’s career began to unravel in 2001, said Ms Glynn, when he was suspended from the Institute of Psychiatry after a complaint from the drug company Sanofi-Synthelab. “After the suspension a picture emerged of a doctor who knew the rules of medical research but deliberately took short cuts,” she added.

Dr Sharma denies the charges of unethical, misleading, dishonest, and unprofessional conduct.
Doctors advise women not to drink alcohol during pregnancy

Lisa Hitchen LONDON

Women who are pregnant or trying to conceive should not drink any alcohol, guidance from the BMA recommends.

Complying with the guidance would eliminate fetal alcohol spectrum disorders, which include fetal alcohol syndrome and can lead to learning and physical disabilities and behavioural problems, notes the report.

Fetal alcohol syndrome is the most clinically recognisable type of fetal alcohol disorder and is characterised by abnormal facial features, growth deficiency, intellectual disabilities, and hyperactivity. In 2002-3 a total of 128 cases were recorded in England. However, there is no reliable evidence on the incidence of fetal alcohol spectrum disorders in the United Kingdom, something which needs to change, says the BMA.

The report calls on all UK health departments to routinely collect data on fetal alcohol syndrome and for further research to establish the full extent of fetal alcohol spectrum disorder.

Raja Mukherjee, a consultant psychiatrist for people with learning disabilities at the Surrey and Borders Partnership NHS Trust, said, “You can manage [fetal alcohol spectrum disorders] but you can never cure them.”

The BMA guidance is in line with the latest advice from the Department of Health in England.

But it differs from that given by the Royal College of Obstetricians and Gynaecologists, which says, “There is no evidence of harm from low levels of alcohol consumption, defined as no more than one or two units once or twice a week.”

“The difference [between the two sets of guidance] is more apparent than real,” pointed out Sir Charles George, chairman of the BMA board of science. Both are advising not to drink alcohol at all, but the royal college guidance states there is no evidence of harm for less than two units per week, he said.

However, there is a danger that the lack of evidence will be misinterpreted, said Professor Nathanson. Because many people are unaware how many units they are actually drinking and because of stronger drinks and pubs serving larger measures, women can end up drinking more than they intend, she said.

The UK’s binge drinking culture and high rates of teenage pregnancy also indicate that many women are continuing to drink during early pregnancy without being aware of the harm they are doing to their baby.

The BMA spent a year compiling the report only to have it pre-empted by the Department of Health’s recommendations 10 days earlier. The department did not consult the BMA before putting out its revised guidance.

“We are not unhappy with what they have said,” said Professor Nathanson, but she added that the government should go further. All healthcare professionals should have fully funded training to pick up and manage fetal alcohol spectrum disorders and health departments should produce guidance on its identification.

SHIPWEARERS

Healthcare staff should monitor all pregnant women with suspected or confirmed history of alcohol consumption at low to moderate levels and offer them brief intervention counselling early on, the report recommends. Those known to be at high risk of drinking larger amounts should be referred to specialist services.

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“...You can manage [fetal alcohol spectrum disorders] but you can never cure them...”
The ease with which a man infected with extensively drug resistant tuberculosis (XDR TB) flew on several international flights exposes flaws in international public health systems. The asymptomatic US lawyer flew on two transatlantic flights and several European flights for his wedding and honeymoon.

It also led to an international search for passengers who may have been exposed to this almost incurable disease.

Local public health officials in the United States could not prevent him from traveling; the US Centers for Disease Control and Prevention (CDC) failed to contact him; a “no fly alert” did not prevent him from flying; and a border alert to detain him was ignored.

The good news, said Julie Gerberding, head of the CDC, was that the risk of transmission was low.

Mario Raviglione, director of the Stop TB programme at the World Health Organization, told the BMJ that “if the International Health Regulations, 2006, had been in place, the relevant procedures outlined would have been followed correctly. [The regulations] will come into effect on 15 June worldwide and 17 July in the US [United States].

The US man, Andrew Speaker, a 31 year old lawyer from Atlanta, Georgia, is now in isolation at the National Jewish Medical and Research Center in Denver, under a detention order from Denver health officials.

The CDC is investigating a possible link to his father in law, Robert Cooksey, a microbiologist at CDC who works on multidrug resistant tuberculosis. Dr Cooksey said that he has always tested negative for tuberculosis.

The problem began when Mr Speaker had a chest x ray in January for a rib injury. It showed an infiltrate that indicated tuberculosis. A sputum test for tuberculosis was negative, but a more sensitive culture test was positive.

Further tests were under way when Mr Speaker left for his wedding. He and his fiancée flew from Atlanta to Paris, and then to Athens, Mykonos, and Rome.

Mr Speaker was told to turn himself in to Italian health officials, but the couple left their Rome hotel before a CDC representative arrived, flew to Prague, and then to Montreal. From Montreal they drove to the United States.
Fortified maize flour reduces anaemia in Kenyan children

**EFFECT OF EATING IRON FORTIFIED FLOUR**

<table>
<thead>
<tr>
<th>Prevalence ratio relative to placebo</th>
<th>Anaemia</th>
<th>Iron deficiency</th>
<th>Iron deficiency anaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose sodium iron EDTA</td>
<td>0.5</td>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Low dose sodium iron EDTA</td>
<td>0.8</td>
<td>1.2</td>
<td>2.0</td>
</tr>
<tr>
<td>Electrolytic iron</td>
<td>0.4</td>
<td>1.2</td>
<td>1.5</td>
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</table>

Efforts to reduce the high prevalence of iron deficiency anaemia in children in developing countries include adding elemental iron to flour made from cereals such as wheat and maize. Phytates in these flours bind electrolytic iron and reduce its bioavailability, so researchers did a clinical trial of flour fortified with sodium iron edetic acid (EDTA) instead. Compared with placebo, iron deficiency anaemia fell significantly (~89%, 95% CI ~97% to ~49%) in Kenyan children given maize porridge with high amounts of sodium iron EDTA for a month. A lower dose had no significant effect on the prevalence of anaemia, but it did reduce the prevalence of iron deficiency by 70% (85% to 40%). Flour fortified with electrolytic iron (the traditional form of elemental iron) had no beneficial effects.

This trial is further evidence that adding the right nutrients to staple foods can improve the health of vulnerable groups in the developing world, says an editorial (pp 1766-8). Whole maize flour, a staple of the poorest families in Africa and elsewhere, is particularly hard to fortify because it has such a high phytate content. These researchers show that it can be done, and it works. Children with iron deficiency anaemia at baseline benefited the most from such fortification.

*Lancet* 2007;369:1799-806

World Trade Center dust blamed for respiratory illnesses

In the early aftermath of the terrorist attack on the World Trade Center, some firefighters developed upper respiratory symptoms, which later became known as “World Trade Center cough.” The cough was associated with clinically important loss of lung function, and it was probably caused by inhalation of the toxic cloud of particles and gases generated when the twin towers collapsed. We don’t know exactly what was in the cloud because no one sampled it at the time, says one commentator, but later analyses of settled dust and environmental pollution at the site found volatile carcinogens, particles of building materials, and asbestos.

Survivors, clean-up operators, and local residents may also have been affected, but there is ongoing controversy about the long term health effects of being near the twin towers during and after the disaster. Thousands of people are looking for compensation for respiratory illnesses allegedly caused by the dust, he says. Some have already been successful.

The original pollution is long gone, and scientists have worked over the remaining dust thoroughly. The best we can hope for now is rigorous and long term follow-up of people who lived or worked in the immediate area. This controversy won’t be resolved for decades, if at all, he concludes.


**Switching flu vaccination to schoolchildren could be disastrous for older people**

Flu is most dangerous for infants and older people, but schoolchildren are more efficient at spreading the virus. Because flu vaccines work better in schoolchildren than in older people, might it be more sensible to vaccinate schoolchildren instead? A mathematical modelling study concludes that under certain conditions (low population mixing and low viral transmission), switching vaccination to schoolchildren could eventually reduce sickness and death in older people. But the same strategy would not work, and could be disastrous, in epidemics with high rates of viral transmission. When transmission rates were moderate, switching vaccination to schoolchildren had complex effects on older people, making things worse at first, then better, then worse again.

The impact of a switch in policy would be sensitive to changes in parameters we don’t fully understand, say the authors. For example, in this model the authors assumed that the two different populations—schoolchildren and older people—would be largely separate. This may not be true in cultures where grandparents often live with grandchildren. Until we know more, governments should proceed with caution, perhaps supplementing but not replacing vaccination of older people with vaccination of schoolchildren.


Surgery for sciatica should be optional

**EFFECT OF SURGERY ON ACCUMULATIVE INCIDENCE OF RECOVERY**

Patients with enduring sciatica caused by a herniated intervertebral disc can have a microdiscectomy or more conservative treatment, with the option of later surgery if symptoms don’t improve. After a year, the results were similar for both treatments in a recent trial. More than 90% of patients in both groups recovered. But those who had an early microdiscectomy got better significantly faster (median time to recovery 4.0 weeks, 95% CI 3.7 to 4.4 vs 12.1, 9.5 to 14.9). The main advantage of early surgery was faster recovery from leg pain. The authors used validated scales to measure disability, pain, and patients’ global perception of recovery.

All the participants had had sciatica for six to 12 weeks before the trial began. Patients assigned to surgery had a microdiscectomy with a median delay of less than two weeks. The rest were encouraged to stay mobile and given analgesics and physiotherapy if needed. Almost 40% (55/142) of them had surgery eventually—after a median of 14.6 weeks.

Patients with sciatica should be reassured that the long term prognosis is reasonably good, even with conservative treatment, say the authors. Patients who don’t want surgery can safely wait and see if they recover spontaneously. For those who can’t wait, early surgery might be best.

Failure to ask about cocaine use may put patients at risk

Junior doctors in emergency and internal medicine seem to be aware of cocaine use as a risk factor for acute coronary syndrome, but when faced with a potential patient, they are less likely to ask about or record it than other risk factors.

Of 34 residents and fellows given a case scenario of acute coronary syndrome, 31 were aware of cocaine as a risk factor but only 18 stated they routinely inquired, whereas nearly all claimed they inquired about other recognised risk factors. This failure was validated by referring to 156 records of consecutive patients with suspected or proved acute coronary syndrome and finding a record of use or non-use of cocaine in only eight. The pathophysiology, and hence the treatment, of acute coronary syndrome caused by cocaine is totally different from that caused by atheroma, so failure to inquire may result in inappropriate management.

Postgrad Med J 2007;83:325-8

“Light” cigarettes are not less risky

Low tar, low nicotine cigarettes impair coronary microvascular function as severely as standard cigarettes. Investigators undertook echocardiography, including measuring coronary flow velocity reserve in 20 smokers of each type of cigarette and in 22 non-smoking controls. The velocity reserve was lower at baseline in smokers than in non-smokers. After 12 hours’ abstinence by the smokers, the coronary flow velocity reserve was measured again, 20-30 minutes after two of their usual cigarettes. The velocity reserve fell acutely, whereas blood pressure and heart rate rose in both groups equally.

The authors conclude that cigarettes with reduced tar and nicotine yields remain hazardous to the coronary circulation and that action should be taken to prohibit misleading terminology such as “light.”

Heart May 2007; doi: 10.1136/hrt.2006.100255

BMJ press release led to increase in mumps notification

In May 2005 a BMJ press release, quoted in many media outlets, highlighted two papers describing a UK mumps epidemic in adolescents and young adults in the previous year. Notifications of mumps to the Health Protection Agency rose from 28.3 (95% confidence interval 26.5 to 30.1) per 100 000 population in the week before 13 newspapers reported the BMJ’s findings to 42.8 (40.6 to 45.0) per 100 000 two weeks later. The Royal College of General Practitioners’ weekly return service showed a similar rise—from 9.8 (7.4 to 12.1) per 100 000 population to 21.2 (17.7 to 24.6) per 100 000 population.

UK doctors are known to under-report communicable disease, and increased media reporting seems to have sharpened their awareness, increased diagnostic suspicion, and therefore voluntary reporting. The investigators state that their findings have important implications for the analysis and interpretation of disease reporting and for any subsequent action related to public health.

J Epidemiol Community Health 2007;61:385-8

No need to double antibiotic dose in children with non-severe pneumonia

Children aged 2-59 months in Pakistan with “non-severe” pneumonia were randomised to receive a standard dose of amoxicillin (45 mg/kg per day for three days) or double that dose. At follow-up visits at five and 14 days, cumulative therapy failure was 26/437 (6%) in those receiving the standard dose and 35/439 (8%) after a double dose. The difference was non-significant.

Although many cases might have been viral, the World Health Organization recommends using antibiotics in “non-severe” pneumonia in the developing world without trying to discriminate aetiology. This trial suggests that no advantage results from doubling the recommended dose of amoxicillin.

Arch Dis Child 2007;92:291-7

The fisherman’s tale

A Greek fisherman unintentionally fired a trident from a fishing gun into the right side of his neck. On arrival in the emergency department, he had (apart from the neck wound) fever, tachycardia, hypertension, and a tremor. Blood tests confirmed the clinical impression of a thyroid storm. He recovered after removal of the trident together with a subtotal right thyroidectomy.

Emerg Med J 2007;24:355-6
COLD TURKEY

Highly popular cold remedies could be banned from sale because of their link to a dangerous drug epidemic that has yet to surface in the UK. Rebecca Coombes asks whether the authorities are over-reacting.

UK drug regulators are favouring making products containing the nasal decongestants pseudoephedrine and ephedrine available on prescription only to try to limit their use in the illicit manufacture of the class A drug methylamphetamine, also known as methamphetamine or crystal meth.

A consultation by the Medicines and Healthcare Products Regulatory Agency could result in the UK having the toughest restrictions on pseudoephedrine in the world as early as this Christmas. Critics, including general practitioner representatives and an eminent pharmacologist, have been swift to liken the move to taking a sledgehammer to crack a nut. They say the drug regulators have been taken in by media hype and over-cautiousness among the police.

Although potentially very harmful, methylamphetamine is much less widely used in the UK than in countries such as the United States, Australia, and the Czech Republic, where it is a big problem. In 2004, nearly 12 million people in the US had tried methylamphetamine. Recent estimates suggest that in Australia more people are dependent on methylamphetamine than on heroin. But none of these countries has taken such a hard line on pseudoephedrine. Instead, pack size has been reduced, sales limited to one pack, and names of customers recorded.

The proposal to remove pseudoephedrine from retail sale has also split the medical fraternity—the BMA is in the prescription-only camp, but the Royal College of General Practitioners fears this puts up needless obstacles for patients otherwise happy to self treat colds and coughs and will increase general practitioners’ workload.

Industry bodies, such as the Proprietary Association of Great Britain, are unsurprisingly angry that popular consumer products with a 40 year safety record face being withdrawn from counter sale. There are 103 licensed products containing pseudoephedrine and 32 containing ephedrine on the UK market—most are available over the counter. Over 10 million packs of medicines containing these drugs are sold each year. The association argues that policy should be grounded in UK experience, rather than a fear of what might happen based on international events.

Assessing the threat

But the argument goes that if methylamphetamine takes hold in the UK the consequences would be serious. International experience shows that once a small number of illicit domestic laboratories become established, abuse of crystal meth rises sharply, leading to an increase in amphetamine related psychoses and, as seen in the US, widespread problems of violence.

In Australia, for example, where half a million people report using the drug, indicators of harm such as psychosis, emergency department presentations, and crystal meth related crime have risen considerably. Between 1999-2000 and 2003-4 amphetamine related psychosis increased by 59%. A study in the Medical Journal of Australia this year found that amphetamine related presentations at emergency departments account for 1% of all admissions.

UK authorities have plenty of unsettling reports from overseas to show how crystal meth can take a grip on communities. Methylamphetamine is a highly addictive, potent stimulant that affects the central nervous system. When smoked in its crystalline form it can produce effects similar to crack cocaine but lasting considerably longer, up to 12 hours. Methylamphetamine is easy to make from over the counter products containing pseudoephedrine—you don’t need any sophisticated equipment, just a kitchen. And step by step instructions on converting pharmacy products into methylamphetamine are readily available on the internet.

But is the UK really on the brink of a...
Regulation of decongestants

crystal meth epidemic? In April, health minister Caroline Flint told the House of Commons that police had found multiple packs of flu remedies containing pseudoephedrine in raids on drug factories. “They have also identified that, in part, these packs were obtained from numerous pharmacies to obtain adequate quantities for manufacturing,” she said.

Although admitting that incidence of illicit activity was low, Ms Flint had been advised that conditions were in place for the drug to take off in the UK. This may well be true. International evidence shows how quickly illicit methamphetamine production and use can increase. For example, the number of illegal laboratories discovered in the US grew from around 300 in 1995 to over 18 000 in 2004.

A 2005 report on methylamphetamine by the Advisory Council on the Misuse of Drugs concluded that use of the drug in the UK was “very limited.” Data on its use are scarce because the British Crime Survey, the most comprehensive source of illicit drug taking in the UK, does not differentiate between methamphetamine and ecstasy.

Newly available data from the Association of Chief Police Officers sets out “key threats to the UK: “There have been several laboratories discovered in England and Wales, the largest . . . was capable of producing a kilo of methamphetamine per cycle,” according to its analysis. But only in one case—on the Isle of Wight, where a small scale laboratory was uncovered and the ringleader jailed for 10 years—was there clear evidence of use of pharmacy products.

An appropriate response

The limited hard data available on the extent of use of crystal meth do not explain why the UK is proposing such a crackdown on pseudoephedrine cold products. In Australia, for example, where problems far outweigh those in the UK, Alex Wodak, director of the alcohol and drug service at St Vincent’s Hospital, Sydney, says that government is unlikely to take a tougher stance. “Australian politicians toyed recently with banning all ephedrine and pseudoephedrine products. There was an outcry and nothing more was heard,” he says.

Les Iversen, a member of the Home Office Advisory Council on the Misuse of Drugs, the body which recommends the classification of drugs, and professor of pharmacology at the University of Oxford, is mystified by the UK position. “I deplore the suggestion that pseudoephedrine use be restricted. This is one of the most effective (Cochrane review positive) cold treatments available over the counter. Its illegal use for methamphetamine production is small and could be controlled (as in the USA) by pharmacists issuing only a single box of tablets at a time and taking names of customers. The illegal production of methamphetamine relies more on large scale factories than on home based labs. The MHRA has acted precipitately without consulting, for example, the Home Office Advisory Council on Misuse of Drugs.”

The chair of the Royal College of General Practitioners, Mayur Lakhani, said...
more hard facts were needed before the UK should take the radical step of banning pseudoephedrine from chemists. “Our view is that any response has to be proportionate. It is too easy to suggest making things prescription only. The impact on GP workload would also need to be examined—most GPs do not normally prescribe these drugs. This goes against the move to self care and patient empowerment. The solution must lie with pharmacists.”

The Proprietary Association of Great Britain claims that 29 million people who have a cold treat it themselves and 12 million adults with blocked sinuses self treat. If popular remedies such as hot lemon preparations are reclassified as prescription only, general practitioners would see a sharp increase in patients with cold and flu. “If just a third of people who currently self medicate were to go to the GP, each GP would have an additional 389 patient visits a year and it would cost the NHS £350m,” according to the association.

However, the BMA says that making the products prescription only would not deprive consumers of over the counter remedies for coughs and colds, pointing to “safer” alternative drugs such as phenylephrine. A BMA spokesman said: “Any change in the status of these drugs will need to involve a publicity campaign that encourages patients to discuss the alternatives with their pharmacy.”

The move to control pseudoephedrine remedies has garnered lots of headlines in the UK, such as “Lemsip turned into a club drug” (Sunday Times, 25 March) and “The Cold War” (Mirror, 26 March 2007). Newspapers have been taking an interest in crystal meth since early 2006, just before it was reclassified from class B to class A. But even then, a BMJ editorial questioned whether the Home Office advisory council had succumbed to a flurry of media reports about the drug’s harms. “Could this be seen as a knee jerk response to a media storm?” questioned Michael Glossop. How proportionate this latest assault will be remains to be seen.

Rebecca Coombes is a journalist, London rcroombes@bmigroup.com

Competing interests: None declared.

See editorial, p 1176

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Crystal meth has been blamed for a rise in HIV among New York’s gay community

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Faith based health policy: the urge to privatise

Who owns health systems matters less than that the various enterprises are on a level playing field

Privatising publicly owned and operated enterprises in health systems has become a new fashion in health policy. The movement is based on the credo (and a pure credo it is) that the management of anything by investor owned, private enterprise is by that very fact more efficient than management of the same activity by publicly owned enterprise. Like most credos—such as the belief in the Virgin Birth—this one lacks robust empirical support; but it matters little. The believers march on undaunted and have been successful in spreading the faith.

One illustration is the firm belief of President Bush and his supporters in Congress that the long term fiscal sustainability of the hitherto government run Medicare programme for elderly people in the United States can be assured only by entrusting that programme to private health insurance plans. On the basis of that credo, they wrote into the Medicare Modernization Act of 2003 a provision under which US tax payers must now pay private health plans an average of 12% more for enrolling a Medicare beneficiary than it would have cost under the traditional, government run Medicare programme. In such systems it is on this facet of health care—only if that energy and that ingenuity are constrained to that end by identical rules and payment levels—both forms of health care facility will be forced into similar behaviour. In fact, in such systems it may be desirable to have different ownership models compete with one another over clinical quality and patients’ satisfaction.

By contrast, in a market driven health system in which both healthcare delivery and health insurance are entrusted to the hands of investor owned enterprises, people’s socioeconomic and health status will inevitably influence their healthcare experience. A distinguished literature in economics shows that private health insurers competing in an unregulated market will inexorably segment their clientele into risk classes, with prospectively sicker people being charged much higher, “actuarially fair” insurance premiums than prospectively healthier people. As has been shown in the United States for over half a century now, such a system will also leave a large segment of the population without the benefits of health insurance.

Forthright economists agree with the late Milton Friedman’s dictum that the proper goal of investor owned, private enterprise is to run the affairs of the firm so as to maximise the owner’s wealth, without breaking the laws of the land. The stock market in general, and private equity buyout firms in particular, make sure that managers pursue that singular goal with utter devotion. But their energy and ingenuity will also serve society’s larger goals—such as a particular distributive ethic in health care—only if that energy and that ingenuity are constrained to that end by appropriate laws, rules, and payment systems. It is on this facet of health systems that the critics of privatisation should focus their scrutiny, rather than on patterns of ownership themselves.

Uwe E Reinhardt is James Madison professor of political economy, Princeton University, Princeton, NJ, United States
reinhard@princeton.edu
**OBSERVATIONS**

**MEDICINE AND THE MEDIA**

**The dangers of triage by television**

The much criticised “win a kidney” game show may have turned out to be a hoax that was later hailed as a “fantastic stunt,” but that still doesn’t justify it, write Inez de Beaufort and Frans Meulenberg

“Shameful,” “Disgusting,” and “An idea so sickening: it must stem from Holland”—these were some of the headlines on 25 May, the day the Netherlands’ BNN Broadcasting Company announced its Big Donor Show. The idea of the programme was that a terminally ill woman, 36 year old Lisa, would talk live in the studio with three pre-selected young patients, all in need of a kidney. Then she would choose which of them would receive her kidney before her death. Viewers would be able to advise her via SMS messages.

Predictably, news of the show provoked a worldwide storm of moral disgust: “Outcry over TV kidney competition,” reported the BBC, while the New Zealand Herald referred to “Organ Idols.” When the programme was broadcast on 1 June, 1.2 million people tuned in, 23,000 “voted,” and 50,000 people downloaded or ordered a donor-registration form.

The founder of BNN, one of the Netherlands’ public networks, died from kidney disease in 2002, after two transplants. Defending the show, BNN’s chairman said, “We know that this programme is super-controversial and . . . that some people will find it tasteless, but we think the reality is even more shocking and more tasteless.”

