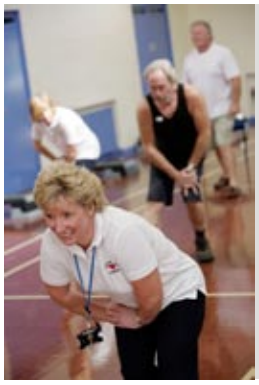
Exercise after stroke

Is beneficial but how best to increase physical activity is unknown



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RESEARCH, p 273

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Competing interests: GM has received external funding (from Chest Heart and Stroke Scotland, Scottish Government, Edinburgh Leisure, and Greater Glasgow Health Board) to help produce the first UK course for exercise instructors on stroke, provided by Queen Margaret University, Edinburgh.

Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2009;339:b2795
doi: 10.1136/bmj.b2795

Stroke is the third most common cause of death and the most common cause of severe disability in the United Kingdom. Low levels of physical activity substantially increase the risk of a first ever ischaemic stroke and haemorrhagic stroke.[1] Although data about the association between physical activity and recurrent stroke are lacking, it is biologically plausible that physical activity after stroke might improve the profile of vascular risk factors and so reduce the risk of recurrent stroke and other vascular events.[2] In the linked study, Boysen and colleagues report a randomised controlled trial of repeated encouragement and advice aimed at increasing physical activity after stroke.[3]

Levels of physical activity in community dwelling adults with mild motor impairment after stroke are about half those of healthy older people.[4] Physical fitness (including aerobic fitness, muscle strength, and muscle power) is substantially lower in people after stroke than in age matched controls.[5] Physical fitness training after stroke—structured exercise to increase physical fitness—improves aspects of physical function and physical fitness.[6] Several clinical guidelines now recommend exercise after stroke.[2 7 8]

Professional advice and guidance with continued support can encourage sedentary people without previous stroke to be more physically active in the short term and medium term,[9] but whether this type of approach is effective in people after stroke is not known. The intervention in Boysen and colleagues' trial consisted of a one to one meeting with a physiotherapist or neurologist on six occasions over 24 months, and a telephone reminder between meetings. The primary end point was self reported activity levels. At the end of follow-up no significant difference was seen in activity levels between the intervention and the control group, irrespective of whether the data were analysed by intention to treat or per protocol. The authors concluded that giving repeated advice does not increase levels of physical activity.[3]

Assuming that exercise after stroke is beneficial, how can we encourage people after stroke to become more active? Council run leisure centres and health boards in the UK have started to develop exercise referral schemes for people who have completed their usual stroke rehabilitation; these schemes can provide a choice of exercise programmes delivered in a small group or in a one to one gym session. SkillsActive, the sector skills council for the active leisure and learning industry, has published UK national occupational standards for designing and delivering physical activity to people after stroke.[10] These standards are the foundation to the first UK course for exercise instructors on stroke, available through Queen Margaret University, Edinburgh, UK.[11] Exercise referral schemes should be evaluated to determine how many patients who have had a stroke attend, how many drop out, and whether the programmes achieve similar benefits to those seen in clinical trials.

Although exercise classes improve physical fitness and physical function in ambulatory people after stroke, some people may decline to participate. The barriers and motivators to exercise after stroke are not well understood, and little research has been carried out in this area. In the general population, uptake of and adherence to exercise is a well known problem. Several models of health behavioural changes provide insight into how decisions are made. For example, the theory of planned behaviour suggests that performance of any behaviour is codetermined by behavioural intention and perceived behavioural control; this model applies to participation in physical activity in healthy people.[12] It is not known whether this or other health behavioural models apply to people after stroke, and research in this area using a range of qualitative methods is warranted.

Other important gaps exist in our knowledge about exercise after stroke, such as the optimum type, frequency, intensity, and timing (during or after usual rehabilitation) of exercise and its cost effectiveness. Ongoing trials may provide more information about these aspects.

Little is known about the effectiveness of suitably adapted exercise programmes for patients who are unable to walk after stroke and those with difficulties in communicating, because these people have been under-represented in previous trials.[5 6] The role of new complex interventions, such as interactive computer games to increase activity, should be tested in people who have had a stroke.

In everyday clinical practice, how can health professionals help people after stroke to increase physical activity? A pragmatic approach is needed to identify perceived barriers to exercise and to tackle them wherever possible. Health professionals should seek opportunities to develop stroke specific exercise programmes in the community in collaboration with leisure services, based on SkillsActive's standards.[10] In addition, after a stroke people should be offered the opportunity to participate in clinical research in this under-researched area.

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Oral quinine for the treatment of uncomplicated malaria

Is ineffective in outpatients and should be used only in rare cases

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RESEARCH, p 283

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Competing interests: None declared.
Provenance and peer review: Commissioned; not externally peer reviewed.
Cite this as: *BMJ* 2009;339:b2066
doi: 10.1136/bmj.b2066

Artemisinin combination therapy is the first line treatment for uncomplicated malaria in nearly all malaria endemic countries in sub-Saharan Africa. This treatment is relatively expensive, but it kills parasites faster than any other method and has few adverse effects.[1] The combination artemether-lumefantrine (Coartem) is co-formulated, can be taken in a convenient schedule over three days, and is popular with patients and healthcare providers.[2] The linked study by Achan and coworkers confirms the excellent cure rate (all patients were cured after adjusting for reinfection) of this drug in children with uncomplicated malaria in Uganda.[3]

However, oral quinine is often used to treat uncomplicated malaria either because artemisinin combinations are not available,[4] or on the assumption that it must be effective because it is still the drug of choice for severe malaria in African children (although it is now known to be inferior to artesunate in Asian adults[5]). But although strains of *Plasmodium falciparum* in sub-Saharan Africa remain susceptible to quinine,[6-9] this may not translate into drug effectiveness. To complete the treatment regimen, Coartem should be taken twice daily for three days, whereas quinine must be taken three times daily for seven days. The bitter taste of quinine and its unpleasant side effects may leave caregivers struggling with their children, hoping that the full seven days of treatment are not needed and deciding to stop treatment after a few days as the fever subsides.

In their open label effectiveness study, Achen and colleagues planned to treat 302 children randomised to a three day course of Coartem or a seven day course of oral quinine. The safety monitoring board stopped the trial after 178 patients had been recruited, however, because although cure rates at day seven were similar between the treatment arms, after 28 days of follow-up more than a third of children (35%) treated with quinine were parasitaemic compared with only 4% of children treated with Coartem (all of whom were later found to have new infections). Both drugs were given at home and adherence