But indignation reigned. The public for the most part (61%, according to a poll) was against the show. The Dutch minister of education, culture, and media, Ronald Plasterk, said he disliked the “competition element.” The transplantation centres stated that the programme makers had not contacted them. The Royal Dutch Medical Association advised doctors not to cooperate, saying, “People’s sufferings should not be the topic of an amusement show.” The Kidney Foundation reacted cautiously, saying the programme makers “encourage initiatives that lead to more discussion on organ donation . . . but the format—a show programme—would very certainly not be our choice.”

Only a few hours before the broadcast, Dutch prime minister Jan-Peter Balkenende expressed his regret and worries about “the Dutch image abroad.”

**Background**

In the Netherlands, which has a voluntary registration system for postmortem donation, people can register as donors, they can refuse donation, or they can register for others to decide on their behalf. Out of a population of 12 million adults, 2.8 million people are registered as potential organ donors.

Every year hundreds of people die because of the lack of an organ. On 1 May 2007, 1049 people were on the waiting list for a kidney from a postmortem donor; 151 were on the list for a liver and 144 for a lung transplant. However, in 2006 only 360 kidneys, 83 livers, and 52 lungs became available from deceased donors; 274 kidneys were given by living donors. One in three people on the waiting list dies without having had a transplant. Besides a declining willingness to donate, there is also the problem of family members who refuse donation when the deceased has left the decision to them or made no arrangements on the matter (280 refusals out of 398). Several government campaigns to increase the number of organ donors have not resulted in the availability of enough organs.

**What are important arguments in the debate?**

There is no law against bad taste and the notion of impropriety is notoriously difficult to pin down. But impropriety has to do with witnessing private moments that are “none of your business” (for example, to publish the pictures of Princess Diana after her road crash), and with people publicly being put in embarrassing or humiliating situations.

Pleading for yourself publicly in a matter of life and death is degrading. To be manoeuvred into such a position implies deep desperation and an ensuing willingness to do anything, including advertising one’s personality to a sensation-greedy public. But as the candidates in The Big Donor Show autonomously agreed to participate, doesn’t that “undo” the impropriety? People can compete for the oddest goals and in the oddest situations on television, so why not for a kidney? Don’t desperate situations justify desperate measures, as the argument of BNN ran? No. One could still argue that people shouldn’t be put into this situation and they should be protected against such an exhibition. Not only was the dignity of the candidates at stake, but also that of the audience. Was this not a modern version of the freak show, rejoicing in the circus of the needy? Impropriety attracts attention.

**Nothing personal?**

The show also thrived on the idea that people enjoy having power over others, even in life or death, and love to decide the fate of their fellow men. As the public (23000 of them) sent messages naming their preferred candidate, all too eager to assist Lisa in her God-like role, they apparently knew who deserved the kidney.

Of course we all pass judgments on each other. But in the realm of medical scarcity, allocation criteria should be relevant for the treatment in question, and public popularity based on “X factor” charm and eloquence is unrelated to the need for a transplant. There are unattractive, uninteresting people with no media X factor desperately needing a transplant. They should have equal access and be able to trust the fairness of the allocating system. Not to have a transplant because of bad luck, or the bitter arbitrariness of fate, is hard to cope with, but it is even more cruel to be rejected because the public inquisition weighed you and found you wanting.

**The slippery slope**

If the selection for kidneys can be turned into a spectacle, where does it end? Will there be an increasing industry of shows, games, and lotteries to perform triage for scarce medical resources? Who is the best mother whose baby deserves to be on the ventilator? Who wins a bone marrow transplant for his child? “Temp-
MEDICINE AND THE MEDIA

Fainting schoolgirls wipe $1bn off market value of Gardasil firm
Simon Chapman and Ross MacKenzie

On 22 May news broke that 25 girls at a Catholic high school in Melbourne who had just had their first injection of Gardasil, the vaccine against human papillomavirus (HPV), presented to the school’s sick bay with symptoms that included headache, nausea, and dizziness. CSL, the vaccine’s Australian developer, reports that four pupils were sent to hospital for further examination. It said, “One had chest pain and palpitations; she had a past history of these symptoms. She was discharged the same day. The second had hyperventilation paraesthesiae and was sent home the same day. The third and fourth had neurological symptoms and were admitted. The fourth girl had reported progressive muscular weakness. Overnight both got better and were seen by the neurologist in the morning who diagnosed non-organic illness.”

Other than the mother of one girl, who dismissed suggestions of the episode’s psychogenic origin as “absolute rubbish” during a television interview, no one has since disputed this summary. The Royal Melbourne Institute of Technology’s Stephen Downes argued in the Australian online media service Citkey that the incident indicated “mass sociogenic illness” (www.citkey.com.au, 28 May, “Gardasil, nausea and the power of the mind”), the medical euphemism for mass hysteria, whereby contagion transmits by “line of sight,” rumour, and anxiety (Drug Safety 2003;26:599-604).

As news coverage of the incident took off (24 reports in Australian national and state capital newspapers between 23 and 31 May and eight television reports), the stock price of CSL, which had unalteringly doubled in a year, began to dive—from $A496.67 (£41; €60; $81) to $A87.31 by 1 June), wiping an estimated $A1bn off the company’s market capital. The swift market reaction was possibly boosted by publicity of claims on a US “you can’t trust government” website, Judicial Watch, that Gardasil was implicated in three deaths in the United States (www.judicialwatch.org/6299.shtml). A quotation in the article from the president of Judicial Watch set the tone: “The FDA [US Food and Drug Administration] adverse event reports on the HPV vaccine read like a catalog of horrors.” However, the FDA’s reports on two of the three cases found that significant pre-existing health problems were relevant in each death (www.judicialwatch.org/archive/2007/GardasilIVAERSDeaths.pdf). The report on the third death, that of a female patient of unknown age who died from thrombosis allegedly “three hours after being vaccinated,” contained the clarification that the patient had not been vaccinated by the reporting agency. Investigations into whether she had in fact ever been vaccinated continue.

Sombre television reports in Australia repeatedly recycled the same footage of a Melbourne girl who was said variously to have “totally collapsed,” been “temporarily paralysed,” had her “legs and arms paralysed,” or had been “left paralysed for six hours.” The rapidly recovered girl’s claim on national television that her classmates had been “dropping like flies” was repeated in four bulletins. Medical and government authorities who were interviewed consistently explained the incidents as commonplace anxiety reactions to vaccination.

Gardasil has attracted opposition from extreme elements on the religious right, who argue that it might encourage adolescent sex, and a number of Australian schools have refused to administer the vaccination (www.news.com.au/dailytelegraph, 23 May, “Promiscuity fears killing a lifesaver”). Christian promoters of the “virginity pledge” have been joined in their opposition by the ever vigilant antivaccination lobby, which opportunistically opposes all vaccines, and by a self declared feminist duo comprising an anti-abortionist and a founder of the now defunct Feminist International Network of Resistance to Reproductive and Genetic Engineering, whose opinion piece in the Melbourne Age referred readers to the official sounding United States National Vaccine Information Center, a citadel of antivaccinationist advocacy (www.theage.com.au, 25 May, “Why are we experimenting with drugs on girls?”).

Interest groups with a variety of agendas can amplify trivial incidents into major news stories (Epidemiologic Reviews 2003;27:107-14), undermining public confidence in vaccines, diverting the efforts of public health authorities, bringing about serious share market reactions, and, occasionally, resulting in confused or risk averse local government and educational authorities suspending their support. In the field of tobacco control the tobacco industry’s highly orchestrated public efforts over decades to dissemble the risk of smoking (BMJ 2000;321:371-4) has now virtually disappeared, thanks to major efforts at exposing and discrediting this “vector” for public disinformation. Public health officials would do well to give the same sort of serious attention to researching the nature of the anti-immunisation “vector” for disrupting national vaccination campaigns (Australian and New Zealand Journal of Public Health 1998;22:17-26).

Simon Chapman is professor of public health and Ross MacKenzie is research officer, School of Public Health, University of Sydney
sc@med.usyd.edu.au

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See News, p 1182

The apothecosis

Just as Lisa was about to reveal who would get her kidney, the host of the show stopped her and revealed that “Lisa” was Leonie, an actress in perfect health and not donating a kidney. The three candidates were real patients who had known all along that this was a stunt. The aim of the programme was to draw attention to the scarcity of organs.

So, the controversial “show” was a hoax, a publicity campaign. Immediately after the show Minister Plasterk said that it was “a fantastic stunt.” But is it? Three mechanisms proved to be effective: the medium of television, the personification of the problem, plus the sense of moral outrage. Evoking the latter was especially impressive. But the show’s long term effect remains to be seen. Will more people register? Will they donate as living donors? According to one newspaper, six people volunteered as living donors right after the show. But the programme could have the opposite effect: people could feel they were fooled, and turn their back on the issue of organ donation. Certainly BNN stressed the need to keep the scarcity of organs high on the political agenda.

We wonder: those who watched the programme and felt a preference for one of the candidates: are they ashamed? We were (and we watched only for the purposes of writing this article).

Inez de Beaufort is professor of health care ethics and Frans Meulenberg is a science writer and research associate, Department of Medical Ethics and Philosophy of Medicine, Erasmus MC/University Medical Center Rotterdam ldebeaufort@erasmusmc.nl

Slippery slope arguments must be used with caution. One has to argue why a slope would indeed be slippery and why it would be a realistic scenario. In this case the argument seems convincing: the fact that so many people watched and participated in the “voting” is telling and worrying.
Should genetic information be disclosed to insurers?

Søren Holm professor, Centre for Ethics, Law and Society, Cardiff Law School, Cardiff CF10 3AX and Section for Medical Ethics, University of Oslo, Oslo holms@cardiff.ac.uk

YES

The main argument for disclosing genetic information to insurers is that there are no good reasons for not disclosing it. If we accept that life or health insurers can legitimately seek and obtain other kinds of health information that predicts insurance risk, then we should also accept that they can seek genetic information that is predictive in the same way. There is no reason for treating genetic information differently.

What is the purpose of insurance?

The main purpose of life or health insurance is to spread the costs of expensive but unpredictable events across the pool of the insured, thereby converting a possibly catastrophic loss to a predictable regular expenditure. The actuarily fair price is the price that adequately reflects my risk plus the administration costs. This is, for instance, the reason that the price of car insurance reflects the value and type of the car, the age and sex of the driver, and the postcode of the owner, since all of these predict the chance of theft or damage and the cost of the potential loss.

In life insurance the actuarily fair price is the price that accurately reflects my likelihood of dying within the insured period and the amount I am insured for. Because my personal risk cannot be estimated with precision, insurers set premiums for groups of people with broadly similar risks.

If we choose to have such a system, or a hybrid system where you can get basic insurance without surrendering any health information but have to give this information for more extensive policies (along the lines of the current UK policy on genetic information1), we choose it not because health information is special but because we think that justice or solidarity demands risk sharing between healthy and unhealthy people.

However, we allow insurers to obtain some kinds of health information (body mass index, cholesterol concentration, results of a physical examination, etc) we no longer have any principled reasons for excluding genetic information. Genetic information is not special. It is not inherently more specific, predictive, sensitive, or private than other kinds of health information.

It is also extremely difficult to define what counts as genetic information. Genetic information can be obtained without anything we would usually classify as a genetic test (is taking a family history a genetic test?). The most common genetic test is probably routine blood typing in hospitals, but does that mean that knowledge of my blood type is one of the pieces of knowledge that an insurer may not seek?

We may have good reasons to allow insurers access only to information that is properly validated and for which there is sufficient evidence that it predicts risk, but this is again a consideration that applies across the whole range of health information. It is true that many so called genetic risk factors are not well validated, but the same is true of other risk factors measured by non-genetic means.

Genetic information is not special. It is not inherently more specific, predictive, sensitive, or private than other kinds of health information.

What information should insurers be allowed?

We could have a system for life and health insurance that denied insurers access to any kind of health information. This would mean that they could differentiate premiums only according to very general risk markers (age, sex, place of residence, occupation, etc). If we think that life or health insurance is a basic social good that is essential for citizens in modern societies, such a system is attractive. It will mean that healthy people subsidise unhealthy people, but that may be acceptable as an expression of social solidarity or equality.

Other considerations

It is often argued that if we allow insurers access to genetic information it will deter people from having genetic tests that are relevant to their health care. This may well be true, but the same is true for other health information (similar discussions were had about HIV testing) and it does not provide a reason to treat genetic information differently.

Another worry is that insurers may not interpret genetic information correctly and deny people insurance or levy inappropriate premiums based on faulty calculations of risk.³ This is again an obvious risk but is no reason to single out genetic information. Genetic information is not more inferentially fertile than any other kind of information and not more liable to misinterpretation. Again the earlier debates about HIV are instructive. It was claimed, probably correctly, that residence as a single man in certain areas of major cities was interpreted as a risk factor for homosexuality and HIV infection. Even if the only information we allowed insurers was the name of the person seeking insurance, surely a rather restrictive requirement, sound (but not necessarily true) probabilistic inferences could be made concerning age, sex, ethnicity, social status, etc.³ Because so many kinds of information can be interpreted wrongly or in discriminatory ways a better solution to the problem is to allow people to challenge decisions to deny coverage for life or health insurance, forcing insurers to make their reasoning transparent.

References are in the full version on bmj.com

Competing interests None declared.
UK insurers have said that they may seek approval to use the results of genetic tests for cancer from next year. Søren Holm believes they should have to pass the results on to insurance companies, but Richard Ashcroft argues that the risks of disclosure justify privacy in most cases.
Formula estimation of glomerular filtration rate: have we gone wrong?

Paul D Giles and David A Fitzmaurice argue that the introduction of estimated glomerular filtration rate to screen for chronic kidney disease in primary care will lead to pressure on specialist services and create patient anxiety without clear proof of benefit.

Chronic kidney disease is a public health problem worldwide. The estimated prevalence of established renal failure is around 1400 per million in the United States and more than 600 per million in the United Kingdom. Patients with chronic kidney disease have increased risk of cardiovascular disease. A test that reliably detects early kidney disease could help minimise cardiovascular disease and renal failure.

Estimating glomerular filtration rate

The best known function of the kidneys is plasma filtration—measured by the glomerular filtration rate (GFR). Many of the kidney’s functions are related to GFR (box 1). Inulin clearance and modern isotopic methods are not practical for measuring GFR in routine practice. Creatinine based tests are used instead but have several disadvantages. Creatinine clearance involves timed urine collection and is prone to error. Measuring serum creatinine is easier but this test cannot detect early kidney disease. Routine reporting of estimated GFR using formulas based on serum creatinine concentration plus age, sex, and racial group was first advocated in the US and has now been recommended in many other countries.

In the UK the second part of the national service framework for renal services, published in 2005, required clinical biochemistry laboratories to develop automatic reporting of formula based GFR estimates. In 2006 the quality and outcomes framework asked primary care to establish registers of patients with estimated GFR worse than 60 ml/min/1.73 m² (chronic kidney disease stages 3-5 in the international classification; table). Many registers have been populated using computer programs that find serum creatinine results in general practitioners’ information systems and then calculate estimated GFR using the “four variable version of the modification of diet in renal disease” (MDRD) formula (box 2).

Labelling patients as having chronic kidney disease in this way has caused controversy. We challenge some of the applications of GFR estimated from this formula.

Clinical indications for assessing glomerular function

Glomerular function is assessed for three different reasons, which have an important bearing on the qualities required of the test.

Detecting changes in renal function over time

A test to monitor change in renal function over time in individual patients will need to be reproducible. Serial serum creatinine measurements are useful in this context because they are analytically precise and vary little over time in patients with stable disease, although meat rich meals and other non-renal factors can interfere. Because formula estimated GFR is a mathematical transformation of serum creatinine that takes into account three factors that have no measurement error and that do not change (sex and ethnic group) or change slowly (age), it is just as sensitive as serum creatinine at detecting change over time. It does not, however, provide a more reliable measure, except in the longer term, as changes in estimated GFR mirror changes in creatinine, and errors in measuring creatinine or interference in serum creatinine by non-renal factors translate into errors in estimated GFR.

Box 1 | Functions of the kidneys related to glomerular filtration rate

- Excretion of nitrogenous waste, sodium, free water, potassium, phosphate, and water soluble medicines (such as digoxin and gentamicin)
- Control of blood pressure
- Acid-base balance
- Secretion of erythropoietin
- Hydroxylation of vitamin D1 (activation)
- Gluconeogenesis in the fasting state
- Catabolism of peptide hormones (including insulin)

Box 2 | Estimating glomerular filtration rate (GFR) using the four variable version of the modification of diet in renal disease equation

GFR (ml/min/1.73 m²)=186×(S_{cr}/88.4)^{-1.154}×\text{age in years}^{-0.203}×0.742\text{ if female}×1.21\text{ if African American}

Where S_{cr} is serum creatinine in μmol/l

Classification of chronic kidney disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal GFR (&gt;90 ml/min/1.73 m²) with other evidence of chronic kidney damage</td>
</tr>
<tr>
<td>2</td>
<td>Mildly impaired GFR (60-89 ml/min/1.73 m²) with other evidence of chronic kidney damage</td>
</tr>
<tr>
<td>3</td>
<td>Moderately impaired GFR (30-59 ml/min/1.73 m²)</td>
</tr>
<tr>
<td>4</td>
<td>Severely impaired GFR (15-29 ml/min/1.73 m²)</td>
</tr>
<tr>
<td>5</td>
<td>Established renal failure (GFR&lt;15 ml/min/1.73 m²)</td>
</tr>
</tbody>
</table>

GFR=glomerular filtration rate
Disease staging in patients with chronic kidney disease

The classification of chronic kidney disease is based on GFR, so a reproducible and accurate method is needed for correct staging. Formula estimates of GFR must agree closely with reference method determinations, not just on average across a tested population but for each individual being tested. In stages 3–5 of disease estimated GFR has no bias against isotopic reference methods, and in plots of the two methods the scatter between individuals decreases as GFR decreases. Estimated GFR is arguably accurate enough to stage patients with known chronic kidney disease with a GFR less than 60 ml/min/1.73 m² (fig 1). Different patients with the same serum concentration of creatinine can have widely divergent degrees of renal impairment, so the formula can clarify loss of function in a way that is not directly apparent from the creatinine concentration itself. As estimated GFR improves, however, the scatter of estimated GFR plotted against reference GFR becomes progressively wider, and some biochemistry departments do not specify actual values for estimated GFRs higher than 60 ml/min/1.73 m². It should be noted that the average serum creatinine concentration in the original MDRD data was around 200 μmol/l, the average GFR was about 40 ml/min/1.73 m² (disease stage 3), and few patients had serum creatinine within the reference range (≤124 μmol/l).

Detecting chronic kidney disease in mixed populations

This is what primary care has been asked to do by creating disease registers on the basis of estimated GFR less than 60 ml/min/1.73 m² and what a laboratory does if it reports estimated GFR with all adult creatinine results. Effectively, a screening test has been introduced without reference to the criteria for screening programmes.

GFR estimates based on the MDRD formula have been implemented in a setting far outside the original evidence base, with no proof of reliability in the new context, and without evaluating the balance of benefit to harm for tested individuals or the use of healthcare resources. This is in stark contrast to the methodical way in which the National Screening Committee assessed and rejected the evidence for urine testing to screen for bladder cancer and glomerulonephritis in 2002 (reconfirmed in 2006). In such a screening situation we need to know the sensitivity and specificity of the test and hence the predictive values of positive and negative tests in the tested population (using the prevalence of the disease in the population where the test is being applied). Here, the value of formula estimated GFR is unclear.

Although estimated GFR reflects the true filtration rate in patients with chronic kidney disease, several studies have shown that formula estimated GFR underestimates renal function in people without known kidney disease. This problem is compounded by enormous variation between individuals, and this unpredictable scatter gets worse as GFR increases (fig 1). These effects increase the overlap in estimated GFR values when testing patients with and without chronic kidney disease and significantly compromise the ability of estimated GFR to separate these two patient groups.

The risk of many false positives occurring is high. False positives are acceptable in screening tests if simple confirmatory tests can distinguish between true and false positives, and if patients are unharmed while the uncertainty is resolved. The problem here is that the follow-up “test” may be referral to a renal clinic (a precious resource in limited supply); also, patients may be entered on a kidney disease register, which may result in their having difficulty getting life insurance and being prescribed drugs (including angiotensin converting enzyme inhibitors) on the basis of an inadequate test. Primary care clinicians realise this and may not label people as having chronic kidney disease even when estimated GFR values are below 60 ml/min/1.73 m².

Analytical considerations

Numerous versions of the traditional method of determining creatinine concentrations (Jaffe chemistry) exist as well as more specific enzymatic methods. There are analytical differences between these techniques and a lack of standardisation. Figure 2 shows a scatter plot of estimated GFR against GFR measured by an isotopic reference method in people with normal serum concentrations of creatinine. Two estimated GFR values were calculated for each patient—one using the Jaffe chemistry and one using results of an enzymatic assay. The MDRD formula underestimated GFR for both creatinine assays, but more so for the Jaffe related results (about 27%) than those based on the enzymatic assay (about 10%).

Laboratories should obviously try to minimise variations between creatinine methods, but even if all analytical problems were resolved concerns remain...
Creatinine is a fundamentally flawed filtration marker, as too many non-renal factors affect its concentration in serum; we need a more reliable indicator of early loss of GFR. In the meantime, the uncritical introduction of estimated GFR in biochemistry laboratories and in primary care in adults with normal serum creatinine and no other indication of renal disease lacks a good scientific basis; it will lead to pressure on specialist services and create patient anxiety without clear proof of benefit.

**Summary Points**

Estimated glomerular filtration rate (GFR) has come into widespread use as a result of the recent UK recommendations. Estimated GFR is useful for staging progress in patients with established kidney disease but collection of blood samples and creatinine assays should be standardised. The use of estimated GFR to screen for chronic kidney disease in primary care needs careful evaluation.

**Fig 2:** Scatter plot of estimated GFR against isotopic reference GFR in subjects with normal serum creatinine using two different creatinine assays (enzymatic and Jaffe methods).

Formula calculations underestimate GFR for both assays. The negative bias is less with the enzymatic assay, but the scatter of results is wide with both methods. Adapted from Verhave et al. about using estimated GFR in patients with lower serum creatinine concentrations. Even within one enzymatic method, one study showed a significant overall negative bias and substantial interindividual scatter of results—an estimated GFR at the threshold value of 60 ml/min/1.73 m² could correspond to a reference method GFR between about 40 ml/min/1.73 m² and more than 100 ml/min/1.73 m².

**Conclusion**

In some patients, the glomerular filtration rate may be half that seen in healthy people before serum creatinine rises above the population reference interval. Because serum creatinine is so insensitive for detecting early loss of renal function, it is tempting to suppose that estimated GFR is a better measurement. But this is not true.

Our view is that estimated GFR is useful for staging disease in patients with stage 3-5 chronic kidney disease, and many nephrologists use estimated GFR and serum creatinine to monitor progress in such patients. To make estimated GFR more reliable laboratories should work towards greater uniformity in the assay of serum creatinine, and sample collection should be standardised to minimise the impact of non-renal factors (such as meat intake) on serum creatinine results. Serial measurements of serum creatinine and estimated GFR in individual patients may help clinicians detect changes in renal function even when serum creatinine remains in the population reference interval.

However, none of these initiatives will overcome the underlying weak association between estimated GFR and GFR measured by reference methods in people with normal or near normal renal function. Creatinine is a fundamentally flawed filtration marker, as too many non-renal factors affect its concentration in serum; we need a more reliable indicator of early loss of GFR. In the meantime, the uncritical introduction of estimated GFR in biochemistry laboratories and in primary care in adults with normal serum creatinine and no other indication of renal disease lacks a good scientific basis; it will lead to pressure on specialist services and create patient anxiety without clear proof of benefit.

**References**

At what age can schoolchildren provide effective chest compressions? An observational study from the Heartstart UK schools training programme

Ian Jones, research officer,1 Richard Whitfield, R & D lead officer,1 Michael Colquhoun, senior lecturer in prehospital care,2 Douglas Chamberlain, honorary professor of resuscitation medicine,2 Norman Vetter, reader in public health and epidemiology,3 Robert Newcombe professor of medical statistics3

ABSTRACT
Objective To determine at what age children can perform effective chest compressions for cardiopulmonary resuscitation.

Design Observational study.

Setting Four schools in Cardiff.

Participants 157 children aged 9-14 years in three school year groups (ages 9-10, 11-12, and 13-14).

Interventions Participants were taught basic life support skills in one lesson lasting 20 minutes.

Main outcome measure Effectiveness of chest compression during three minutes’ continuous chest compression on a manikin.

Results No year 5 pupil (age 9-10) was able to compress the manikin’s chest to the depth recommended in guidelines (38-51 mm). 19% of pupils in year 7 (age 11-12) and 45% in year 9 (age 13-14) achieved adequate compression depth. Only the 13-14 year olds performed chest compression as well as adults in other reported studies. Compression depth showed a significant relation with children’s age, weight, and height (P<0.001). Multivariate analyses showed that, if the age and weight of the children were both known, the height (which is closely related to both) was no longer significant (P=0.95). No association was found between pupils’ age, sex, weight, or height and the average rate of chest compressions over the three minute period. Similarly, no relation was found between year group and ability to place the hands in the correct position. During the three minutes’ compression, compression rate increased and depth decreased.

Conclusions The children’s ability to achieve an adequate depth of chest compression depended on their age and weight. The ability to provide the correct rate and to employ the correct hand position was similar across all the age ranges tested. Young children who are not yet physically able to compress the chest can learn the principles of chest compression as well as older children.

INTRODUCTION
Resuscitation skills should be learnt at school,1,2 since children are easily motivated, learn quickly, and retain skills.3 After pioneering work in Norway, such training has been introduced in several countries.5,8 Skills are introduced successively according to children’s cognitive and psychomotor development. In the United Kingdom a national syllabus and training programme, developed by the British Heart Foundation through “Heartstart UK,” introduces chest compression to schoolchildren at 11 years of age.

Studies of skill acquisition have concentrated on older children.3,4,9 No study reports when children are capable of the more physically demanding tasks, particularly chest compression. Recommended ages vary from 9 to 13.8 This study investigated when children can provide effective chest compressions.

PARTICIPANTS AND METHODS
Participants
We recruited schoolchildren in year groups 5 (9-10 years old), 7 (11-12 years), and 9 (13-14 years) from four schools in Cardiff that had expressed interest in the Heartstart UK programme. The study was explained to parent and teacher groups, written consent being obtained from all parents and verbal consent from participating children. Children’s weight, height, sex, and date of birth were recorded.

Training
Chest compressions were taught on a Laerdal Little Anne training manikin according to Heartstart UK schools training programme level 3 skill card 7a.10 Each child attended one training session lasting 20 minutes and was assessed within one hour of being trained. Each class consisted of four pupils and an instructor, with each pupil and the instructor having an individual training manikin.

Skills assessment
Children performed continuous chest compressions on a Laerdal Resusci Anne SkillReporter manikin for three minutes. The time remaining was announced every 30 seconds; no other audio or visual feedback was provided during the assessment.

Compression rate and depth and percentage with correct hand position were recorded with Laerdal PC...
Pupils

§

‡

†

* A bias of 31 girls to 23 boys in Year 7 did not influence analysis.

† No statistical relation to age (b=1.6 per year (95% CI -1.1 to 4.3)), P=0.233.

§ Significant relation to age (b=3.2 per year (95% CI 2.4 to 4.0)), P=0.001.

Fig 1 | Proportions of children in each school year group correctly performing chest compressions in terms of compression rate (90-110/min) and depth (38-51 mm) and correct hand positions for 80-100% of compressions

SkillReporter software version 2.0. The software produced averages for compression rate and depth for the three minute assessment, and averages for each minute were calculated with software tools. Correct compression depth and rate were defined as 38-51 mm and 90-110 per minute.

Statistical analysis

To investigate associations between variables, we used parametric (Pearson) correlations, bivariate and multivariate linear regression, t-tests, and χ² tests.

The power calculation was based on a median of 82 satisfactory chest compressions (interquartile range 55-100) that had been achieved by adults on similar manikins. Applying this average to the mean rate 100 per minute. However, multivariate analyses showed that, once hand position was achieved by 40% of pupils in year 5, 22% in year 7, and 31% in year 9. For 80-100% correct, the corresponding figures were 58%, 46%, and 52%.

DISCUSSION

None of the children aged 9-10 years and only 19% of those aged 11-12 were strong enough to compress the chest to an adequate depth in simulated cardiopulmonary resuscitation on an adult size manikin. However, 45% of those aged 13-14 provided adequate compression depth, a similar success rate to that of children aged 11-12.
WHAT IS ALREADY KNOWN ON THIS TOPIC

Bystander cardiopulmonary resuscitation at least doubles the chances of survival. Chest compressions receive increased prominence in current resuscitation guidelines. Schoolchildren are widely taught resuscitation techniques, but the age when they can perform effective chest compressions is unknown.

WHAT THIS STUDY ADDS

Children aged 13-14 performed compressions as well as adults in comparable studies. Although younger children were not strong enough to compress the chest sufficiently, they learnt the theory of the technique just as well as older children achieved by adults tested in comparable studies. Current recommendations to teach full, single rescuer cardiopulmonary resuscitation at age 13-14 are therefore appropriate.

Comparison with other studies

Previous studies in schoolchildren have tested factual knowledge with questionnaires and assessed practical skills with manikins. Studies assessing practical ability have concentrated on older children and teenagers. Few assessed performance of chest compressions, concentrating instead on airway and breathing skills. Van Kerschaver assessed hand position and compression rate in children aged 12 years and older but did not report compression depth. Lester reported that children aged 11-12 often failed to compress the chest adequately, but did not report quantitative data.

Compression depth declined in successive minutes, as in some adult studies, which have shown a decline in compression quality with time.

Limitations of study

A manikin may offer greater or lesser resistance than a real casualty. Emotional factors in real life resuscitation may also affect performance. Quality of compression beyond three minutes was not assessed. Compressions given in cycles alternating with rescue breaths might be less accurate than continuous compressions.

Conclusions

In our study, children aged 9-10 years used the correct hand position and same compression rate as older children. Although they were not able to compress the chest sufficiently, they learnt the methods of performing chest compression as well as the older children. Teaching younger children provides knowledge for when they are adequately developed. They might also advise an adult or perform adequately on a chest more compliant than that of the manikin. By starting training young, revision is possible at school, with the prospect of greater skill attainment and retention.

We thank the pupils and staff of Cardiff High School, Oakfield Primary School, Radyr Comprehensive School, and Ton-Yr-Ywen Primary School for their enthusiastic participation. We thank Richard Davies, chief education officer, Welsh Assembly Government, for his advice during the planning of this study. We thank Laerdal Medical for its support and advice and for the loan of a Laerdal Resusci Anne SkillReporter System. Lastly we thank those staff of the Welsh Ambulance Service who helped at all stages of the study.

Contributors: MC had the idea for the project and acts as guarantor. All authors contributed to the design of the project. L and RW carried out the study and collected the data. Data processing was by IL and RN. L and MC wrote the first drafts of the paper, all authors contributed to the final version.

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Competing interests: None declared.

Ethical approval: Dyfed Powsy Local Research Ethics Committee approved the study.

Interventions to promote walking: systematic review

David Ogilvie, MRC fellow,1 Charles E Foster, senior researcher,2 Helen Rothnie, research associate,3 Nick Cavill, research associate,2 Val Hamilton, research assistant,4 Claire FitSimons, SPARColl project coordinator,3 Nanette Mutrie, professor of exercise and sport psychology,3 on behalf of the Scottish Physical Activity Research Collaboration (SPARColl)

ABSTRACT

Objective To assess the effects of interventions to promote walking in individuals and populations.

Design Systematic review.

Data sources Published and unpublished reports in any language identified by searching 25 electronic databases, by searching websites, reference lists, and existing systematic reviews, and by contacting experts.

Review methods Systematic search for and appraisal of controlled before and after studies of the effects of any type of intervention on how much people walk, the distribution of effects on walking between social groups, and any associated effects on overall physical activity, fitness, risk factors for disease, health, and wellbeing.

Results We included 19 randomised controlled trials and 29 non-randomised controlled studies. Interventions tailored to people's needs, targeted at the most sedentary or at those most motivated to change, and delivered either at the level of the individual (brief advice, supported use of pedometers, telecommunications) or household (individualised marketing) or through groups, can encourage people to walk more, although the sustainability, generalisability, and clinical benefits of many of these approaches are uncertain. Evidence for the effectiveness of interventions applied to workplaces, schools, communities, or areas typically depends on isolated studies or subgroup analysis.

Conclusions The most successful interventions could increase walking among targeted participants by up to 30-60 minutes a week on average, at least in the short term. From a perspective of improving population health, much of the research currently provides evidence of efficacy rather than effectiveness. Nevertheless, interventions to promote walking could contribute substantially towards increasing the activity levels of the most sedentary.

INTRODUCTION

Physical inactivity increases the risk of many chronic diseases—notably, coronary heart disease, type 2 diabetes, and cancer of the colon. Accumulating 30 minutes of moderate intensity physical activity on most days is enough to provide substantial health benefits,2 but most adults in the United Kingdom do not currently achieve this.34 Increasing the population level of physical activity, particularly among the most sedentary, has therefore become a leading aim of contemporary public health policy.56

Walking has been described as near perfect exercise.7 Even walking at a moderate pace of 5 km/hour (3 miles/hour) expends sufficient energy to meet the definition of moderate intensity physical activity.8 Compared with many sports and other recreational pursuits, walking is a popular, familiar, convenient, and free form of exercise that can be incorporated into everyday life and sustained into old age.9 It is also a carbon neutral mode of transport that has declined in recent decades in parallel with the growth in car use.1 There are therefore compelling reasons to encourage people to walk more, not only to improve their own health but also to address the problems of climate change.10-12

Numerous systematic reviews have examined the effectiveness of interventions to promote physical activity in general,134 but we know of none that has examined how best to promote walking in particular; furthermore, many—including those underpinning recent guidance issued by the National Institute for Health and Clinical Excellence (NICE)—have been restricted to particular types of intervention or study design.7 Walking may be influenced by environmental and societal conditions as well as by interventions targeted at individuals.18 We therefore conducted a systematic review of the best available evidence across all relevant disciplines to determine what characterises interventions effective in promoting walking; who walks more and by how much as a result of effective interventions; and the effects of such interventions on overall physical activity and health.

METHODS

Search strategy

We searched 25 databases for studies of interventions or changes related to walking published from 1990 onwards. We imposed no limits on characteristics of participants, study design, intervention, or language. We also searched a purposive sample of 12 websites as well as reference lists, existing systematic reviews, and our own archives. We then invited an international group of experts to nominate additional primary

**Study selection and inclusion criteria**

We included randomised controlled trials and non-randomised controlled before and after experimental or observational studies of the effects of any type of intervention—including environmental and fiscal, legislative, and other policy interventions—on how much people walk. The effects of the intervention had to be compared with those observed in a “no intervention,” “attention control,” or “minimal intervention” control or comparison group, area, or population. Studies had to report a specific measure of walking (self reported, objective, or both) at both baseline and follow-up. We excluded studies in which the “control” condition consisted of an alternative intervention intended or likely to promote walking and that exceeded “standard” or “usual” care, treatment, or practice, or in which the purpose, setting, and outcome of the intervention were all primarily clinical (see http://sparcoll.org.uk/images/bmj supp.pdf). After obviously irrelevant references had been removed, one of several reviewers assessed all remaining titles and abstracts for inclusion. Another reviewer cross checked all undecided cases, plus a 10% sample of exclusion decisions. Articles obtained in full text were then reassessed for inclusion by one of several reviewers, with a 10% sample of exclusion decisions (other than obviously irrelevant studies) being cross checked by another reviewer and all undecided cases being reviewed by the team in plenary session (fig 1).

**Data extraction and validity assessment**

For each included study, a pair of reviewers extracted data, assessed validity, and verified each other’s work, with any discrepancies being resolved by discussion.

We summarised study validity using seven binary criteria based on those used in previous systematic reviews and applicable across the range of included study designs (tables 1 and 2).17 19 20 We extracted the available outcome measures on walking and the results of statistical tests (95% confidence intervals or P values) where authors reported them, and systematically considered the suitability of the data reported in each study for meta-analysis. We also extracted any available evidence on how effects on walking were distributed between social groups; evidence of effects on overall physical activity, cardiorespiratory fitness, other risk factors for disease, health, and wellbeing; evidence about adverse effects; and data on economic evaluation.

**Data synthesis**

We categorised studies according to the main approach of the intervention studied. We summarised the outcome for each study in terms of the net change in walking after adjustment for changes in the control group, using the most inclusive measure of walking available for each study, and tabulated the key characteristics and outcomes of the studies within each category in descending order of study validity. The types of interventions, study designs, participants, and outcome metrics and the durations of follow-up were too heterogeneous to permit meta-analysis, even within categories of intervention; in addition, many studies did not report confidence intervals so we could not construct a conventional forest plot. By making a set of simplifying assumptions (box), however, we were able to plot the relation between estimated effect size, sample size, and study validity (figs 2 and 3).

**Calculation of a common primary outcome metric**

Studies used a wide range of metrics to quantify the net change in walking in the intervention group compared with the control group. The most promising candidate for a single common metric with which to synthesise the results of all studies was the net change in time spent walking (minutes/week). Some studies reported outcomes using other metrics that we were able to convert to an approximate net change in time spent walking (minutes/week) using the following assumptions: average duration of a “session” of walking=30 minutes"; average distance of a trip in which the main mode of transport was walking=0.7 miles (1.1 km); average walking speed=3 miles/hour (5 km/hour); average step rate=100 steps/minute; 10 trips to and from school/week. Six studies reported outcomes using metrics that could not be expressed in these terms;11 12 13 14 15 16; these are listed in table 1 and 2 but do not appear in figures 2 or 3.

**RESULTS**

We screened 53 491 references and assessed the full text of 441 documents (fig 1). Forty eight studies met our inclusion criteria: 19 randomised controlled trials and 29 non-randomised controlled studies.11 12 14 16 Twenty seven studies were concerned with walking
in general (tables 1, 3, and 4); 21 studies were concerned solely with walking as a mode of transport (tables 2 and 5) (see also http://sparcoll.org.uk/images/bmjsupp.pdf).

Effects of interventions on walking in general

**Brief advice to individuals**—Six studies [1–6] (five randomised controlled trials) reported the effects of brief advice given face to face either in the workplace [1] or by clinicians [2–6] or an exercise specialist [4–5] in primary care. A significant net increase in self reported walking was found in both studies with follow-up periods of up to six weeks [1, 2] but in only two of the four studies with longer follow-up [3–5].

**Remote support to individuals**—Three randomised controlled trials evaluated interventions delivered by telephone or internet; all found a significant net increase in self reported walking [7–9].

**Group based approaches**—Six studies [three randomised controlled trials] evaluated interventions involving various approaches (such as lay mentored meetings, led walks, or educational sessions) delivered in groups [10–16]. The randomised studies [10–13] were more likely to find a significant net increase in self reported walking than the less robust, non-randomised studies [14–16].

**Pedometers**—In seven studies [six randomised controlled trials] pedometers, coupled with various supporting measures, formed a key part of the

### Table 1: Summary validity assessment for included studies on walking in general

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomisation*</th>
<th>Exposure†</th>
<th>Representative-ness‡</th>
<th>Comparability§</th>
<th>Attraction or sample size¶</th>
<th>Period of assessment**</th>
<th>Instrument††</th>
<th>Total criteria met</th>
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*Were participants, groups, or areas randomly allocated to intervention and control status?  †Did authors show both that participants did not receive concurrent intervention that could have differentially influenced walking in intervention and control groups and that control group was not contaminated by receiving part or all of intervention being studied?  ‡Were study samples randomly recruited from study population with response rate of at least 60%, or were they otherwise shown to be representative of study population?  §Were baseline characteristics of intervention and control groups, populations, or areas comparable, or if there were important differences in potential confounders at baseline were these appropriately adjusted for in analysis?  ¶Were outcomes studied in cohort or panel of respondents with attrition rate of less than 30%, or were results based on repeated cross sectional design with minimum achieved sample of at least 100 participants in each wave in both intervention and control groups?  **Was quantity of walking assessed over period of 1 day?  ††Was instrument used to assess walking appropriate to research question(s) of study—that is, capable of measuring outcome under consideration and either shown to be a valid and reliable measure in published research or in pilot study or recognised as acceptable measure—or example, previously used in national physical activity or travel survey?
intervention (or one intervention arm of a more complex trial). 3\textsuperscript{17}-\textsuperscript{24} Three studies, all with follow-up periods of up to three months, found a significant net increase in self reported walking or in step counts\textsuperscript{w17-w20}; the three studies with longer follow-up all found that a significant net increase in step counts after 4-16 weeks was not sustained at 24 weeks\textsuperscript{w22} or 12 months.\textsuperscript{w24}

Community level approaches—Five non-randomised studies of interventions applied to whole geographical communities measured effects in whole populations rather than in those participating directly in an intervention.\textsuperscript{w25-w30} All involved a combination of approaches such as mass media campaigns augmented by community events and other local supportive measures,\textsuperscript{w27 w28 w30} modest environmental improvements,\textsuperscript{w25 w29} formation of walking groups,\textsuperscript{w25 w26 w29} and written materials or brief advice for individuals.\textsuperscript{w23} Three studies found a significant net increase in self reported walking, but one was reported only briefly\textsuperscript{w30} and another had significant methodological limitations\textsuperscript{w29}; the most robust evidence of effectiveness was for an intervention with a substantial mass media component.\textsuperscript{w27 w28}

Effects of interventions on walking as a mode of transport

Targeted or individualised promotion of active travel—One randomised controlled trial of an intervention to promote active commuting to work found a significant net increase in self reported walking.\textsuperscript{w31} Thirteen non-randomised studies of individualised marketing of “environmentally friendly modes” of transport to households\textsuperscript{w32-w50} consistently reported a net increase in the proportion of trips made on foot (usually

Table 2 | Summary validity assessment for included studies on walking as a mode of transport

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomisation*</th>
<th>Exposure†</th>
<th>Representativeness‡</th>
<th>Comparability§</th>
<th>Attrition or sample size¶</th>
<th>Period of assessment**</th>
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*Were participants, groups, or areas randomly allocated to intervention and control status?
†Did authors show both that participants did not receive concurrent intervention that could have differentially influenced walking in intervention and control groups and that control group was not contaminated by receiving part or all of intervention being studied?
‡Were study samples randomly recruited from study population with response rate of at least 60%, or were they otherwise shown to be representative of study population?
§Were baseline characteristics of intervention and control groups, populations or areas comparable, or if there were important differences in potential confounders at baseline were these appropriately adjusted for in analysis? (See also footnote ††.)
¶Were outcomes studied in cohort or panel of respondents with attrition rate of less than 30%, or were results based on repeated cross sectional design with minimum achieved sample of at least 100 participants in each wave in both intervention and control groups?
**Was quantity of walking assessed over period of >1 day?
††Was instrument used to assess walking appropriate to research question(s) of study—that is, capable of measuring outcome under consideration and either shown to be a valid and reliable measure in published research or in pilot study or recognised as acceptable measure—for example, previously used in national physical activity or travel survey?
‡‡Studies met criterion of comparability by indicating that control group was recruited either from same population as intervention group or from neighbouring area chosen for its similarity. They did not show that baseline characteristics of individuals or households in intervention and control groups were similar or adjust for any differences in such characteristics.
measured in the local population as a whole) and an increase in time spent walking in those studies that reported this outcome. The methods of these non-randomised studies, however, were often not clearly described, and only one reported the statistical significance of the observed increase in walking.

School travel initiatives—Three studies evaluated interventions aimed at changing the mode of children’s travel to school. Only one—a small non-randomised trial of an active commuting pack—found a significant net increase in self-reported walking on the school journey.

Miscellaneous transport interventions—We found four other non-randomised studies. A directive that employers should subsidise employees who chose not to commute by car was associated with a significant increase in the proportion walking to work, and a three year multifaceted initiative to promote cycling in a city was associated with a net increase in walking after adjustment for trends in control areas and other confounders. Two less robust studies of a sustainable transport campaign and a car sharing club found no significant effect on walking.

Characteristics of interventions found to be effective
The most convincing evidence of effectiveness was for interventions delivered at the level of the individual or household or through group based approaches. Although no single method of promoting walking emerged as the most effective, and we were not able to reach any conclusions about the relative merits of different types of provider (such as doctor, nurse, exercise specialist) on the effectiveness of interventions, we were able to identify two general characteristics of those interventions found to be effective: targeting and tailoring.

Targeting—Most interventions associated with an increase in walking as a mode of transport were offered only to those individuals or households identified through prior screening as already motivated to change their behaviour. Interventions to promote walking in general were often aimed at target groups such as sedentary people or patients with particular conditions. Many of the interventions found to be effective were targeted at sedentary people; the potential value of such targeting was also shown indirectly by other studies in which significant net increases in walking were observed only in the most sedentary subgroup within the study population. The value of targeting specific clinical populations was less clear. A group based lay mentoring intervention for patients with heart disease was effective, but studies of other approaches (brief advice or pedometers) targeted at patients with diabetes or osteoarthritis did not find them to be effective at final follow-up.

Tailoring—Effective interventions typically involved content tailored to participants’ requirements or circumstances. Such tailoring ranged from the provision of individualised counselling or written materials (for example, tailored to the participant’s position in the transtheoretical model of behaviour change), through inviting households to choose from a menu of information resources and incentives promoting environmentally friendly modes of transport, to the mapping of individual children’s journeys to school.

Magnitude and social distribution of effects on walking
Magnitude of effect—Evidence from the most promising studies suggests that, among targeted participants, successful interventions could increase walking in general by up to 30-60 minutes a week on average; more robust studies were most likely to report significant net increases in walking than less robust studies (fig 2). In the transport sector, successful interventions could increase walking as a mode of transport in the general population by rather less, up to about 15-30 minutes a week on average; this estimate depends on a group of studies that are larger but less robust than the studies of walking in general (fig 3).

Social distribution of effects—In 29 studies, most of the participants were women (see http://sparcoll.org.uk/images/bmjaup.pdf); in three studies, men were
more likely than women to increase their walking.\(^{5,20,29}\) Most (34/48) studies, however, did not report how the effect of interventions on walking varied between demographic or socioeconomic groups (see http://sparcoll.org.uk/images/bmjsupp.pdf).

**Effects on overall physical activity and health**

Twenty studies reported effects on overall measures of physical activity (see http://sparcoll.org.uk/images/bmjsupp.pdf). Of these, seven reported some evidence of a net increase in overall physical activity at final follow-up, but in each of these studies different measures of physical activity gave conflicting results.\(^{9,12,20,24,25,26,29}\) Three of the studies that found a significant net increase in walking also reported effects on cardiorespiratory fitness or functional capacity in terms of maximal oxygen uptake (VO\(\text{Max}\)) or one mile (1.6 km) walking time in sedentary women or adolescent girls.

### Table 3 Effects of interventions at individual or group level on walking in general

<table>
<thead>
<tr>
<th>Study</th>
<th>How delivered or supported</th>
<th>Study population</th>
<th>Ages</th>
<th>Location</th>
<th>Sample size</th>
<th>Follow-up</th>
<th>Random allocation</th>
<th>Validity(^*)</th>
<th>Reported net effect†</th>
<th>Min/week‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purath(^{11})</td>
<td>Nurse</td>
<td>Sedentary female university employees</td>
<td>18-65</td>
<td>USA</td>
<td>271</td>
<td>6 weeks</td>
<td>Yes</td>
<td>7</td>
<td>+26.9 min/week (P&lt;0.001)</td>
<td>+27</td>
</tr>
<tr>
<td>Calfas(^{12})</td>
<td>Doctor or nurse</td>
<td>Sedentary</td>
<td>≥18</td>
<td>USA</td>
<td>212</td>
<td>4-6 weeks</td>
<td>—</td>
<td>6</td>
<td>+13 min/week (P=0.025)</td>
<td>+13</td>
</tr>
<tr>
<td>Kerse(^{13})</td>
<td>General practitioner</td>
<td>Community dwelling</td>
<td>≥65</td>
<td>Australia</td>
<td>267</td>
<td>12 months</td>
<td>Yes</td>
<td>6</td>
<td>+88 min/fortnight (95% CI 8 to 168)</td>
<td>+44</td>
</tr>
<tr>
<td>Halbert A(^{14})</td>
<td>Exercise specialist</td>
<td>Sedentary</td>
<td>≥60</td>
<td>Australia</td>
<td>274</td>
<td>12 months</td>
<td>Yes</td>
<td>5</td>
<td>+1 session/week (P&lt;0.03)</td>
<td>+30</td>
</tr>
<tr>
<td>Halbert B(^{15}) (subtrial of A)</td>
<td>Exercise specialist</td>
<td>Sedentary with osteoarthritis</td>
<td>≥60</td>
<td>Australia</td>
<td>69</td>
<td>12 months</td>
<td>Yes</td>
<td>5</td>
<td>+0 session/wk (NS)</td>
<td>0</td>
</tr>
<tr>
<td>Norris(^{16})</td>
<td>Doctor</td>
<td>Workplace HMO enrollees</td>
<td>≥30</td>
<td>USA</td>
<td>822</td>
<td>6 months</td>
<td>Yes</td>
<td>5</td>
<td>+0.1 min/week (P=0.41)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Remote support to individuals**

<table>
<thead>
<tr>
<th>Study</th>
<th>How delivered or supported</th>
<th>Study population</th>
<th>Ages</th>
<th>Location</th>
<th>Sample size</th>
<th>Follow-up</th>
<th>Random allocation</th>
<th>Validity(^*)</th>
<th>Reported net effect†</th>
<th>Min/week‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Napolitano(^{17})</td>
<td>Internet</td>
<td>Low active hospital employees</td>
<td>18-65</td>
<td>USA</td>
<td>52</td>
<td>3 months</td>
<td>Yes</td>
<td>6</td>
<td>+61.69 min/week (P&lt;0.05)</td>
<td>+62</td>
</tr>
<tr>
<td>Jarvis(^{18})</td>
<td>Telephone</td>
<td>Sedentary</td>
<td>≥60</td>
<td>USA</td>
<td>52</td>
<td>3 months</td>
<td>Yes</td>
<td>5</td>
<td>+50 min/week (P=0.02)(^$)</td>
<td>+50</td>
</tr>
<tr>
<td>Nies(^{19})</td>
<td>Telephone</td>
<td>Sedentary women</td>
<td>30-60</td>
<td>USA</td>
<td>160</td>
<td>6 months</td>
<td>Yes</td>
<td>5</td>
<td>+4.6 min/day (P&lt;0.01)</td>
<td>+32</td>
</tr>
</tbody>
</table>

**Group based approaches**

<table>
<thead>
<tr>
<th>Study</th>
<th>How delivered or supported</th>
<th>Study population</th>
<th>Ages</th>
<th>Location</th>
<th>Sample size</th>
<th>Follow-up</th>
<th>Random allocation</th>
<th>Validity(^*)</th>
<th>Reported net effect†</th>
<th>Min/week‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coull(^{20})</td>
<td>Lay mentored meetings</td>
<td>With heart disease</td>
<td>≥60</td>
<td>Scotland</td>
<td>289</td>
<td>12 months</td>
<td>Yes</td>
<td>6</td>
<td>+73 min/week (95% CI 137 to 137)</td>
<td>+73</td>
</tr>
<tr>
<td>Fisher(^{21})</td>
<td>Led walking programme</td>
<td>Sedentary</td>
<td>≥65</td>
<td>USA</td>
<td>582</td>
<td>6 months</td>
<td>Yes</td>
<td>5</td>
<td>Effect size 0.20 (P=0.05)</td>
<td>—</td>
</tr>
<tr>
<td>Pereira(^{22}w^{23})</td>
<td>Led walking training</td>
<td>Postmenopausal</td>
<td>50-65</td>
<td>USA</td>
<td>196</td>
<td>10 years</td>
<td>Yes</td>
<td>5</td>
<td>+420 kcal/week (P&lt;0.01) or +7.3 miles/week (SSNR)</td>
<td>+146</td>
</tr>
<tr>
<td>Ferreira(^{24})</td>
<td>Educational sessions</td>
<td>Physically active women</td>
<td>50-72</td>
<td>Brazil</td>
<td>62</td>
<td>12 weeks</td>
<td>—</td>
<td>3</td>
<td>NS change in min/week</td>
<td>0</td>
</tr>
<tr>
<td>Michalowski(^{25})</td>
<td>Educational sessions</td>
<td>Female</td>
<td>28-89 (most &gt;59)</td>
<td>USA</td>
<td>48</td>
<td>4 months</td>
<td>—</td>
<td>3</td>
<td>~0.3 h/week (NS)</td>
<td>-18</td>
</tr>
<tr>
<td>De Kraker(^{26})</td>
<td>Workplace lunchtime walking coordinator</td>
<td>Employees in sedentary jobs</td>
<td>38 (9%</td>
<td>Netherlands</td>
<td>249</td>
<td>12 months</td>
<td>—</td>
<td>1</td>
<td>~0.2 session/fortnight (P=0.67)</td>
<td>-3</td>
</tr>
</tbody>
</table>

**Pedometers**

<table>
<thead>
<tr>
<th>Study</th>
<th>How delivered or supported</th>
<th>Study population</th>
<th>Ages</th>
<th>Location</th>
<th>Sample size</th>
<th>Follow-up</th>
<th>Random allocation</th>
<th>Validity(^*)</th>
<th>Reported net effect†</th>
<th>Min/week‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schofield(^{27})</td>
<td>Group review sessions</td>
<td>Low active girls</td>
<td>15-18</td>
<td>Australia</td>
<td>68</td>
<td>12 weeks</td>
<td>Yes</td>
<td>7</td>
<td>+2591 steps/day (P&lt;0.03)</td>
<td>+181</td>
</tr>
<tr>
<td>Merom(^{28})</td>
<td>Postal support</td>
<td>Inactive</td>
<td>30-65</td>
<td>Australia</td>
<td>369</td>
<td>3 months</td>
<td>Yes</td>
<td>6</td>
<td>+54 min/week (P=0.002)</td>
<td>+54</td>
</tr>
<tr>
<td>Barlotti(^{29}w^{30})</td>
<td>10 000 step goal</td>
<td>On university campus</td>
<td>≥18</td>
<td>USA</td>
<td>67</td>
<td>6 weeks</td>
<td>—</td>
<td>5</td>
<td>+57.5 min/week (P&lt;0.03)</td>
<td>+58</td>
</tr>
<tr>
<td>Croteau(^{31})</td>
<td>Individual review sessions</td>
<td>In assisted-living facility</td>
<td>68-95</td>
<td>USA</td>
<td>15</td>
<td>6 weeks</td>
<td>Yes</td>
<td>5</td>
<td>~1124 steps/week (NS)</td>
<td>-11</td>
</tr>
<tr>
<td>Talbot-Boyes(^{32})</td>
<td>Individual goal setting</td>
<td>With osteoarthritis</td>
<td>≥60</td>
<td>USA</td>
<td>34</td>
<td>24 weeks</td>
<td>Yes</td>
<td>5</td>
<td>+687 steps/day (NS)</td>
<td>+48</td>
</tr>
<tr>
<td>Tudor-Locke(^{33})</td>
<td>Group review sessions</td>
<td>Overweight and sedentary with type 2 diabetes</td>
<td>40-60</td>
<td>Canada</td>
<td>38</td>
<td>24 weeks</td>
<td>Yes</td>
<td>5</td>
<td>+1367 steps/day (P=0.17)</td>
<td>+96</td>
</tr>
<tr>
<td>Baker(^{34})</td>
<td>Graduated goals</td>
<td>On university campus</td>
<td>42 (11%</td>
<td>Scotland</td>
<td>61</td>
<td>12 months</td>
<td>Yes</td>
<td>4</td>
<td>NS change in steps/week</td>
<td>0</td>
</tr>
</tbody>
</table>

HMO=health maintenance organisation; NS=authors reported no significant difference; OR=odds ratio; SSNR=significance not reported.

\(^*\)No of criteria met (maximum 7, see table 1).

†Continuous outcome measure converted to common outcome metric (min/week) when possible. Dash indicates conversion not possible.

\(^\$\)Studied effect size is that observed in most sedentary subgroup, not across whole study population.

\(\ddagger\)Mean (SD) age of sample.
Adverse effects and economic evaluation

Few studies attempted to ascertain adverse effects; none reported adverse effects such as an increase in injuries clearly attributable to an intervention to promote walking. Only six studies included even a rudimentary economic evaluation. We were therefore unable to synthesise any meaningful data with which to compare these aspects of alternative approaches to promoting walking.

DISCUSSION

Principal findings

We found clear evidence that people can be encouraged to walk more by interventions tailored to their needs, targeted at the most sedentary or at those most motivated to change, and delivered either at the level of the individual or household or through group based approaches. The balance of available evidence about interventions applied at the level of the institution (workplace or school), community, or area is less convincing; evidence that these have led to a significant overall increase in walking typically depends on isolated studies or subgroup analysis.

Strengths and weaknesses of the review

The main strength of this review is its comparative inclusivity. We searched widely for evidence in diverse fields, which enabled us to make fair comparisons across the whole range of potential approaches to promoting walking rather than selecting on the basis of study design, length or nature of follow-up, or even ideological or professional preference. We included only studies that specifically reported changes in girls or exercise tolerance in adults with ischaemic heart disease. None found a significant difference between intervention and control groups.

Two of the studies that found a significant net increase in walking also reported effects on other risk factors (anthropometry, resting heart rate, blood pressure, lipid profile, or fasting blood glucose) in specific clinical populations (adults with ischaemic heart disease or type 2 diabetes). Neither found any significant differences between intervention and control groups.

Six of the studies that found a significant net increase in walking also reported effects on self reported health, wellbeing, or quality of life measured with either a generic instrument such as the SF-36 or a more specific symptom or mood score. Three found a significant overall difference between intervention and control groups; two found significant differences, but only on subscales of the SF-36; one found no significant difference.

Study Validity No

<table>
<thead>
<tr>
<th>Study</th>
<th>Validity</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutrie</td>
<td>6</td>
<td>194</td>
</tr>
<tr>
<td>Socialdata (Perth)</td>
<td>5</td>
<td>1959</td>
</tr>
<tr>
<td>Troelsen</td>
<td>5</td>
<td>–1000</td>
</tr>
<tr>
<td>Sustrans (Frome)</td>
<td>5</td>
<td>749</td>
</tr>
<tr>
<td>Sustrans (Gloucester pilot)</td>
<td>5</td>
<td>624</td>
</tr>
<tr>
<td>Marinelli</td>
<td>5</td>
<td>589</td>
</tr>
<tr>
<td>Socialdata (Pihl)</td>
<td>5</td>
<td>413</td>
</tr>
<tr>
<td>Socialdata (Melville)</td>
<td>4</td>
<td>2410</td>
</tr>
<tr>
<td>Sustrans (Nottingham)</td>
<td>4</td>
<td>1337</td>
</tr>
<tr>
<td>Sustrans (Bishopston)</td>
<td>4</td>
<td>993</td>
</tr>
<tr>
<td>Sustrans (Sheffield)</td>
<td>4</td>
<td>986</td>
</tr>
<tr>
<td>Sustrans (Gloucester)</td>
<td>4</td>
<td>889</td>
</tr>
<tr>
<td>Sustrans (Cramlington)</td>
<td>4</td>
<td>796</td>
</tr>
<tr>
<td>McKee</td>
<td>4</td>
<td>55</td>
</tr>
<tr>
<td>Hodgson</td>
<td>3</td>
<td>1218</td>
</tr>
<tr>
<td>TAPED (Vienvheim)</td>
<td>2</td>
<td>987</td>
</tr>
<tr>
<td>Haq</td>
<td>2</td>
<td>227</td>
</tr>
</tbody>
</table>

Table 4 | Effects of interventions at community level on walking in general

<table>
<thead>
<tr>
<th>Study</th>
<th>How delivered or supported</th>
<th>Study population</th>
<th>Ages</th>
<th>Location</th>
<th>Sample size</th>
<th>Follow-up</th>
<th>Random allocation</th>
<th>Effect on walking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brownson (Booth)</td>
<td>Multifaceted (see text)</td>
<td>Rural</td>
<td>18</td>
<td>USA</td>
<td>1233</td>
<td>13-20 months</td>
<td>—</td>
<td>†</td>
</tr>
<tr>
<td>Brownson (Glaziers)</td>
<td>Multifaceted (see text)</td>
<td>Rural</td>
<td>18</td>
<td>USA</td>
<td>1531</td>
<td>12 months</td>
<td>—</td>
<td>5</td>
</tr>
<tr>
<td>Reger-Nash (Wheeling)</td>
<td>Mass media and supporting activities</td>
<td>Sedentary</td>
<td>50-65</td>
<td>USA</td>
<td>730</td>
<td>12 months</td>
<td>—</td>
<td>5</td>
</tr>
<tr>
<td>NSW Health</td>
<td>Park modifications and supporting activities</td>
<td>Suburban</td>
<td>35-65</td>
<td>Australia</td>
<td>840</td>
<td>12 months</td>
<td>2</td>
<td>$</td>
</tr>
<tr>
<td>Reger-Nash (Welch)</td>
<td>Mass media and supporting activities</td>
<td>Rural</td>
<td>35-65</td>
<td>USA</td>
<td>173</td>
<td>—</td>
<td>1</td>
<td>60</td>
</tr>
</tbody>
</table>

NS=authors reported no significant difference.
*No of criteria met (maximum 7, see table 1).
†Net change in walking after adjustment for changes in control group; 95% confidence intervals or P values included if reported by authors.
‡Continuous outcome measure converted to common outcome metric (min/week) when possible. Dash indicates conversion not possible.
§Tabulated effect size is that observed in most sedentary subgroup, not across whole study population.
walking and were thus unable to examine unreported or unanalysed data on walking that may lie buried in the composite measures of physical activity used in many other trials.

**Strengths and weaknesses of the available evidence**

The available evidence (particularly that from the most robust study designs) is somewhat skewed in favour of studies of interventions that seem easier to evaluate, or perhaps easier to randomise, typically individually focused interventions such as brief advice or pedometers, often studied in small, convenience, or volunteer samples (as illustrated by the increases in walking observed in the control groups in many studies) and sometimes over short follow-up periods of only a few weeks. From a perspective of improving population health, much of this research therefore constitutes, at best, evidence of efficacy rather than effectiveness. This caveat is particularly well illustrated by the case of pedometers. None of

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**Table 5: Effects of interventions on walking as a mode of transport**

<table>
<thead>
<tr>
<th>Study</th>
<th>How delivered or supported</th>
<th>Selected characteristics of intervention and study design</th>
<th>Effect on walking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Study population, Ages, Location, Sample size, Follow-up</td>
<td></td>
</tr>
<tr>
<td>Mutrie et al.</td>
<td>Self help pack</td>
<td>Public sector employees, 19-69, Scotland, 194, 6 months</td>
<td>+64 min/week (P&lt;0.05)†, +64</td>
</tr>
<tr>
<td>Marinelli et al.</td>
<td>Individualised marketing</td>
<td>Households, NR, Australia, 589, 3-11 months</td>
<td>+18 trips/year (SSNR), +5</td>
</tr>
<tr>
<td>Socialdata (Perth)</td>
<td>Individualised marketing</td>
<td>Households, NR, Australia, 413, 12 months</td>
<td>+3 min/day (SSNR), +21</td>
</tr>
<tr>
<td>Socialdata (Perth)</td>
<td>Individualised marketing</td>
<td>Households, NR, Australia, 1959, 8 months</td>
<td>+3 min/day (SSNR), +21</td>
</tr>
<tr>
<td>Sustrans (Frome)</td>
<td>Individualised marketing</td>
<td>Households, NR, England, 749, 4 months</td>
<td>+31 trips/year (SSNR), +8</td>
</tr>
<tr>
<td>Sustrans (Gloucester)</td>
<td>Individualised marketing</td>
<td>Households, NR, England, 624, 4 months</td>
<td>+25 trips/year (SSNR), +7</td>
</tr>
<tr>
<td>Socialdata (Melville)</td>
<td>Individualised marketing</td>
<td>Households, NR, Australia, 2410, 10 months</td>
<td>+5 min/day (SSNR), +35</td>
</tr>
<tr>
<td>Sustrans (Bishopston)</td>
<td>Individualised marketing</td>
<td>Households, NR, England, 993, 9 months</td>
<td>+2 min/day (SSNR), +14</td>
</tr>
<tr>
<td>Sustrans (Cramlington)</td>
<td>Individualised marketing</td>
<td>Households, NR, England, 796, 9 months</td>
<td>+1 min/day (SSNR), +7</td>
</tr>
<tr>
<td>Sustrans (Gloucester)</td>
<td>Individualised marketing</td>
<td>Households, NR, England, 889, 9 months</td>
<td>+2 min/day (SSNR), +14</td>
</tr>
<tr>
<td>Sustrans (Nottingham)</td>
<td>Individualised marketing</td>
<td>Households, NR, England, 1337, 6 months</td>
<td>+2 min/day (in one area), +3 min/day (in another) (SSNR), +18</td>
</tr>
<tr>
<td>Sustrans (Sheffield)</td>
<td>Individualised marketing</td>
<td>Households, NR, England, 986, 9 months</td>
<td>+2 min/day (SSNR), +14</td>
</tr>
<tr>
<td>Hao et al.</td>
<td>Individualised marketing</td>
<td>Households, NR, England, 227, 6 months</td>
<td>+0.1 km/week (SSNR), +1</td>
</tr>
<tr>
<td>TAPESTRY (Viemheim)</td>
<td>Individualised marketing</td>
<td>City residents, NR, Germany, 987, 12 months</td>
<td>+16 trips/year (SSNR), +4</td>
</tr>
<tr>
<td>School travel initiatives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McKee et al.</td>
<td>Active commuting pack</td>
<td>Primary schools, 9-10, Scotland, 55, 7 weeks</td>
<td>+555 m/trip (95% CI 315 to 795) +69</td>
</tr>
<tr>
<td>Rowland et al.</td>
<td>School travel coordinator</td>
<td>Primary schools, 6-10, England, 1386, 14 months</td>
<td>OR for not using car 0.98 (95% CI 0.61 to 1.59) —</td>
</tr>
<tr>
<td>TAPESTRY (Hertfordshire)</td>
<td>Walk to school week</td>
<td>Primary schools, 4-11, England, 1403, 3-4 weeks</td>
<td>+2% walking at least once a week (NS) —</td>
</tr>
<tr>
<td>Miscellaneous transport interventions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoup et al.</td>
<td>Subsidised non-car travel</td>
<td>Employees, NR, USA, 1807, 1-3 years</td>
<td>+1.1% in walking share of trips (P&lt;0.01) —</td>
</tr>
<tr>
<td>Troelsen et al.</td>
<td>National cycling city</td>
<td>City residents, 16-74, Denmark, 1000, 3-5 years</td>
<td>+0.1 km/day (SSNR), +9</td>
</tr>
<tr>
<td>Hodgson et al.</td>
<td>Sustainable transport campaign</td>
<td>Households, NR, England, 1218, 2 years</td>
<td>−0.2 trips/week (NS) —</td>
</tr>
<tr>
<td>Cervero et al.</td>
<td>Car sharing club</td>
<td>Members, NR, USA, NR, 8-9 months</td>
<td>−3.4% in walking share of trips (NS) —</td>
</tr>
</tbody>
</table>

NS = authors reported no significant difference; OR = odds ratio; SSNR = statistical significance not reported.
*Number of criteria met (maximum 7, see Table 1). Only Mutrie et al. and Rowland et al. had random allocation.
†Net change in walking after adjustment for changes in the control group. 95% confidence intervals or P values included if reported by authors.
‡Continuous outcome measure converted to common outcome metric (min/week) where possible. Dash indicates conversion not possible.
§Tabulated effect size is that observed in the most sedentary subgroup, not across the whole study population.
¶Not reported. Most studies in the category ‘Targeted or individualised promotion of active travel’ included travel of all household members.
the studies in our review found that any short term benefits associated with pedometers were sustained. The limited evidence base for the effects of attempts to change the societal or environmental determinants of walking may simply reflect the political or practical difficulties of implementing changes at the required scale to influence population patterns of activity\textsuperscript{19}\textsuperscript{20} or the scientific challenges of detecting comparatively dilute effects in whole population samples.\textsuperscript{81}

Implications for policy and practice

About a third of adults in Britain report fewer than one episode of 30 minutes’ moderate intensity physical activity of any kind each week.\textsuperscript{34} Against this background, the average increase in walking of 30-60 minutes a week observed among targeted participants [typically sedentary, motivated to change, or both] in the most promising studies in this review is important. Over the longer term, or at the level of the population as a whole, the increase in walking attributable to a single intervention is likely to be substantially lower than this. Nevertheless, the successful implementation of combinations of interventions to promote walking clearly has the potential to make a substantial contribution towards increasing the activity levels of the most sedentary. In the absence of evidence to the contrary, however, we should remain alert to the possibility that targeted interventions of this kind may be preferentially taken up by better-off groups in the population and may therefore have the potential to increase health inequalities.

Our findings are consistent with (but certainly not proof of) an assumption that different types of people may respond to different approaches, tailored to their psychological characteristics or life circumstances. In other words, one size may not fit all and various approaches should be offered: some people may respond best to personal advice from their doctor, others may prefer the private feedback from a device such as a pedometer, others (perhaps those in a more advantaged socioeconomic position) may benefit from interventions delivered through the internet, others may benefit from the social support of a walking group, and others may increase their walking in response to prompts about reducing their car use on environmental grounds.

Unanswered questions and future research

Our findings illustrate an evaluative bias or “inverse evidence” law whereby to date we know least about the effects of interventions most likely to influence the health of the largest number of people.\textsuperscript{22,23} We do not yet know whether or how the benefits of individual and group level interventions shown to be effective in selected groups or in the short term can be sustained and generalised, particularly (in many cases) to populations outside the United States and Australia. We need to establish more convincing evidence about the effects of interventions in the transport sector, which could be obtained by efforts to replicate the findings of promising but isolated studies and, more specifically, by testing the claims made for individualised marketing in an independent randomised controlled trial. We should also devote more effort to investigating the effects of large scale community level interventions, both planned health promotion activities and natural experiments involving major changes to the built environment.\textsuperscript{15,22,24}

Few studies in this review found unequivocal improvements in health, risk factors for disease, or even overall levels of physical activity attributable to an increase in walking. Most studies did not look for (or were inadequately powered to detect) such benefits or possible adverse effects. Future intervention studies should therefore include the capacity to investigate whether increases in walking are sufficiently frequent, intense, or sustained to produce measurable improvements in anthropometric, physiological, biochemical, or clinical outcomes, or alternatively whether increases in walking might be counterbalanced or outweighed by decreases in other forms of physical activity or an increase in injuries.

At present, the epidemiological evidence for the health benefits of moderate intensity physical activity in general is not matched by a comparable degree of certainty about the effects and benefits of interventions to promote walking in particular, but the need for more intervention research does not obviate the need for those working both in and outside the health services to do something to tackle the public health problems associated with sedentary contemporary lifestyles.\textsuperscript{1,12} Therefore, while we still have much to learn about exactly who will benefit from what type of intervention and by how much, this uncertainty should not be used as an excuse for inaction.

We thank the Centre for Reviews and Dissemination at the University of York for executing parts of our search strategy; authors and experts who contributed information about studies considered for inclusion in the review; and Mark Petticrew for advice and comments on the draft manuscript.

Contributors: DO led the review on behalf of the Scottish Physical Activity Research Collaboration (http://sparcoll.org.uk: NM, Fiona Bull, CEF, Jo Inchley, Myra Nimmo, DO, and Catharine Ward Thompson) and with the support of SPARColl’s international reviewers (Adrian Bauman, Bille Giles-Corti, Sally Macintyre, Pelika Oja, and James Salis) and steering group: VH, DO, CEF, and NM designed the search strategy; parts of which were executed by DO and CEF.
VH, HR, DO, and NC screened the initial results of the literature searches. HR, DO, NC, CFF, and CEF appraised and extracted data from primary studies and analysed the findings. DO and HR drafted the manuscript. All authors contributed to the critical revision of the manuscript and approved the final version. DO is guarantor.

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**Competing interests:** NC sells pedometers in his capacity as a health promotion consultant. NM is an author of three of the primary studies included in the systematic review but played no part in the appraisal of those studies for the review.

**Ethical approval:** Not required.

10 Ogilvie D, Egan M, Hamilton V, Petticrew M. Promoting walking and cycling as an alternative to using cars: systematic review. *BMJ* 2004;329:763-6.

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Side effects of phenobarbital and carbamazepine in childhood epilepsy: randomised controlled trial

Selina H Banu, clinical neurophysiologist and paediatric neurologist,1 Moshrat Jahan, primary care physician trained in childhood epilepsy,1 Ummul Kulsum Koli, child psychologist,1 Saadia Ferdousi, child psychologist,1 Naila Z Khan, professor of child development and neurology,1 Brian Neville, Prince of Wales’s professor of childhood epilepsy2

INTRODUCTION

Epilepsy is the most common neurological disorder in children; 80% of affected children live in countries with limited resources where 90% of epilepsy is not consistently treated.1 For a sustainable treatment programme antiepilepsy drugs must be affordable, available, and effective and have minimal side effects.

The World Health Organization recommends phenobarbital as the first choice of drug for most seizures and epilepsies in developing countries mainly because of cost, but carbamazepine is also recommended for all but typical absences2 3 and is used in Bangladesh.4 Several studies have shown that 30-50% of children treated with phenobarbital experience behavioural side effects,5-8 and one study showed a persistent reduction in IQ.9 Others have found no such effect.10-12 There is a need for robust evidence about the use of phenobarbital,13 14 particularly in areas with limited resources.

We compared the behavioural side effects of phenobarbital and carbamazepine in a Bangladesh clinic.

METHODS

We carried out a double blind randomised controlled trial from the multidisciplinary child development centre at a children’s hospital.1 Children were recruited by clinical referral from April to October 2001 and followed up for 12 months.

From previous studies we hypothesised a 25% excess of behavioural side effects with phenobarbital compared with carbamazepine. With a predicted rate of side effects of 15% in carbamazepine and a 25% difference between the two groups, for 80% power at 5% significance (two tailed) we calculated that we would need 46 children in each group.15 Allowing for a 20% drop out rate, we planned to enrol 54 children into each group.

Children were aged 2-15 years with “active epilepsy” defined as two or more generalised tonic-clonic, partial or secondary generalised seizures during the previous year. Exclusions were absence, myoclonic or severe malignant epilepsy, major motor and cognitive impairments, or current treatment with antiepilepsy drugs. We included children with minor non-epilepsy impairments who were able to carry out age appropriate, independent daily living activities.

All parents gave written informed consent. We obtained a history of seizures, associated neurodevelopmental problems, pregnancy and birth related problems, early development, immunisation, and family and socioeconomic information from patients, parents, and family members. All children underwent electroencephalography; other investigations were performed as clinically indicated. We used a standard classification of seizures, epilepsies, and epilepsy syndromes,16 17 modified for limited investigations4

Results

91 children were followed up for 12 months. Six required a change of antiepilepsy drug. Side effects were compared in 85 children. In the last quarter of the 12 month follow-up, 71 children were seizure free after one year’s treatment. Thirty two in the phenobarbital group and 39 in the carbamazepine group had no seizures for 74 and 102 days after randomisation, respectively. Ten children had increased behavioural problems, which were unacceptable in four (one in the phenobarbital group and three in the carbamazepine group). Independent t tests, however, showed no difference between the two trial drugs.

CONCLUSION

There was no excess in behavioural side effects with phenobarbital in children with epilepsy in a country with limited resources.

Trial registration NCT00381537.

REFERENCES

by using the two categories of syndrome: symptomatic including cryptogenic and without other impairments.

Children underwent an initial general and central nervous system examination and multidisciplinary assessment of functional neurodevelopment. Psychological assessments used were the Bayley scale of infant development (BSID) for those aged 2-3 years, the independent behaviour assessment scale (IBAS) for those aged 3-6 years, and Wechsler intelligence scales for children-revised (WISC-R) for those aged ≥16 year. Cognitive level was designated “normal” or “impaired,” with a cut-off IQ of 70.

We assessed behaviour using age appropriate behavioural screening questionnaires, which we and others have used in similar settings. We used the Bayley scale for those aged ≤2 years and the Richman behavioural assessment questionnaire for those aged 2 years 1 month to 3 years 11 months. Many similar studies have used Conners’ rating scale-revised for children aged 5-15. We reassessed behaviour after 12 months of treatment or at drug withdrawal using the same assessment scale.

The Conners’ short questionnaire for parents (CPRS-R:S) was translated from English into Bangla, revised after feedback about common use, and tested for reliability and concurrent validity measure. We examined test and re-test reliability on 20 children at an interval of two weeks for each index and found no significant difference, which suggests that parental responses were reliable and stable.

We categorised behavioural state as “no change,” “improved,” or “deteriorated” compared with entry condition on the basis of behavioural assessment questionnaires and subcategorised deteriorated behaviour as acceptable or unacceptable on the basis of parental concern.

On entry, participants were randomly assigned to treatment with phenobarbital or carbamazepine. One researcher (SHB) prepared 108 envelopes containing a paper designating drug A or B. These were sealed, shuffled, and kept securely. An independent assistant selected an envelope after a telephone request from the treating physician. For practical and ethical reasons the treating physician was aware of the allocation but the psychologist, therapist, and researcher were blind. The researcher was unblinded at data analysis.

We reviewed patients at two weeks, one month, three months, and six months interval after randomisation, depending on therapeutic response and travel. Compliance was measured by verbal reply, counting tablets, and blood concentrations of anti-epilepsy drugs in samples taken on a single occasion without notice.

Phenobarbital and carbamazepine (immediate release) were available as strips of 30 mg and

| Characteristics of children with epilepsy and their families according to allocation to antiepilepsy drug (54 children in each group): baseline data. Figures are numbers of children unless stated otherwise |
|---------------------------------|-----------------|----------------|
|                                  | Phenobarbital   | Carbamazepine  |
| **Family type:**                |                 |                |
| Nuclear*                        | 33              | 35             |
| Joint†                          | 21              | 19             |
| Residence:                      |                 |                |
| Rural                           | 35              | 32             |
| Urban                           | 19              | 22             |
| Socioeconomic status by monthly income: |         |                |
| Poor                            | 20              | 33             |
| Middle income                   | 13              | 14             |
| Higher income                   | 2               | 8              |
| Maternal literacy:              |                 |                |
| None                            | 25              | 19             |
| Primary                         | 16              | 16             |
| Secondary school                | 7               | 9              |
| Higher secondary school         | 2               | 3              |
| Further education               | 4               | 7              |
| Sex:                            |                 |                |
| Male                            | 37              | 24             |
| Female                          | 17              | 30             |
| Age at onset (years):           |                 |                |
| ≤1                              | 13              | 8              |
| >1                              | 41              | 46             |
| Median (IQR)                    | 2.4 (1.2-5.3)   | 3 (1.6-6.3)    |
| Age at presentation (years):    |                 |                |
| ≤2                              | 7               | 5              |
| >2-5                            | 23              | 21             |
| >5                              | 24              | 28             |
| Median (IQR)                    | 4.1 (2.6-8.3)   | 5.1 (3-9)      | 4.6 (2.8-9) |
| IQR=interquartile range.        |                 |                |

*Parents and children.
*Nuclear family plus wider family living together.
200 mg tablets, respectively. Treatment started at a low weight related dose and was increased after two weeks following the WHO recommendation.\(^2\)\(^3\) Starting and initial maintenance doses were 1.5 mg/kg/day and 3 mg/kg/day for phenobarbital and 5 mg/kg/day and 16 mg/kg/day for carbamazepine taken in two divided doses daily. Drugs were administered either to a maximum of 4 mg/kg and 20 mg/kg daily, respectively, or until seizure were controlled. If seizures were not controlled despite a full dose and a blood concentration within the therapeutic range, or if there were intolerable side effects, treatment was changed to the other study drug, with weaning from the first drug, and the child withdrawn from the behavioural outcome analysis. If there was still no improvement in seizure control a third antiepilepsy drug was used. All children were followed up for a minimum of 12 months.

### Table 2: Characteristics of children with epilepsy and their families according to allocation to antiepilepsy drug (54 children in each group): details of seizures and other problems. Figures are numbers of children unless stated otherwise

<table>
<thead>
<tr>
<th>Characteristics of children with epilepsy and their families according to allocation to antiepilepsy drug (54 children in each group): details of seizures and other problems. Figures are numbers of children unless stated otherwise</th>
<th>Phenobarbital</th>
<th>Carbamazepine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classification of seizures:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalised</td>
<td>29</td>
<td>22</td>
<td>51</td>
</tr>
<tr>
<td>Partial</td>
<td>25</td>
<td>32</td>
<td>57</td>
</tr>
<tr>
<td><strong>Aetiological classification:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without other impairment</td>
<td>40</td>
<td>31</td>
<td>71</td>
</tr>
<tr>
<td>Symptomatic*</td>
<td>14</td>
<td>23</td>
<td>37</td>
</tr>
<tr>
<td><strong>Duration of seizures before start of regular drug treatment (years):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>27</td>
<td>23</td>
<td>50</td>
</tr>
<tr>
<td>1-2</td>
<td>16</td>
<td>13</td>
<td>29</td>
</tr>
<tr>
<td>2-3</td>
<td>5</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>3-5</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>&gt;5</td>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td><strong>Median (IQR) (months):</strong></td>
<td>13 (3-25)</td>
<td>16 (4.5-30)</td>
<td>15 (3-30)</td>
</tr>
<tr>
<td><strong>Baseline mean behavioural scores (95% CI):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSID</td>
<td>100.00 (72.99 to 127.11)</td>
<td>109.33 (84.20 to 134.46)</td>
<td>—</td>
</tr>
<tr>
<td>Richman</td>
<td>31.17 (20.00 to 31.44)</td>
<td>31.58 (21.64 to 40.52)</td>
<td>—</td>
</tr>
<tr>
<td>CPRS-R:S</td>
<td>61.33 (55.05 to 73.10)</td>
<td>57.39 (51.57 to 63.21)</td>
<td>—</td>
</tr>
<tr>
<td><strong>No of seizures in previous year:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>18</td>
<td>21</td>
<td>39</td>
</tr>
<tr>
<td>10-20</td>
<td>15</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>&gt;20</td>
<td>21</td>
<td>18</td>
<td>39</td>
</tr>
<tr>
<td><strong>Previous treatment with antiepilepsy drug:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>42</td>
<td>40</td>
<td>82</td>
</tr>
<tr>
<td>Yes</td>
<td>12</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td><strong>Motor impairment:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>45</td>
<td>45</td>
<td>90</td>
</tr>
<tr>
<td>Present</td>
<td>9</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td><strong>Cognitive impairment:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>37</td>
<td>37</td>
<td>74</td>
</tr>
<tr>
<td>Present</td>
<td>17</td>
<td>17</td>
<td>34</td>
</tr>
<tr>
<td><strong>Pre-existing behavioural problems:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>43</td>
<td>43</td>
<td>86</td>
</tr>
<tr>
<td>Present</td>
<td>11</td>
<td>11</td>
<td>22</td>
</tr>
</tbody>
</table>

*Includes cryptogenic.

### Outcome measures

Our main outcome measure was behavioural side effects after one year’s treatment, assessed by comparing the results of the two behavioural assessments. Seizure outcome was measured as “seizure remission,” defined as no seizures during the last quarter of 12 month follow-up. Drug efficacy was assessed by date of treatment allocation, time to first seizure after randomisation, time to withdrawal from treatment because of adverse effects, and date of last follow-up.

### Analysis

We carried out intention to treat analysis for seizure outcome. Our primary aim was to compare the side effects of the drug, which required children to take that drug up to the time of behavioural reassessment but we noted any reasons for discontinuing treatment. We measured differences in behavioural side effects using independent sample \(t\) tests and Mann-Whitney \(W\) tests. Paired sample \(t\) tests were used to compare the difference between behavioural assessment scores before and after treatment within the trial groups. We compared drug efficacy using time to first seizure after randomisation as the primary data. Actuarial (Kaplan-Meier) techniques were applied to the intervals from randomisation to first seizure, date of last follow-up when no seizures were recorded, or time to drug withdrawal. We used multiple logistic regression analysis to assess significant relations between behavioural side effects and individual variables such as age, sex, minor motor impairment, cognitive impairment, and pre-existing behavioural problems.

### RESULTS

The figure shows the flow of children through the trial. Tables 1 and 2 show the characteristics of the families and children and the classification of seizures and epilepsy at randomisation. Most children came from poor and middle income families in rural areas without automobile access or made up roads and thus travel was by walking or boat, and this was fairly representative of the general population. Clinic visits often involved great effort and sometimes hardship. The male to female ratio was 1.3:1 in the whole population, but more girls were allocated to carbamazepine. Mean and median age at randomisation and at onset of seizures was higher in the carbamazepine group (table 1). O

Over four fifths of children had their first non-febrile seizure after the age of 1 year. Two in the carbamezpine group and one in the phenobarbital group had a history of a prolonged seizure with fever, but the other children had no history of convulsive status. There were more generalised seizures in the phenobarbital group, and more partial seizures in the carbamazepine group. The seizure rate and total number of seizures during the previous year were higher in the phenobarbital group (table 2). Median duration of epilepsy was longer by three months in the carbamazepine group. Three quarters of the children had never had daily long term treatment with antiepilepsy drugs, while the...
remainder had had a minimum of three months’ treatment. Associated minor motor and cognitive comorbidities were similar in the groups (table 2). Seventy four children had a normal IQ (74), and 43 in each group had normal behaviour before treatment.

**Behavioural side effects and seizure outcome**

Table 3 gives details of the outcome at one year. In 59 children there was no change in behaviour, and in 16 behaviour improved. Ten children experienced excessive restlessness and hyperactivity (4/54) in the phenobarbital group and 6/54 in the carbamazepine group (difference 3.7%). Table 4 shows the mean difference between behavioural assessment scores before and after treatment. There was a significant improvement in behaviour after regular treatment with antiepilepsy drugs in both groups of 2-5 year olds. There were no significant differences between the mean, median, and range of behavioural outcome scores or between the two groups by independent t-test (table 5). Logistic regression analysis showed no association between the outcome behaviour and age, sex, motor disability, cognitive developmental delay, anti-epilepsy drugs, or pre-existing behavioural problems (table 6).

One child in the carbamazepine group withdrew after four months because of severe headaches and aggressive outbursts. Another child in the carbamazepine group experienced occasional severe headaches. At the initiation of treatment three in the phenobarbital group and one in the carbamazepine group experienced disturbed sleep. Also in the phenobarbital group one child reported irritability and four had gastrointestinal disturbances.

Seizures became worse (increased and evolving to myoclonic seizures) in three in the carbamazepine group (two were shifted to phenobarbital and one to a third antiepilepsy drug as there was no improvement of seizure control after the shift to the other trial drug). Two in the phenobarbital group had poor seizure control with full dose and then shifted to the carbamazepine with good results (see figure). Three children taking phenobarbital and four taking carbamazepine discontinued the drug for more than seven days for various reasons—for example, returning home, running out of drugs, and substituting homeopathic treatment. Of these, four children had convulsive status epilepticus while not taking the drug (two in each group), three within 7-10 days and one after 30 days after they stopped taking the drug. All were admitted to hospital and restarted treatment. Fifty three children remained without seizures for six months to one year, and another 18 were seizure free during the three months before the one year follow-up (table 3). Seven (6.5%) children were seizure free from the time of initial treatment. An additional 39 (36%) were seizure free for the six months before the final assessment and 25 more were seizure free for the last three months, so the total who were seizure free for the last three months was 71 (60%) (table 3).

Actuarial analysis estimated the mean time without seizures was 102 days for phenobarbital and 74 days for carbamazepine. The cumulative seizure curves for children in both groups showed no difference in efficacy.

**DISCUSSION**

In this trial we found no significant difference in behavioural side effects with phenobarbital and carbamazepine using objective masked assessments and parental reporting in children with epilepsy without severe additional impairment. Our study was designed to find at least a 25% difference at 5% level. Ten children showed deterioration of behavioural state, of whom four received phenobarbital and six carbamazepine. Intolerable behavioural problems were more common

### Table 3 | Outcome at one year in children with epilepsy according to allocation to antiepilepsy drug. Figures are numbers of children

<table>
<thead>
<tr>
<th></th>
<th>Phenobarbital</th>
<th>Carbamazepine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance with visits:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>29</td>
<td>35</td>
<td>64</td>
</tr>
<tr>
<td>Positive recalled*</td>
<td>13</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>Negative recalled†</td>
<td>12</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Drug compliance:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continued assigned drug</td>
<td>40</td>
<td>45</td>
<td>85</td>
</tr>
<tr>
<td>Changed drug</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Behavioural outcome:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>28</td>
<td>31</td>
<td>59</td>
</tr>
<tr>
<td>Improved</td>
<td>8</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Behavioural problems:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Unacceptable</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>No with behavioural problems/total in group:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3/9</td>
<td>4/28</td>
<td>7/37</td>
</tr>
<tr>
<td>Male</td>
<td>1/31</td>
<td>2/17</td>
<td>3/48</td>
</tr>
<tr>
<td>Age at first presentation (years)*:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1/6</td>
<td>0/4</td>
<td>1/10</td>
</tr>
<tr>
<td>&gt;2-5</td>
<td>0/18</td>
<td>5/19</td>
<td>5/37</td>
</tr>
<tr>
<td>&gt;5</td>
<td>3/16</td>
<td>1/22</td>
<td>4/38</td>
</tr>
<tr>
<td>Seizures at 1 year (in all children):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None in the 3 months before end of follow-up</td>
<td>32</td>
<td>39</td>
<td>71</td>
</tr>
<tr>
<td>None in the 6 months before end of follow-up</td>
<td>19</td>
<td>27</td>
<td>46</td>
</tr>
<tr>
<td>None since started treatment</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>

*Missed several follow-ups but could be traced. †Missed several follow-ups and could not be traced.

### Table 4 | Mean differences (95% confidence interval)* in the behavioural test scores before and after treatment within the trial group

<table>
<thead>
<tr>
<th></th>
<th>Phenobarbital</th>
<th>Carbamazepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSID (2 years)</td>
<td>-2.83 (±7.16 to 1.49), P=0.153 (n=6)</td>
<td>2.67 (±6.26 to 8.76), P=0.633 (n=44)</td>
</tr>
<tr>
<td>Richman (7-15 years)</td>
<td>5.44 (±1.09 to 9.80), P=0.017 (n=18)</td>
<td>7.00 (±0.65 to 7.15), P=0.021 (n=19)</td>
</tr>
<tr>
<td>CPRS-R:S (5-15 years)</td>
<td>4.40 (±4.36 to 13.16), P=0.348 (n=16)</td>
<td>4.30 (±64 to 5.92), P=0.109 (n=22)</td>
</tr>
</tbody>
</table>

BSID=Bayley scale of infant development; CPRS-R:S=Conners’ rating scales-revised.

*Paired t test for behavioural score before and after treatment within trial group.
†Age group on presentation.
with carbamazepine, and sleep disturbance and gastrointestinal problems were more common with phenobarbital. Headache and worsening of seizures were common with carbamazepine, but the differences between the groups with respect to side effects were not significant. Behaviour improved in 16 children (eight in each group), probably reflecting a reduced burden of seizures, improved sleep and feeding, and reduced irritability.

Comparison with other studies
Our population characteristics are similar to those in studies in Kenya and India with high rates of seizures. Our results support the findings from those two resource poor countries and from one study in a developed country where no severe behavioural side effects with phenobarbital were found.10-12

A trial in the United States in children with partial seizures found no difference in behavioural or cognitive effects between the two drugs.12 In the North American cross-balanced randomised controlled trial of phenobarbital versus valproate in 28 children of normal intelligence with relatively mild seizure disorders, the authors found only marginal difference in hyperactivity between the two drugs, which was subtle and not clinically identified.6

In a trial in the United Kingdom, de Silva et al studied four antiepilepsy drugs (phenobarbital, carbamazepine, phenytoin, and valproate) in children with relatively mild seizure disorders, with most having had fewer than 10 seizures before randomisation.5 The phenobarbital arm of the study was stopped when six of the first 10 children were reported to have unacceptable behavioural side effects. There were widespread views about such effects in children, which resulted in the phenobarbital arm of the trial being stopped. The study, however, did not use a standardised behavioural assessment tool.

The Los Angeles study found marked behavioural problems in more than 30% of the children with febrile seizures treated with phenobarbital compared with those untreated.7 These would be younger, usually normal children and no behavioural scale was used.

Although total numbers are not large, all these together suggest that behavioural side effects are reported less often in countries with limited resources than in more affluent countries. The children in our study were mainly from rural areas, and cost of travel was an important factor in long term compliance, suggesting the need for a community based service for the children with epilepsy. The characteristics related to seizures and epilepsy in our study were comparable with those in other studies in countries with limited resources.10-11

Age at randomisation, characteristics of seizures, and associated prognostic features—that is, age at first seizure, total number of seizures before start of treatment, and associated non-convulsive disorders—differed in our study population compared with study populations in developed countries. Proportions of seizure types, however, were comparable with those in the UK and Indian studies. Four out of seven children who stopped medication had convulsive status epilepticus. This was probably because of withdrawal of the drug as only three had a history of febrile status epilepticus. The treatment was effective, despite the high rate of seizures and length of history, in that 78% had total remission and another 11% more than 80% remission after one year. Rate of seizure remission in other studies varied from 67% to 73%.11-20

In Kenya, Feksi et al included children and adults with a similar background of high frequency of seizures and time between the onset of seizures and starting appropriate treatment.10 Over half (53%) were seizure free in the 6-12 month follow-up period; this was 51% in our study. In a US study of children treated with phenobarbital, 67% with partial seizures were seizure free after one year of treatment14 compared with 78% in our study. In the Northern Ecuador study 65% were seizure free at 6 months and 72.7% at one year.20

Table 5 Independent t test showing difference between mean final behaviour score for children with epilepsy treated with phenobarbital or carbamazepine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Difference in mean (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSID</td>
<td>-12.08 (-13.58 to 19.41)</td>
<td>0.50</td>
</tr>
<tr>
<td>Richman</td>
<td>0.95 (0.78 to 13.53)</td>
<td>0.16</td>
</tr>
<tr>
<td>CPRS-R:S</td>
<td>-0.24 (-10.16 to 9.67)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

BSID=Bayley scale of infant development; CPRS-R:S=Conners’ rating scales-revised.

Table 6 Main effect model showing correlation between behavioural problem at one year and individual variables by using logistic regression with mutually adjusted odds ratios

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No with behavioural problems/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-5</td>
<td>5/47</td>
<td>1</td>
</tr>
<tr>
<td>&gt;5</td>
<td>5/38</td>
<td>0.99 (0.98 to 1.01)</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3/48</td>
<td>3.38 (0.83 to 3.88)</td>
</tr>
<tr>
<td>Female</td>
<td>7/37</td>
<td>1</td>
</tr>
<tr>
<td>Cognitive impairment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>7/57</td>
<td>1</td>
</tr>
<tr>
<td>Present</td>
<td>3/28</td>
<td>0.98 (0.95 to 1.00)</td>
</tr>
<tr>
<td>Minor motor impairment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>9/71</td>
<td>1</td>
</tr>
<tr>
<td>Present</td>
<td>1/14</td>
<td>2.49 (0.55 to 11.13)</td>
</tr>
<tr>
<td>Pre-existing behavioural problems:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>9/68</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>1/17</td>
<td>1.00 (0.19 to 5.20)</td>
</tr>
<tr>
<td>Total</td>
<td>10/85</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions
From this study in Bangladesh, we conclude that phenobarbital is not associated with excess behavioural side effects when compared with carbamazepine and is therefore an effective and suitable drug to use for children with epilepsy in this setting.
**WHAT IS ALREADY KNOWN ON THIS TOPIC**

Phenobarbital is a highly effective antiepilepsy drug recommended by WHO for use in countries with limited resources. Several studies in developed countries have shown a high rate of behavioural side effects with phenobarbital.

**WHAT THIS STUDY ADDS**

Phenobarbital was not associated with a high rate of behavioural side effects in children in Bangladesh.

We thank Stewart Boyd for his help and support, A L Johnson for his advice in statistical analysis, and Dhaaka Shishu (Children’s) Hospital authority for providing logistic support.

**Contributors:** SHB was principal investigator, designed and organised the study, analysed the data under the supervision of BN and NZK, and wrote the paper as part of her PhD. MJ developed strategies to improve compliance and to distribute appropriate service for families and contributed to data collection and data entry. SF tested reliability and validity of the behavioural assessment scale. SF and UKK performed psychological and behavioural tests and compiled data for analysis. NZK shared the project plan implementation and directly supervised and provided support to run the project in Dhaaka Shishu Hospital. BN shared in the study design, supervised the project and data analysis, helped in writing the paper, and is guarantor.

**Funding:** Department for International Development (DFI) administered through the British Council, Dhaaka, and UK.

**Competing interests:** None declared.

**Ethical approval:** Research ethics committee of Great Ormond Street Hospital NHS trust and the Institute of Child Health London and the ethical review committee of Bangladesh Institute of Child Health.

Herpes zoster is a clinical manifestation of the reactivation of latent varicella zoster virus infection. It is a cause of considerable morbidity, especially in elderly patients, and can be fatal in immunosuppressed or critically ill patients. The pain associated with herpes zoster can be debilitating, with a serious impact on quality of life, and the economic costs of managing the disease represent an important burden on both health services and society. Here we provide an overview of the disease and a summary of “best practice guidance” for the management of herpes zoster and its sequelae.

What is herpes zoster and who gets it?
Herpes zoster, or shingles, is the painful eruption of a rash, usually unilateral, caused by the varicella zoster virus. Varicella zoster virus usually persists asymptptomatically in the dorsal root ganglia of anyone who has had chickenpox, reactivating from its dormant state in about 25% of people to travel along the sensory nerve fibres and cause vesicular lesions in the dermatome supplied by that nerve.

Herpes zoster is more common in people with diminished cell mediated immunity. This includes elderly people, patients with lymphoma, those receiving chemotherapy or steroids, and people with HIV. In contrast to herpes simplex, precise triggers for herpes zoster are not known.

How common is herpes zoster in general practice?
Population based studies show that the incidence of herpes zoster rises with age from approximately 2-3/1000 patient years in people aged 50 to 8/1000 patient years in those aged 70 and over. The average general practice of 1500 patients would therefore expect to have between three and five cases a year.

What are the clinical features?
Replication and transmission of the virus in the nerves and skin lead to the cardinal features of herpes zoster—pain and rash. In some people the rash is preceded by a prodromal phase lasting 48-72 hours or longer, consisting of throbbing pain and paraesthesia in the region of the affected sensory nerve. This may sometimes be confused with other acute medical conditions such as angina, cholecystitis, or renal colic, depending on the dermatome involved. The rash of herpes zoster is typically vesicular, affects a single dermatome, and lasts for three to five days before the lesions pustulate and scab (figure).

In immunocompetent patients, the most frequent site of reactivation is the thoracic nerves followed by the ophthalmic division of the trigeminal nerve (herpes zoster ophthalmicus), which can progress to involve all structures of the eye. If the mucocutaneous division of the VII cranial nerve, which innervates the ear and side of the tongue, or the VIII cranial nerve is involved, the development of lesions in the ear, facial paralysis, and associated hearing and vestibulary symptoms are known as Ramsay Hunt syndrome. Herpes zoster may also cause facial nerve palsy without vesicles occurring in the external meatus. Other rare complications include encephalitis, myelitis, retinitis, and hemiparesis, all of which are more common in immunocompromised patients.

How is herpes zoster diagnosed?
Herpes zoster can usually be diagnosed clinically. However, early zoster and zoster presenting in the sacral and cervical area may be difficult to distinguish from herpes simplex. In these cases, the diagnosis can be confirmed by sending swabs to the local virology laboratory, but treatment should not be delayed while waiting for test results. The top of the lesion should be lifted and a sterile swab used to rub the base of the lesion. The swab should then be wiped across a sterile glass slide or over three wells on a Teflon coated slide. The slide should be air dried and sent to the laboratory for staining with immunofluorescent antibodies. The swab can also be placed...
in viral transport medium or sterile saline, which is suitable for transporting to the laboratory within the next one to three days for detection of viral DNA by polymerase chain reaction.

Reactivation of varicella zoster virus in immunocompromised patients, especially those who have had bone marrow or solid organ transplants, may spread to involve the gut, liver, and other viscera. Although a typical rash is common, some cases present with abdominal pain and no evidence of rash. In the absence of rash, the diagnosis can be confirmed by measuring virus in the blood by polymerase chain reaction.\(^1\)

How serious is herpes zoster?

The rash is accompanied by severe pain, which, in some people, does not subside after healing but persists for months or years. This prolonged zoster associated pain, usually defined as pain persisting for more than four months after the rash has healed, is known as postherpetic neuralgia and is the most common complication of herpes zoster. The pain can be debilitating, exacerbated by the slightest touch, and lead to loss of employment, depression, and social isolation.

Identification of patients at risk of developing postherpetic neuralgia is therefore crucial, as they stand to gain most from treatment. Several clinical and laboratory parameters have been suggested and evaluated as risk factors predicting postherpetic neuralgia (box 1), but they are by no means exhaustive.\(^5,6\)

Health economic studies estimate that shingles and postherpetic neuralgia cost the United Kingdom up to £73.8m (€108m; $147m) a year. The main medical costs—drugs, visits to the general practitioner, and hospital admissions—equal to between £74 and £198 for each episode of acute herpes zoster and £777 for each episode of postherpetic neuralgia.\(^7\) In patients aged under 65, acute herpes zoster is estimated to cost £526 per episode when the costs to wider society resulting from loss of productivity are also included.\(^8\)

How is herpes zoster treated?

Many trials have compared interventions, concentrating on reductions in severity of pain as the key outcome measure. As zoster associated pain is a continuous spectrum ranging from the pain of the prodrome to the pain of established postherpetic neuralgia, considerable heterogeneity exists in the populations studied, making comparisons of the efficacy of agents across studies difficult. Also, as the severity of pain during an acute attack is an important predictor for the development and the severity of postherpetic neuralgia, interventions used during the acute phase may influence the outcome of interventions subsequently used to treat postherpetic neuralgia. Nevertheless, as clinicians are most likely to be confronted with either a patient with a herpes zoster rash or a patient with established postherpetic neuralgia, we will cover these two problems as separate entities.

What is effective treatment for an acute attack of herpes zoster?

Table 1 shows the drugs available for treating acute herpes zoster in immunocompetent adult patients.

### Table 1 | Treatment of acute herpes zoster in immunocompetent adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/frequency</th>
<th>Treatment duration</th>
<th>Efficacy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aciclovir</td>
<td>800 mg five times daily*</td>
<td>7-10 days</td>
<td>Reduces acute pain and development of PHN</td>
<td>Most effective if started within 72 hours of onset of rash</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>750 mg daily* or 250 mg three times daily</td>
<td>7 days</td>
<td>Reduces acute pain and development of PHN</td>
<td>Most effective if started within 72 hours of onset of rash</td>
</tr>
<tr>
<td>Valaciclovir</td>
<td>1 g three times daily*</td>
<td>7 days</td>
<td>Reduces acute pain and development of PHN</td>
<td>Most effective if started within 72 hours of onset of rash</td>
</tr>
<tr>
<td>Brivudin</td>
<td>125 mg daily</td>
<td>7 days</td>
<td>Reduces acute pain and development of PHN</td>
<td>Licensed for treatment in Austria, Belgium, Germany, Greece, Italy, Luxembourg, and Spain</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>60 mg daily initially, then taper dose</td>
<td>21 days</td>
<td>Reduces acute pain</td>
<td>Use only in combination with antivirals. Reduce dose to 30 mg after 7 days and to 15 mg after a further 7 days, then stop</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>25 mg daily</td>
<td>3 months</td>
<td>Reduces incidence of PHN; effect on acute pain uncertain</td>
<td>Use with care in elderly patients. An electrocardiogram should be done before treatment</td>
</tr>
</tbody>
</table>

PHN=postherpetic neuralgia.

* Dose given in British National Formulary.
Table 2 | Summary of evidence based treatments for established postherpetic neuralgia

<table>
<thead>
<tr>
<th>Drug class and supporting studies</th>
<th>Study design</th>
<th>Measure of treatment effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tricyclic antidepressants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline v placebo**96</td>
<td>Double blind, placebo controlled, crossover trial</td>
<td>ARR=65%; NNT=1.6 (1.2 to 2.4)</td>
</tr>
<tr>
<td>Amitriptyline v lorazepam and placebo**97</td>
<td>Randomised, placebo controlled, multi-armed, crossover trial</td>
<td>NNT=3.2 (2.1 to 6.6)</td>
</tr>
<tr>
<td>Amitriptyline v nortriptyline**98</td>
<td>Randomised, double blind, placebo controlled, crossover trial</td>
<td>NA</td>
</tr>
<tr>
<td>Amitriptyline v maprotiline**99</td>
<td>Randomised, double blind, crossover trial</td>
<td>NNT=32 for amitriptyline</td>
</tr>
<tr>
<td>Desipramine v benztropine**100</td>
<td>Randomised, active placebo controlled trial</td>
<td>ARR=63%; NNT=1.6 (1.1 to 2.6)</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin v placebo**11</td>
<td>Randomised, dose titrated, double blind, placebo controlled trial</td>
<td>NNT=2.2 (1.7 to 3.0); NNH=10.3</td>
</tr>
<tr>
<td>Gabapentin v placebo**12</td>
<td>Randomised, dose titrated double blind, placebo controlled trial</td>
<td>ARR=29.5%; NNT=5.3 (3.6 to 10.2); NNH=11.2</td>
</tr>
<tr>
<td>Pregabalin v placebo**13</td>
<td>Randomised, placebo controlled trial</td>
<td>NNT=3.3 (2.3 to 5.9); NNH=3.7</td>
</tr>
<tr>
<td><strong>Opioids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone v placebo**14</td>
<td>Double blind, placebo controlled, crossover trial</td>
<td>ARR=65%; NNT=2.5 (1.7 to 5.1); NNH=38</td>
</tr>
<tr>
<td>Morphine or methadone v nortriptyline/desipramine and placebo**15</td>
<td>Double blind, placebo controlled, crossover trial</td>
<td>NNT=3 (2 to 5.5) for opioids; NNT=6.2 (3.2 to 294) for tricyclics</td>
</tr>
<tr>
<td>Tramadol v placebo**16</td>
<td>Randomised, placebo controlled trial</td>
<td>NNT=4.7 (2.9 to 19)</td>
</tr>
<tr>
<td><strong>Topical lidocaine, aspirin, and capsaicin</strong></td>
<td>Randomised, double blind, placebo controlled, crossover trial</td>
<td>NNT=2 (1.4 to 3.3)</td>
</tr>
<tr>
<td>Lidocaine gel v placebo**17</td>
<td>Randomised, double blind, placebo controlled, crossover trial</td>
<td>NA</td>
</tr>
<tr>
<td>Lidocaine polyethylene patch v placebo**18</td>
<td>Enriched enrolment, randomised, double blind, placebo controlled trial</td>
<td>NNT=2.5 (1.7 to 5.1); NNH=38</td>
</tr>
<tr>
<td>Aspirin cream v indometacin cream, diclofenac cream, and placebo**19</td>
<td>Randomised, double blind, placebo controlled, crossover trial</td>
<td>ARR=32%; NNT=3 (1.7 to 26.1)</td>
</tr>
<tr>
<td>Capsaicin v placebo**20</td>
<td>Randomised, double blind, placebo controlled trial</td>
<td>NNT=3.2 (2.1 to 6.3)</td>
</tr>
</tbody>
</table>

ARR=absolute risk reduction; NA=not available; NNH=number needed to harm; NNT=number needed to treat.

Systemic antivirals
Meta-analyses and randomised controlled trials suggest that the oral antiviral agents aciclovir, famciclovir, and valaciclovir started within 72 hours of the onset of rash reduce both the severity and the duration of acute pain, as well as the incidence of postherpetic neuralgia. The nucleoside analogue brivudin has been shown to be as effective as famciclovir but superior to aciclovir in both healing acute lesions and reducing postherpetic neuralgia. The pharmacokinetics of oral antivirals differ considerably, so the patient’s ability to adhere to a multiple dosing regimen should be considered when selecting an agent for treatment. Antiviral treatment is effective at an early stage when viral replication is still occurring. It should be given to patients who present within 72 hours of the onset of rash and to those aged over 50 with new vesicle formation or complications whenever they present. Published guidelines advise that herpes zoster ophthalmicus should always be treated with antivirals and the advice of an ophthalmologist sought. Likewise, visceral herpes zoster requires prompt admission to hospital and use of intravenous aciclovir (10 mg/kg, eight hourly).

Corticosteroids
The addition of oral prednisolone to aciclovir treatment has been shown to reduce pain, speed healing of lesions, and enable a more rapid return to daily activities. Coadministration of steroids and antivirals should therefore be considered for older patients with appreciable pain who do not have a contraindication to steroids (such as diabetes or peptic ulcer disease). Expert opinion also supports the use of steroids in the

Box 1 | Risk factors for development of postherpetic neuralgia after an attack of herpes zoster

- Advanced age (>50 years)
- Female sex
- Presence of a prodrome
- Severe or disseminated rash
- Severe pain at presentation (visual analogue score >5)
- Polymerase chain reaction detectable varicella zoster virus viraemia

Box 2 | Complications of herpes zoster ophthalmicus

- Conjunctivitis, episcleritis, and scleritis
- Keratitis, iridocyclitis
- Choroiditis, papillitis
- Oculomotor palsy
- Retinitis
- Optic atrophy
treatment of acute idiopathic facial palsy in combination with aciclovir.15

Although oral steroids are of benefit in the acute attack, they have not been shown to have an effect on preventing postherpetic neuralgia.12 Likewise, a single dose of epidural methylprednisolone combined with a local anaesthetic is a useful addition to antiviral treatment for resolution of acute pain but has no effect on the development of postherpetic neuralgia.19 Repeated administration of epidural steroids combined with continuous infusion of anaesthetic for up to 21 days has been shown to reduce postherpetic neuralgia,20 but the risks and practicalities of interventions that need epidural administration remain to be resolved. The role of steroids in the management of herpes zoster is controversial, and the results of a systematic review of their efficacy in postherpetic neuralgia are awaited.22

**Tricyclic antidepressants**

Tricyclic antidepressants have been widely used in the management of chronic neuropathic pain conditions.23 Use in the acute phase of herpes zoster in elderly patients has been evaluated in a randomised placebo controlled trial of amitriptyline. Effects on reduction of acute pain were not evaluated, but a reduction in the prevalence of postherpetic neuralgia at six months was reported in the amitriptyline treated group.21 Although this trial provides some evidence for the efficacy of tricyclic antidepressants in preventing postherpetic neuralgia, antivirals were also given but only at the attending physicians’ discretion. If prescribed, tricyclic antidepressants should be used with caution, especially in elderly patients, in whom anticholinergic side effects may precipitate acute confusion or cardiac arrhythmias.

**Other agents**

Although opioid analgesics and non-steroidal anti-inflammatory drugs are widely used in the management of acute pain syndromes, only the opioids oxycodone and tramadol have been subjected to formal trials in herpes zoster. Oxycodone reduces acute pain, but evidence for the prevention of postherpetic neuralgia is lacking; conversely, tramadol is efficacious in established postherpetic neuralgia but has not been studied for acute treatment.22 A randomised controlled trial has recently shown that a single 900 mg dose of the anticonvulsant gabapentin reduces acute pain in herpes zoster.23

**Management of acute ophthalmic zoster**

Herpes zoster affecting the first division of the trigeminal nerve is particularly aggressive and must be treated with antivirals, even if more than 72 hours have elapsed since onset. Oral antiviral agents should be accompanied by topical antiviral cream applied to the eye and corticosteroids where appropriate.17 Box 2 shows the complications of acute ophthalmic zoster.

**What is effective treatment in established postherpetic neuralgia?**

An expert subcommittee of the American Academy of Neurology has done a systematic review of treatments for established postherpetic neuralgia.24 Several recommendations were made, the strength of the evidence supporting them was ranked, and where possible absolute risk reduction rate, number needed to treat, and number needed to harm were calculated. Tricyclic antidepressants, the anticonvulsants gabapentin and pregabalin, controlled released oxycodone or morphine sulphate, and lidocaine patches were all classed as moderately to highly effective. Some evidence of efficacy was also found for topical capsaicin and aspirin creams and for intrathecally administered methylprednisolone. Non-drug treatments such as transcutaneous electrical stimulation and acupuncture were also evaluated and found to be ineffective. Table 2 summarises the supporting evidence.

**Can we prevent herpes zoster?**

A live attenuated vaccine derived from the oka strain of varicella zoster virus has been shown to be highly effective in preventing primary varicella in children and was introduced into the US vaccination programme in 1996. A reduction in the number of cases of primary varicella zoster virus could have a major impact on the incidence of zoster in both the short term and longer
SUMMARY POINTS

Herpes zoster and postherpetic neuralgia are common causes of debilitating neuropathic pain. Systemic antiviral agents reduce both the acute pain of herpes zoster and the incidence of postherpetic neuralgia. Corticosteroids, tricyclic antidepressants, gabapentin, and opioids reduce acute pain and may have additional effects on the reduction of postherpetic neuralgia. Tricyclic antidepressants, gabapentin, opioids, and lidocaine patches are effective in established postherpetic neuralgia. Large scale vaccination of children and older adults may have an important impact on the incidence of herpes zoster and postherpetic neuralgia.

term. Although the eradication of primary varicella would also lead to the eradication of herpes zoster, the cell mediated immunity responsible for suppression of latent infection needs to be repeatedly boosted by exposure to wild type virus circulating in the community. Concern exists that a reduction in the number of childhood cases of varicella could lead to a short term increase in herpes zoster in latently infected people. Early analyses of the incidence of herpes zoster in the United States after introduction of the vaccination programme have yet to support this theory. A large clinical trial of varicella zoster virus vaccine in adults aged over 60 in an attempt to boost waning immunity was recently reported. The vaccine was found to be highly effective at reducing both the number of cases of herpes zoster and the incidence of postherpetic neuralgia, suggesting that this may be an extremely useful intervention for reducing the burden of herpes zoster disease.

Ongoing research

Herpes zoster and postherpetic neuralgia will remain important clinical problems for the foreseeable future. Several areas need further research, some of which are being tackled in ongoing studies. These include the development of biomarkers to identify people at risk of developing postherpetic neuralgia and clinical trials to determine exactly who should be treated when presenting more than 72 hours after onset of the rash. Research on the molecular pathogenesis of varicella zoster virus and mechanisms underlying latency will help in the design of more effective antiviral agents and inactivated (non-infectious) vaccines for use in immunocompromised patients.

Contributors: DWW did the initial literature search and prepared and wrote the first draft. JB advised on subsequent revisions and preparation of the final draft.

Competing interests: JB has received funding for work on the oka vaccine and varicella zoster virus from Merck, Sanofi Pasteur-MSD, GlaxoSmithKline, the Medical Research Council, and the Wellcome Trust. DWW: none declared.


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The patient

A 9 year old girl with a history of conservatively managed left sided Perthes’ (Legg-Calvé-Perthes) disease presented to her orthopaedic team via her general practitioner with onset of right hip pain and subsequent limp. She was otherwise well. On clinical examination she had a limp with moderate pain and some limitation of abduction and internal rotation. She did not have a fever, and routine haematology and biochemistry gave normal results.

Differential diagnosis and prognosis

Assuming the disease can confidently be localised to the hip (rather than knee, pelvis, or lower back), a presumptive diagnosis of the painful hip is reasonable, based on age and presentation.

• In a younger, febrile, or unwell child, septic arthritis needs to be excluded urgently.
• Perthes’ disease typically affects children aged between 3 and 10 years (peaking between 5 and 7 years); it affects about four boys for each girl affected; and it occurs bilaterally in about 10% of cases.
• Slipped upper femoral epiphysis tends to occur in adolescents (aged 10-16 years), again more commonly in boys (ratio 3:1), patients of Afro-Caribbean origin, and obese patients.
• Transient synovitis typically has an acute onset, and spontaneous recovery with no radiological abnormality or systemic upset. It occurs between the ages of 2 and 10 years (peaking between 5 and 6 years) and is more common in boys, often preceded by viral infection.

Various methods are used to classify the severity of Perthes’ disease; these broadly stratify according to the proportion of epiphyseal involvement. Prognosis is variable and depends on amount of epiphyseal involvement and age of the patient. The younger the patient and the smaller the affected area, the more likely that repair will occur without important abnormality. The older the child and the more extensively affected, the more likely they are to have modelling deformities of the femoral head and acetabulum, with resultant premature degenerative change.

What test should I order?

In this context, the differential lay between transient synovitis and Perthes’ disease. Several tests are available to help in deciding the diagnosis.

Plain x rays

Both hips should be imaged (fig 1); the improved diagnostic accuracy provided by comparison with the other hip outweighs the small increase in radiation exposure (which can be mitigated by coning or the use of a gonadal shield in the lateral view). Both an anteroposterior and lateral or “frog leg” view (hips flexed and externally rotated) of the whole pelvis must be done (fig 2). The anteroposterior view will show the more advanced changes of Perthes’—enlargement, flattening, sclerosis, or fragmentation of the epiphysis—but early changes such as the crescentic subchondral lucency, particularly in the anteromedial aspect (the site of maximal load bearing), are easily missed and best seen on the lateral view. In older children, slipped upper femoral epiphysis can be missed if the lateral film is omitted.

Ultrasonography

Ultrasound is the most sensitive tool for confirming a hip joint effusion (although a large effusion can sometimes be suspected from the plain x ray). As
FIG 2 | Lateral coned hip x ray of the same child showing the classical subchondral lucency of early avascular necrosis (arrow), not visible on the initial film, indicating early right sided Perthes’ disease

Ultrasound is quick, cheap, free of ionising radiation, and can be used for guidance in fluid aspiration, it can be used as the first line imaging modality in children with hip pain and no relevant previous history. Its main disadvantage is its lack of specificity. In most cases ultrasound cannot differentiate the causes of an effusion—a transient synovitis and septic arthritis cannot be distinguished with certainty2—and Perthes’ disease may also be complicated by an effusion in the acute setting. Another potential problem is a lack of suitably confident and trained paediatric or musculoskeletal radiologists or sonographers.

Magnetic resonance imaging

If further investigations are necessary because the diagnosis is still not clear, magnetic resonance imaging can identify the earliest (pre-radiographic) changes, illustrate the extent or severity of the disease (allowing an estimate of prognosis), and offer multiplanar 3D imaging for surgical planning.3 4 In everyday practice it is rarely required: diagnosis can usually be made from plain films, and most cases are managed conservatively with rest and physiotherapy. Bracing and splinting are occasionally required with surgery reserved for the older and more severely affected children.

Other tests

Bone scintigraphy shows both the early avascular and later revascularisation or reparative phases of Perthes’ disease, but it is seldom used in practice as it offers no more information than magnetic resonance imaging and involves ionising radiation.5 In the same way, although computed tomography can detail bony anatomy and the extent of disease, magnetic resonance imaging offers adequate preoperative 3D imaging without exposing the patient to radiation.

Patient outcome

The plain films show established Perthes’ in the left hip of our patient, but avascular necrosis was apparent in her right hip only on the lateral view. We diagnosed (bilateral metachronous) Perthes’ disease. The patient was managed conservatively. She was advised to be relatively active and is now well, although she avoids contact sports.

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Competing interests: None declared.

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Call for papers for BMJ theme issue on diabetes

If you would like your original research article to be considered for this September’s theme issue, please send it to our online editorial office at http://submit.bmj.com by Monday 11 June. We will give priority to articles that will help readers to make better decisions about diabetes. To ensure we attract the best new research, we are keeping the remit broad: suitable research may aid decisions on risk, prevention, treatment, or management of diabetes and may be relevant to clinical practice, health services, further research, education, or policy making.

Our resources for authors on bmj.com and the recent editorial at BMJ 2007;334:4-5 (doi: 10.1136/bmj.39057.516250.80) should answer your general questions about submitting research to the BMJ.

For specific advice on possible submissions for this theme issue, please email Trish Groves at tgroves@bmj.com.

Fig 2 | Lateral coned hip x ray of the same child showing the classical subchondral lucency of early avascular necrosis (arrow), not visible on the initial film, indicating early right sided Perthes’ disease

USEFUL READING

PREGNANCY PLUS

Management of psoriasis in pregnancy

Sophie Weatherhead, Stephen C Robson, Nick J Reynolds

Many treatments for this chronic skin disease are harmful to the developing fetus, so careful pre-conception planning and management adjustment are crucial for the pregnant patient.

Psoriasis is a common skin condition that causes considerable morbidity and occupational disability.\(^1\) It has an estimated lifetime prevalence of 1.5-2.2% in the adult population,\(^2\) with three quarters of patients presenting before the age of 40.\(^3\) Incidence is similar for the two sexes, although women generally develop the disease earlier than men. The prevalence in pregnant women is unknown but probably reflects that of non-pregnant women of child bearing age. The scenario box on this page shows that balancing treatment of severe psoriasis with the decision to try to conceive requires forward planning, and there is always a chance that the disease will worsen. Our patient was fortunate to become pregnant so quickly; less fortunate women can have a prolonged and difficult course and must decide how long they will try to conceive before resuming systemic treatment.

SCENARIO

A 30 year old woman had had chronic plaque psoriasis since childhood. She had previously needed a prolonged course of PUVA (psoralen and ultraviolet A) and two admissions to achieve control of her psoriasis. She then began intermittent treatment with methotrexate, followed by continuous treatment. When she had been taking methotrexate for five years she decided she wanted to start a family. She therefore stopped methotrexate and took the oral contraceptive pill for three months. Within four weeks of stopping methotrexate her psoriasis flared up but was controlled with an eight week course of narrowband ultraviolet B. The patient became pregnant with twins four months after stopping methotrexate but has needed further ultraviolet B to control her psoriasis throughout pregnancy.

Does pregnancy affect psoriasis?

Chronic plaque psoriasis is thought to improve in 40-60% of patients during pregnancy, with most improvement during the late first and second trimesters.\(^4\) This improvement has been associated with high concentrations of progesterone, which down-regulates the T cell proliferative response.\(^5\) Psoriasis is associated with an altered T cell response biased towards the T helper 2 profile. Pregnancy usually tips the balance towards a T helper 1 cytokine profile,\(^6\) which may explain why psoriasis often changes in pregnancy. Psoriasis deteriorates in 10-20% of women during pregnancy and may require intensified treatment.\(^7\)

Does pregnancy affect the outcome of pregnancy?

Psoriasis does not affect fertility or rates of miscarriage, birth defects, or premature birth.\(^8\) Many treatments for psoriasis are associated with potential problems during pregnancy.

Psoriasis is associated with depression, but no studies have investigated whether pregnancy exacerbates depression more in patients with psoriasis than in the normal population. Having psoriasis should not affect the timing or mode of delivery. Psoriasis can localise into scars (Koebner’s phenomenon), but this phenomenon has not been reported in perinatal scars, although theoretically it can occur at any site of epidermal injury. The risk of infection and delayed healing of caesarean section wounds is theoretically higher, but no studies have assessed this risk.\(^9\)

Psoriasis has a multifactorial mode of inheritance. An individual’s risk of developing psoriasis is estimated at 28% if one parent is affected and 65% if both parents have the disease.\(^3\)

How are patients with psoriasis managed in pregnancy?

If possible, it makes sense to induce a period of remisision or to optimise control of psoriasis before conception to help minimise flare-ups during pregnancy. Patients considering or taking systemic treatments should be warned in advance of the length of time that they will need to be off treatment before it can be considered safe for them to conceive (figure).

Topical treatments are first line treatments for psoriasis, and emollients, topical steroids, and dithranol are considered safe in pregnancy. Manufacturers of vitamin D analogues such as calcipotriol advise avoidance, although significant systemic absorption is unlikely to occur when they are used for localised disease.\(^2\) The safety of coal tar products is unclear as animal studies have suggested teratogenicity, although this has not been reported in humans. Such...
and women should therefore avoid conception for at least three months after taking methotrexate, although the risk to the fetus is largely theoretical for men.17

Hydroxyurea (hydroxyurea) is a neoplastic agent occasionally used as a second line systemic treatment for psoriasis. Although teratogenic in animals, no problems have been reported in the limited number of women exposed to this agent during pregnancy.5 In view of the limited data available, manufacturers advise avoidance in pregnancy.

Fumaric acid esters are widely used as systemic treatment for psoriasis in Europe (particularly Germany)18 but are not licensed in the United Kingdom; they are available on a named patient basis at some UK centres. There are no studies in pregnancy so they should be used cautiously on a case by case basis.

Manufacturers of etanercept and infliximab, which are licensed for use in severe psoriasis, advise avoidance during pregnancy. No toxicity or teratogenicity has been reported in animal studies of etanercept, and limited human data suggest that neither agent causes harm to the fetus.19 However, these drugs are often used in combination with methotrexate. Manufacturers of etanercept have set up a registry to follow patients who have been exposed to etanercept in pregnancy. More information about its safety profile will therefore be available in the future.

How is psoriasis managed postpartum?

More than half of patients have a flare-up within six weeks of delivery, although this is usually not worse than their prepregnancy state.4,6 More than half of patients have a flare-up within six weeks of delivery, although this is usually not worse than their prepregnancy state.4,6 Making women aware of this can allow therapeutic options to be planned in advance, leading to prompt treatment and minimising disease as far as possible.

First line treatment options for breastfeeding women are primarily limited to emollients, moderate to low potency topical steroids, and dithranol. Topical treatment should be applied after breastfeeding, and washed off thoroughly before the next feed.

Acitretin, methotrexate, ciclosporin, hydroxyur- eminal esters, biological agents, and PUVA are contraindicated in breastfeeding women; the safest second-line agent is ultraviolet B. Breastfeeding may need to be curtailed if further treatment options are required.

ADDITIONAL EDUCATIONAL RESOURCES


Zip C. A practical guide to dermatological drug use in pregnancy. Skin Ther Lett 2006;11:1-4


National Teratology Information Service (www.nrytc.nhs.uk/Services/teratology/teratology.html)—UK based service providing information about drug use in pregnancy and lactation. The service is available on +44 (0)191 232 1525; 8.30 am to 5 pm Monday to Friday.
Mild renal impairment increases cardiovascular risk

Research question
Is mild renal impairment an independent risk factor for cardiovascular disease in otherwise healthy adults?

Answer
Yes.

Why did the authors do the study?
People with chronic renal failure have an increased risk of cardiovascular disease. These authors wanted to find out the risks associated with much milder forms of renal impairment. More specifically, they wanted to know how low glomerular filtration rate (GFR) has to fall before cardiovascular risk begins to rise in otherwise healthy adults.

What did they do?
They selected 8913 participants without cardiovascular disease or diabetes from an original cohort of 30,000 adults chosen at random from the Belgian electoral register and followed them up for 10 years after baseline assessments of their GFR and cardiovascular risk factors. The authors recorded all deaths during follow-up and used death certificates and hospital notes to ascertain the causes of death. They looked for an association between GFR at baseline and risk of death from cardiovascular disease, adjusting the results for age, sex, body mass index, smoking, mean arterial blood pressure, serum concentration of total cholesterol, and serum concentration of uric acid.

What did they find?
In these apparently healthy adults, even mild renal impairment was associated with a significantly increased risk of dying from cardiovascular disease. When the authors divided participants by quartiles of GFR, those in the bottom two categories (GFR <89.4 ml/min/1.73 m²) were more than twice as likely to die from cardiovascular disease compared with those in the top quarter (GFR >104.3 ml/min/1.73 m²). The hazard ratios for death from cardiovascular disease were 2.48 (95% CI 1.26 to 4.87) for those with a GFR of 75.6-89.4 ml/min/1.73 m² and 2.21 (1.13 to 4.32) for those with a GFR <75.6 ml/min/1.73 m².

The effect of mild renal impairment on cardiovascular risk was about the same for men and women and was independent of age and traditional cardiovascular risk factors including smoking. The authors estimate that cardiovascular risk goes down by 8% for every 10 ml/min/1.73 m² increase in GFR (hazard ratio 0.92 (0.85 to 0.99)).

What does it mean?
Renal impairment seems to have a detrimental effect on cardiovascular risk at an early stage, even among apparently healthy adults. This study suggests that risk starts to rise once GFR falls below about 90 ml/min/1.73 m², a substantially higher cut-off point than previous estimates and one that the authors describe as “near normal.”


This summarises a paper that has been selected by bmjupdates. To register for bmjupdates (free email about high quality new papers in your favourite subjects) go to http://bmjupdates.com/
10-MINUTE CONSULTATION
Tiredness
George Moncrieff, John Fletcher

During a routine appointment a 48 year old woman tells you that she feels tired all the time. She has changed jobs recently and her daughter has recently returned to university.

What issues you should cover
Reasons for consulting—Tiredness is a common presenting symptom. Often the cause may be physical; diseases such as hypothyroidism, autoimmune disease, liver or kidney disease, or even cancer may result in tiredness. Tiredness is, however, more often due to depression or the stresses of life circumstances. Tiredness may not be the main focus of her concerns, and she may only offer it as an initial symptom to see whether you are sympathetic and interested. Her main issue may be a more sensitive one, such as the menopause or the stress of recent events in her life. Patients may consider tiredness to be a more legitimate symptom to bring to a doctor than, say, unhappiness. Although such a patient may elicit “heartsink” feelings in the doctor, this symptom should provoke careful evaluation, and managing this consultation effectively could enhance the doctor-patient relationship and help avoid a future series of unproductive consultations.

Defining tiredness—Tiredness is not a specific term and patients may use it to cover a number of symptoms. Lack of motivation and low energy are features of depression. Fatigue and weakness may be the result of chronic illness. Daytime sleepiness may be due to obstructive sleep apnoea or sedating treatment. Drowsiness and headaches in the winter months may be symptoms of carbon monoxide poisoning. Fatigue lasting more than six months that isn’t alleviated by rest and that is associated with muscle pain and memory impairment may be chronic fatigue syndrome.

Physical examination—An examination is unlikely to yield more information unless the history indicates a specific diagnosis, but it may reassure the patient and give you time to consider the next steps. Look in particular for signs of pallor, lymphadenopathy, thyroid disease, and heart failure.

What you should do

- Take this symptom seriously. Patients experience more tiredness than they report to doctors, so it is likely that this symptom is important to her.
- Ask whether she means she is “weak and lacking energy” or whether she is “drowsy and not refreshed by her sleep.”
- Two questions may be used to screen for depression (with 97% sensitivity): “During the past month have you often been bothered by feeling down, depressed, or hopeless?” “During the past month have you often been bothered by little interest or pleasure in doing things?” A positive answer to either question suggests depression.
- Try to determine her concerns regarding her “tiredness.” Explore whether she links her symptoms to any distressing circumstances in her life. There is little point reassuring her unless her concerns have been explored. This could just compound her worries about previously unconsidered possibilities.
- Consider whether investigation may be useful. It may diagnose or exclude a physical illness, which may reassure you and the patient. Investigations may also be a prelude to a follow-up consultation to allow further exploration of an emotional or social concern. Decide whether she needs investigation for illness, reassurance of normality, or support at a difficult time.
- Often an innocent physiological explanation can be offered confidently, such as at times of fast growth.
- Empathising with a distressing life predicament can be remarkably helpful, and your advice and interest will be remembered.
- If you think she may be depressed, arrange another consultation soon to consider treatment options.
- Ensure that she has clear instructions about follow-up and when to seek further advice, so that if she has organic disease she does not slip through the net and diagnosis isn’t delayed.

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<th>TIRENESS: SYMPTOMS, DIAGNOSES, AND INVESTIGATIONS</th>
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<td>Depression</td>
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<td>Treatment with a sedative; caffeine withdrawal</td>
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<td>Anaemia; iron deficiency; cancer; renal disease; liver disease; heart failure; thyroid disease; diabetes; autoimmune disease</td>
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<tr>
<td><strong>Investigations</strong>—full blood count; erythrocyte sedimentation rate; liver and kidney function; blood glucose; thyroid function; urinalysis for protein and glucose. Consider monospot, endomysial antibody, or antinuclear antigen testing, chest radiography, or other tests as guided by history and examination</td>
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This is part of a series of occasional articles on common problems in primary care. The BMJ welcomes contributions from general practitioners to the series.
Time to act on behalf of mentally disordered offenders

PERSONAL VIEW Becky Sales, Nigel McKenzie

Over the past six months the British media—general and medical—have increasingly focused on two apparently unlinked issues relating to offenders and the criminal justice system. The first issue is the current overcrowding crisis in prisons, as the number of prisoners exceeds capacity (80,000 in England and Wales). The second is the new Mental Health Act and the debate surrounding it as it passes through parliament. In terms of criminal justice this debate has largely centred on the balance to be struck between the human rights of mentally disordered offenders and protection of the public. What is striking is the focus on patients with potentially treatable disorders (such as personality disorders) rather than any debate concerning—or even with reference to—the human rights of those with treatable disorders, such as those with acute psychosis.

Each year in England between 5% and 8% of all patients (or 1300 to 2000 patients) detained under section in psychiatric hospitals come through the court or prison systems. Unlike their counterparts in the community these patients will wait several months for a hospital bed and are invariably floridly psychotic and untreated. Why untreated? Apart from those sections relating to transfer, the Mental Health Act of 1983 does not apply in prison.

Among the countries of Western Europe, England and Wales currently have the highest rate of incarceration per 100,000 people, although those countries are not alone in having a significant over-representation of people with a psychiatric disorder in the criminal justice system—variously estimated at between 60% and 90%. This problem is common to many countries, including most of Europe and the United States, as is the inability to ensure the rapid transfer of patients with acute mental illness out of prison and into hospital.

Prison healthcare policy in Europe, including the United Kingdom, is underpinned by the concept of equivalence of care with that of patients in the community. Equivalence of care should mean that those patients in prison who need to be admitted to hospital under the Mental Health Act wait no longer than those patients who are sectioned in the community. Equivalence of care—along with the right to health (article 12 of the United Nations’ International Covenant on Economic, Social and Cultural Rights) and the right not to be subject to torture or inhuman or degrading treatment or punishment (article 3 of the European Convention of Human Rights, enshrined in UK law as the Human Rights Act 1998)—should form the basis of health care provided to mentally ill prisoners. The reality is somewhat different.

So why are we failing? The issues relate not only to culture and resources but also to the failure of the Mental Health Act and of health commissioners to provide adequately for these patients. Well known factors contributing to this failure include the lack of diversion of mentally disordered prisoners by the courts and the police; poor care in the community; and the pressure on beds in acute psychiatric intensive care units and in medium secure units. Less recognised factors are the lack of “stepdown facilities” and of appropriate pathways of aftercare, with the consequent bed blocking in medium secure units. Emphasising the role of the patient’s commissioning primary care trust in ensuring timely transfer, without placing any statutory obligation on trusts, is unlikely to produce a satisfactory outcome in a time of NHS financial crisis.

The review of the Prison Mental Health Transfers Programme is due to present its findings later this year. Will it recommend major change to the whole process of transfer of prisoners under section—change that is backed by law and resources—rather than merely altering procedures?

We propose that the new Mental Health Bill be amended to incorporate a time limit for transfer to hospital from prison in the appropriate sections of the bill (sections 47 and 48). This time limit should reflect what would be considered appropriate in community psychiatric settings, thus fulfilling the concept of equivalence of care as well as basic human rights.

We also suggest that the bill should contain statutory obligations to ensure that those patients who are judged as needing hospital treatment while in police custody or in the court system cannot be sent to prison.

Of course, much wider debates may be had regarding the interplay between the criminal justice system and mental illness. The paradox of a prison population with a high number of prisoners awaiting hospital beds at a time of much demand for greater prison capacity is best exemplified by Ashworth, a closed psychiatric hospital wing that has now reopened as a prison (HM Prison Kennet). What is unarguable, however, is that acutely psychotic patients should not be in prison. Surely in the 21st century it is time for us as health professionals to act on behalf of one of the most forgotten, disempowered, and disadvantaged groups of patients?

Becky Sales is lead GP and Nigel McKenzie is consultant psychiatrist, HM Prison Pentonville, London becky.sales@hmps.gsi.gov.uk
Cooper is likely to be surprised by the large number of medical students that we now admit each year and by the heterogeneity of the student body. He might well see these large numbers as a commercial opportunity: to try to get a better look at what is happening to medicine and medical education in the 21st century, says Roger Jones.

In his pomp—for pomp it was—the Guy’s Hospital surgeon Astley Paston Cooper was the highest paid doctor in England, with an annual income in 1815 equivalent to over £1m today. Cooper walked with kings (and embalmed William IV) but also, famously, rode out one freezing Christmas Day at the request of the revolutionary John Thelwall to visit a friend dying in poverty. In the empirical tradition of William Harvey and William Hunter, Cooper was the pre-eminent surgical anatomist and clinical teacher of his day. He lectured to theatres packed with fee paying medical students in the Borough hospitals of Guy’s and St Thomas’s, where he also taught John Keats. Cooper’s lecture notes formed the core of the earliest editions of the Lancet. He was a relentless dissector and vivisectionist, relying on the ghoulish work of the “resurrection men” (body snatchers) to provide his human material. He was also supplied with specimens from London Zoo and once dissected an entire elephant in front of his house.

Cooper was the father of vascular surgery and made pioneering contributions to the treatment of hernias and the surgery of the breast. His body was placed in a lead lined coffin to protect him from the resurrection men and interred in the crypt of the chapel at Guy’s in 1841. I sometimes park my car only a few metres from Cooper’s mortal remains and am sure that, if not actually turning in his grave, he is moving uncomfortably to try to get a better look at what is happening to medicine in the 21st century.

Cooper is likely to be surprised by the large number of medical students that we now admit each year and by the heterogeneity of the student body. He might well see these large numbers as a commercial opportunity: the fees paid by students to attend his lectures at Guy’s were a major source of income in his early career. He fell out with Thomas Wakley, the founding editor of the Lancet, because Wakley stole his lectures and, by publishing them, reduced the need for students to attend (and pay for) the lectures. Cooper stormed round to Wakley’s house to remonstrate with him, posing as a patient to gain entrance. Striding into Wakley’s study, Cooper found him correcting the proofs of one of his very own lectures. The element of farce was not lost on either man—both burst into laughter and became firm friends. Cooper would have been disappointed to see how “walking the wards” and the traditional medical firm structures have been eroded and would probably share a widely held concern about the effectiveness of pastoral care systems in medical schools and universities.

Cooper would also have been concerned to see the gradual replacement of cadaveric dissection with prosection and three dimensional electronic images. Dexterity, precision, and detailed anatomical knowledge were, in an era without antibiotics and anaesthesia, prerequisites for safe and swift surgery and, in Cooper’s view, could be acquired only through relentless dissection. The Anatomy Act of 1832, passed shortly before Cooper’s death, put an end to the lucrative activities of the body snatchers but made dissection the legal fate of the poor—if no one claimed your body, or you were too poor to pay for a funeral, you were sent to the surgeons.

Finally, Cooper would undoubtedly have been horrified by the medical training application service (MTAS), though for reasons different from those that have led to two unprecedented parliamentary apologies. MTAS is designed to simplify applications for medical training posts and to promote equity and selection on merit; Cooper, however, was a great believer in patronage and nepotism. When the governors of the Borough hospitals refused to appoint his nephew and biographer, Bransby Cooper, to succeed him as senior surgeon at Guy’s, the ensuing row led to a split between the two institutions, which persisted until the 1982 re-merger.

Burch’s book has many vivid and gripping accounts of a truly extraordinary man living in extraordinary times. Comparisons with today’s medical leadership are inevitable; Cooper is such a compelling role model, and leaders of his stature are now few and far between. Burch’s lucid writing, with more than a little of the Jan Morris about it, is often tinged with the ghoulish and gruesome but is equally leavened by humour and sympathy. The book falls short of a panegyric—Cooper had his faults—and succeeds brilliantly in bringing him to life against the heady background of early 19th century London medicine and late Georgian society.

Roger Jones is Wolfson professor and head of general practice, Department of General Practice and Primary Care, King’s College, London School of Medicine, London roger.jones@kcl.ac.uk
Wanted: stress monkeys

FROM THE FRONTLINE
Des Spence

I ran, under pursuit. His hot breath was on my neck, but my two extra years kept me those important few metres ahead of my bloody and swearing younger brother. It was an accident. And of course a pitchfork through the hand is going to hurt, but this was nothing to the time he was knocked unconscious by a concrete block: his head wound eventually stopped bleeding and Mum let him sleep it off. Farm work was dangerous. People got gored by cows, kicked by horses, crushed under bales, and sucked down into slurry pits. We were city kids turned feral and we loved it. Thirty years on we laugh about the scars and our children roll their eyes at “the stories.” But our modern children have been reduced to a perpetual state of fear in our health and safety police state.

A recent survey found that 70% of nurses experience work related stress. Occupational health departments, their case load once full of asbestos exposure, burns, and trauma, are now dealing with an explosion in stress related illness. An occupational health principle, “the hierarchy of control,” seeks to limit risk from the top down—stopping children working on farms, for example. But how can we operate this principle with regard to stress? Being a nurse or a doctor is stressful. Sleepless nights, early waking, worry, guilt, anger, and frustration are all part of the package. That survey found that nurses are responding to stress in the time honoured way: by smoking and drinking. I suspect that dark humour and swearing are still widely used stress busters too.

But I don’t think that the stresses stem from poor pay, lack of respect, uncertainty, or long hours, as the survey suggested, for these have much improved. The reality is that working with patients is inherently stressful. All that counselling, Indian massage, whale music, and pan pipes will make no difference. Society is more demanding now, and we have to try to deliver the undeliverable.

Therefore university prospectuses should be more honest. Rather than seeing images of relaxed and smiling doctors in white coats gathered around a microscope we should see hungover, frazzled doctors and nurses huddled at a fire exit smoking. The caption might read, “A career that pushes you to the edge and then flings you over it.” I wonder whether in 30 years I will look back and laugh at all my work based psychological scars.

Des Spence is a general practitioner, Glasgow destwo@yahoo.co.uk

All together now

DRUG TALES AND OTHER STORIES
Ike Iheanacho

Who’s this: youth worker; artist; qualified magician; businessman; environmentalist; pilot; landlord; author; ex-sportsman; architecture activist; defender of faiths; armed forces officer; keen skier; village builder; and champion of organic farming? By any measure, it is an impressive curriculum vitae. And that’s without adding “heir to the throne,” a role that inevitably overshadows his other skills, knowledge, and experience.

The Prince of Wales’s diverse interests are reflected in the 18 not-for-profit organisations that comprise the Prince’s Charities group. Some, like the Prince’s Trust, are well known. But what about the Prince’s Drawing School (“Three men and a pencil,” to give its unofficial nickname)?

Among the group is the Prince’s Foundation for Integrated Health. Established in 1993, it aims to promote understanding of, build confidence in, and widen access to integrated health care. This it defines as “a combination of orthodox and complementary medicine that treats every illness in the wider context of the patient’s circumstances—(eg, exercise, relationships, diet) and with reference to the whole person.”

The foundation has its work cut out, not least because it has commonly been seen as merely a cheerleader for complementary therapy. However skewed and unfair this view, it has (mis)informed the charity’s reputation among patients and advocates of “orthodox” medicine. Partly to counter that unhelpful perception, the charity has just launched a policy and research programme that focuses on integrated approaches for six common chronic illnesses: allergies, back pain, depression, irritable bowel syndrome, obesity, and stress. This is brave stuff. Lessening the burden of any one of these would be a considerable achievement. To improve practice and outcomes for all six will take nerve, ingenuity, and perseverance.

Obvious barriers lie ahead. The foundation states that an integrated approach to health “brings together the safest and most effective aspects of mainstream medical science and complementary healthcare.” Yet these worlds barely speak the same language, let alone understand or willingly work with one another.

And anyway, delivery of health care is often less about the noble ideals of collaboration and more about the raw reality of competition for recognition and validation (such as the public’s attention and trust, media coverage, and grants). In such an atmosphere, cooperation and sharing of ideas with unlike-minded others may represent an unrewarding distraction.

Still, the foundation deserves luck in its efforts. The prince says, “Only through collaborative thinking can we paint a complete picture of world healing.” Difficult to argue with that.

Ike Iheanacho is editor, Drug and Therapeutics Bulletin iheanacho@bmgroupl.com
There have been many doctors who murdered, but few who did so who reached the top of the medical profession. Oddly enough, Robert Louis Stevenson seems, in his short story The Body-Snatcher, to accuse Sir William Fergusson, professor of Surgery at King’s College Hospital, and surgeon to Queen Victoria, of having been both an accessory to murder, and a murderer, in his youth.

In the story, a degenerate doctor called Fettes meets by chance a successful, rich, and eminent London practitioner called Wolfe Macfarlane. It turns out that they knew each other when both were students in Edinburgh, and both were assistants to Mr K, a private teacher of anatomy there. They both took delivery of bodies of people supplied to the anatomy school whom they suspected very strongly to have been murdered by the Irish suppliers. In one case, however, Macfarlane murders a man himself, and delivers the body to Fettes.

Mr K, of course, is Robert Knox, and the Irish suppliers the infamous Burke and Hare. Knox was for a time the most successful anatomy teacher in Scotland, with “a popularity due partly to his own talent and address,” says Stevenson, “partly to the incapacity of his rival, the university professor”—the despised Professor Monro tertius.

Knox in real life had three assistants: William Fergusson, Thomas Wharton Jones, and Alexander Miller. I cannot trace Miller, and suspect that he is the Fettes of Stevenson’s story. Wolfe Macfarlane is either Fergusson or Jones. The latter, having been chased by a mob from Edinburgh where he was suspected of complicity in the murders of Burke and Hare, became a physiologist at Charing Cross Hospital, where he taught T H Huxley, and then professor of ophthalmic medicine at University College Hospital. I do not think he is Macfarlane, and became the most fashionable surgeon in London, as Wolfe Macfarlane of the story becomes a fashionable and rich doctor in London after he, too, leaves Edinburgh. In his confession Burke said of Fergusson: “That worthy gentleman, Mr Fergusson, was the only man who ever questioned me anything about the bodies. He inquired where we got that volunteer, said he nearly died from starvation; he died alone and forgotten in Ventnor, in 1891.

No, Macfarlane is Fergusson, a larger than life bon vivant who left Edinburgh for Plarr’s Biographies of the Fellows of the Royal College of Surgeons says of him, “Not very human, was absorbed in his work; rather unsociable, so that he had but few friends; ill adapted to make money; bitter of speech and outspoken in criticism.” He was once so poor that he nearly died from starvation; he died alone and forgotten in Ventnor, in 1891.

Why would Fergusson have questioned him, though, had he not been suspicious? Mary Paterson appears in Stevenson’s story as Jane Galbraith, and when Fettes speaks to Macfarlane about her, Macfarlane says, “For me, you know, there’s one thing certain—that, practically speaking, a great many of our subjects have been murdered.”

Was Stevenson merely letting his imagination rip, for the sake of a shilling shocker, or did he know more about Fergusson than appeared, say, in Sir Gordon Gordon-Taylor’s article about him in the Bulletin of Medical History? (I suspect that Gordon-Taylor himself suspected Fergusson, for he quotes Burke’s confession as supposed evidence of his innocence.) Did Sir William kill in his youth, to supply Knox’s school of anatomy?

One thing is certain: Stevenson published the story after Fergusson’s death. You cannot libel a dead man.

Theodore Dalrymple is a writer and retired doctor for the weekly Bulletin of Medical History.

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**MEDICAL CLASSICS**

**Geriatrics: The Diseases of Old Age and Their Treatment**

*By Ignatz Leo Nascher*

**First published 1914**

Geriatrics has a long and fascinating history, going back to the epic of Gilgamesh, through the Jewish Bible and up to the 19th century studies of Jean-Marie Charcot. However, many believe that the field entered the modern era with the publication in 1914 of Ignatz Leo Nascher’s seminal text. The book’s origins are interesting in that it began with a ward round. As a medical student in New York, Nascher was part of a team that came to an acutely ill woman, whose condition Nascher’s professor described in words that can still be heard today: “Old age.” When our young hero asked what could be done to help the patient, he was shocked by his teacher’s response: “Nothing!”

Several years later Nascher wrote his definitive text, in which he first formulated the clumsy term “geriatrics” from the Greek “geron” (old man) and “iatrokos” (medical treatment). While apologising for his awkward formulation, Nascher offered that “euphony and mnemonic expediency were considered of more importance than correct grammatical instruction.”

Nascher divided the book, at over 500 pages, into three sections: “Physiological Old Age,” “Pathological Old Age,” and “Hygiene and Medical Legal Relations.” Many but not all of the diseases known to us today are described. Some at the time were not yet named and are alluded to. For example, Alzheimer’s disease was not described as such. (Alzheimer had, only a few years before, published his paper—not much noticed at the time.) However, Nascher clearly understood the syndrome of dementia. For example, “in determining the extent of senile impairment (in cognition), the normal mentality (pre-morbid status) of the individual should be known.” This is not bad advice, even in our day. Nascher goes on: “The impairment, though manifested in any direction, may progress for years before it becomes obvious to friends and family . . . An early symptom is a hesitancy in recalling names, dates and events, fabricating others . . . The patient will forget where he puts things; will repeat questions that had just been answered . . . He becomes careless about details and loses the sense of neatness, leaving his desk disordered, his room untidy, his clothing disarranged.”

The book makes for fascinating reading. Much material, especially that on therapeutics, is of course dated. However, the clinical approach described and, above all, the spirit of hope expressed in the book are as relevant today as they were almost a century ago. Just as we have learnt that the paediatric patient is not merely a little adult, Nascher’s book shows us that the older patient is in many ways very different from the middle aged person she once was. The book is a testimony to this pioneer’s dedication and an appropriate rejoinder to his pessimistic professor of medicine. We remember Nascher. Who knows the name of his teacher? A Mark Garfield is head of geriatrics, Soroka Hospital, Ben Gurion University of the Negev, Beer-Sheva, Israel markclar@bgu.ac.il
Vladimir Ivanovich Kulakov

Leading Russian gynaecologist

Vladimir Ivanovich Kulakov helped to introduce in vitro fertilisation (IVF) to the former Soviet Union in 1986 and performed the first laparoscopic hysterectomy in Russia in 1993. He was director of the All-Union Research Centre on the Protection of Mother and Child (currently Scientific Centre for Obstetrics, Gynaecology, and Perinatology) in Moscow for more than two decades. He was editor in chief of Akusherstvo i Ginekologija (Obstetrics and Gynaecology)—a leading Russian periodical—and president of three national associations—Russian Association of Family Planning, Russian Association of Obstetricians and Gynaecologists, and National Association of Endoscopic Gynaecologists of Russia.

Kulakov was born in 1937 in Meshcherskoe village in the Moscow region to a military officer and a school teacher. He studied at the paediatric faculty of the Pirogov Moscow Medical Institute N2 (now Russian State Medical University) but on graduating decided to specialise in obstetrics and gynaecology at Moscow Regional Research Institute for Obstetrics and Gynaecology. In 1967 he defended his kandidatskaya dissertation (PhD thesis) on pregnancy and the blood coagulating system in women with varicose veins followed by his doctorskaya dissertation (a second thesis required for professorship similar to the habilitation thesis in Germany) on a similar topic 10 years later. In 1975, at the age of 38, he was appointed a director of the institute where he had started his residency 14 years before. In 1982 he became a professor of obstetrics and gynaecology.

In 1985 Kulakov headed the All-Union Research Centre on Protection of Mother and Child—the largest Russian institution in the field. In 1974 he was a consultant gynaecologist at the Fourth Main Department of the Ministry of Health of the USSR (a special department which took care of Soviet nomenklatura, high ranking officials and their families). In 2001 he was appointed a chief obstetrician and gynaecologist of the Ministry of Health of the Russian Federation. He also worked part time as a chair of obstetrics, gynaecology, and perinatology at the Faculty of Postgraduate Training of the Sechenov Moscow Medical Academy.

For many years Kulakov was head of the department of human reproduction in the institution that he directed. The first Soviet test tube baby was born in 1986 at the laboratory of Boris Leonov at Kulakov’s institution, and was delivered by Kulakov by caesarean section. Kulakov was convinced that IVF centres should be established throughout the country to help infertile women, which he estimated to number 6 million in the country. He further estimated that thanks to IVF the number of healthy newborn infants might be as high as 100 000-200 000 annually. However, only 10 000 test tube babies were born in Russia from 1986 to 2001, and half of them at his centre. The number of centres is insufficient and the procedure expensive. It is not covered by state insurance and many couples are unable to pay 100 000 roubles (£2000) for one attempt.

Being a president of the Russian Association of Family Planning, Kulakov supported a programme on sexual education of youngsters, including centralised state purchase of contraceptives for teenagers at risk. With 1.6m abortions in Russia and only 1.2m births yearly, the programme aimed at reducing the number of artificially terminated pregnancies and sexually transmitted diseases. However, the Russian parliament stopped financing it, declaring it immoral propaganda.

In the early 1990s Kulakov started to develop methods of laparoscopic surgery in gynaecology. By the early 2000s more than 70% of all interventions were performed at his centre laparoscopically, including more than 1000 hysterectomies.

He authored and coauthored about 600 scientific publications, including many monographs dedicated to surgical treatment of inflammatory diseases of uterine appendages, IVF for treatment of female and male infertility, endoscopy in gynaecology, clinical use of haemopheresis, etc.

In 1988 Kulakov was elected a corresponding member of the Soviet (since 1992, Russian) Academy of Medical Sciences and in 1994 gained full membership. During 2001-6 he was vice president, but in 2006 he brought his institution under the aegis of the Federal Agency for High Technology Medical Care which promised better financing and participation in federal health programmes. Kulakov was three times a laureate of the Government of the Russian Federation prize. He was also awarded the Demidov prize, one of the oldest and most prestigious scientific awards in Russia won by only two other medical doctors before, one being Nikolai Pirogov. Kulakov was a member of many international societies of obstetrics and gynaecology and an expert for the World Health Organization.

Vladimir Kulakov was gentle and trustful, and sometimes people around him betrayed his confidence. Even when having to fire an employee he first tried to find him or her another place of work. During his last months he suffered from cancer but continued to work. He leaves a step-sister; a wife, Tatiana Evgenievna Samoilova; and two daughters, one from each of his two marriages.

Boleslav Lichterman

Vladimir Ivanovich Kulakov, former professor of obstetrics and gynaecology Moscow (b 1937; q Moscow 1961; MD), died from arterial thrombosis on 10 February 2007.
Nicholas Bennett-Jones

Former consultant general physician and rheumatologist Whiston and St Helens Hospitals, Liverpool (b 1916; q Liverpool 1941; FRCP), d 12 February 2007.

Nicholas Bennett-Jones joined the Royal Army Medical Corps six months into his first house job having graduated with first class honours. He served with the First Battalion Queen’s Regiment in India and Burma for five years, being mentioned in dispatches and returning home in charge of a hospital ship. Nick was consultant at the Whiston and St Helens Hospitals from 1953 to 1981. Rheumatology was his main clinical interest, and in 1960 the Heberden Society awarded him the Bishop Harman prize for his work on preventable hazards in managing steroid treated patients requiring surgery. He was a member and chairman of the St Helens Medical Society and a long term member of the Liverpool Medical Institution. He leaves a wife, Ruth; four children; and eight grandchildren.

Edgar Parry

David Bartlett Bower

Former consultant in obstetrics and gynaecology St Stephen’s (later Chelsea and Westminster) Hospital (b 1929; q Cambridge/St Bartholomew’s Hospital 1953; FRCS), died from renal carcinoma on 18 March 2007.

During his medical training David Bower also qualified as a barrister but soon decided that his future lay in medicine, particularly surgery. He developed an interest in obstetrics and gynaecology and worked for a time in Toronto. There and in London he pioneered new techniques for vaginal hysterectomy. He finally retired at the age of 68. David was a keen sailor. He loved music and was learning to play the organ until the end of his life. With his beard and dressed in leathers, his appearance was sometimes misinterpreted when he dropped in at country inns on his motorbike. He leaves a wife and three children and his partner for much of his life, Maureen.

Beresford Crook, Maureen Sands, J Richard Smith

Charles Edward Daniel Hearn

Former chief medical adviser Gillette (b 1924; q St Bartholomew’s Hospital 1948; MD, MFMC, MFOM RCP), died from oesophageal cancer on 7 February 2007.

After national service in the Royal Air Force and various hospital appointments, Charles Edward Daniel Hearn (“Dan”) chose a career in industrial medicine. This took him to the West Indies in 1959, where he redefined and described bagassosis, a condition not dissimilar to farmer’s lung found in sugarcane workers, and was awarded an MD. Returning to the United Kingdom in 1971 Dan worked for Gillette until his retirement. He was a skilled scuba diver and a fine horseman, riding with the East Dulverton hunt. Predeceased by his wife, Avril, he leaves two children and three grandchildren.

Philip Allen

Kenneth Anthony (“Tony”) Kalanyi Kebbal

Senior scientist and project leader MRC Basic Sciences Programme Entebbe, Uganda (b 1970; q Makerere University, Kampala, 1995; PhD), d 15 February 2007.

In 1997 Tony Kebbal joined the Joint Clinical Research Centre in Kampala in the first HIV vaccine trial in Africa. In 2000 he was awarded a fellowship to study the immunological correlates of protection from HIV infection in exposed but seronegative individuals and in infected people who remained well for long periods of time. Having worked in London and gained his PhD, he decided to stay in Uganda to develop research capacity where it was needed. He received funding from the Wellcome Trust and from other donor agencies, including the International AIDS Vaccine Initiative (IAVI) and the Centre for HIV-AIDS Vaccine Immunology (CHAIVI). He was also appointed honorary lecturer at Imperial College, London. He leaves a wife, Christine, and two daughters.

Frances Gotch

David Mendel

Former consultant cardiologist St Thomas’ Hospital, London (b 1922; q St Bartholomew’s Hospital 1948; FRCP), d 10 March 2007.

David enlisted in the wartime army but was invalided out after a serious injury. His early medical career was interrupted by tuberculosis, and after six months’ bed rest he ate his way back to health in France, returning to one of the restaurants he so discovered over more than 50 years. In 1960 David moved to St Thomas’, initially as senior lecturer and then consultant from 1964, to develop a modern department, retiring in 1986. He wrote The Practice of Cardiac Catheterisation (1968) and Proper Doctoring (1986). David had many talents, including being a flautist and craftsman. After retirement he studied, and became fluent in, Italian at the University of Kent. He had a long correspondence with his friend Primo Levi, translating his work and writing his obituary. He leaves a wife, Meg, and two daughters.

David Thompson

Kieran O’Driscoll

Former professor of obstetrics and gynaecology University College Dublin (b 1920; q University College Dublin 1943; MRCOG, MAO), d 17 January 2007.

Kieran O’Driscoll contributed greatly to the care of women in labour. As master of the National Maternity Hospital in Dublin in 1963 he started publishing papers on the “active management of labour.” This included regular review by consultants in the labour ward, emphasis on the difficulties in diagnosing labour, one to one skilled care for all, a simple precise partogram, the safety of oxytocin in primigravidas, and reducing instrumental delivery and prolonged labour. He was senior author of Active Management of Labour, whose current, fourth, edition reflects experience in over 250 000 births at the hospital, a third to primigravidas. Kieran travelled worldwide as visiting professor. He retired in 1984. Predeceased by a few months by his wife, Ina, he leaves six children.

Dermot Mac Donald Declan Meagher

ADVICE

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MINERVA

Are men and women treated differently in US managed care plans? Apparently so, according to a study of the management of cardiovascular disease and diabetes in Women’s Health Issues (2007 Apr 16 doi: 10.1016/j.whi.2007.03.001). Data from 10 commercial and nine Medicare plans show significant differences—for five of 11 measures with Medicare, with four favouring men, and for eight of 11 measures with commercial plans, with six favouring men. The largest disparity was in the control of low density lipoprotein cholesterol in people with diabetes, with women 19% less likely to achieve control in the Medicare group and 16% less likely in the commercial group.

Rashes are quite often reported among patients taking antiepileptic drugs. A study in Neurology claims that the average rate of rash associated with antiepileptic drugs is 2.8% (2007;68:1701-9). In a multivariate analysis, the only non-drug predictor that was significant was the occurrence of another rash associated with the drugs (odds ratio 3.1, 95% confidence interval 1.8 to 5.1, P<0.0001). The rate in this group was 8.8% compared with 1.7% in patients without another such rash. Rashes were most likely in patients taking phenytoin, lamotrigine, and carbamazepine.

A randomised controlled trial that compared a low fat diet with a weight reduction diet in breast cancer related lymphoedema showed in both groups significant reductions in body weight, body mass index, and skinfold thickness measured at four sites (Cancer 2007;109:1949-56). A non-significant fall in excess arm volume occurred in both groups. The study found significant correlation between weight loss (regardless of diet followed) and a reduction in excess arm volume.

The more open and emotionally aware you are, and the more curiosity you hold, the longer you’ll live with heart disease, independent of all other risk factors and educational attainment, reports a paper in Psychosomatic Medicine (2007;69:319-22). Previous studies had concluded that the connection between emotional openness and longevity was related to educational achievement.

Is it better to knot, or not to knot? A vascular ligation pig model helped surgeons compare braided sutures in a surgeon’s knot, monofilament sutures in a granny knot, a metallic clip, a bipolar diathermy system, and an ultrasonically activated scalpel (Annals of the Royal College of Surgeons of England 2007;89:359-62). All vessels were subjected to more than physiological pressures, and loss of haemostasis was shown by the leaking of coloured perfusion fluid. All the manufacturers’ claims were upheld, and all the methods tested performed as well as the traditional surgeon’s knot in vessels of 5 mm or less.

Wives’ tendency to accept the fiction of fidelity, the discretion of their husbands, and the challenge to such fiction if condoms are used within a marriage, are some of the sociocultural factors that contribute to HIV transmission in many countries. The latest issue of the American Journal of Public Health considers sexual life from a sociocultural perspective (2007;97:971). Other factors that promote men’s extramarital sexual activity include the need to migrate for work, cultural beliefs and norms, gender inequality, and socioeconomic status.

Dental laboratories are going out of business in the United Kingdom, says the Dental Lab Journal (2007;32:6-11). The cause is, once again, the new NHS dental contract. The new system seems to put dentists into a perverse position in which the more they prescribe the less they earn. The long term fall out for the country is the permanent loss of skills and closure of dental laboratories because dentists trying to cut their costs are looking to use laboratories abroad that are not regulated to the same extent as UK laboratories.

An Italian invention for monitoring patients with respiratory disease at home is described in the Annals of Italian National Institute of Health (2007;43:101-9). The instrument directly measures blood oxygen saturation and pulse rate and also digitally records information that comes from several other external instruments, including a spirometer and a capnometer. It connects to all pulmonary ventilators and to the internet, through an internal modem. It was first tested in patients with amyotrophic lateral sclerosis.

Most biological approaches to depression involve the neurotransmitters that mediate traffic between neural synapses. But recent efforts have altered the focus to the possibility of causation being a stem cell neurogenesis. Specifically, declining adult neurogenesis in the hippocampus may be causally connected to depression. A review in the Journal of Psychiatric Research says that this will remain greatly speculative, albeit exciting, unless some critical questions are answered (2007;41:713-23).

People with mild cognitive impairment may do well to drink a glass of wine every day. Data from the Italian longitudinal study on ageing shows that compared with total abstention from alcohol a glass or less a day may reduce the rate of progression to full blown dementia. Heavier drinkers didn’t seem worse off than the abstainers either. Minerva wonders if it has to be Italian wine (Neurology 2007;68:1790-9).

Abdominal crunches are a part of most exercise routines, but beware of taking them too far. An unusual case of empyema in a previously fit and healthy young woman has been ascribed to rupture of a pulmonary sequestration and healthy young woman has been ascribed to rupture of a pulmonary sequestration induced by abdominal crunch exercises (CMAJ 2007;176:1577-8). These congenital malformations are usually asymptomatic and are found in as many as 17 people per 1000 population. They are segments of lower respiratory tract parenchyma that are non-functional and don’t communicate with the rest of the respiratory tree.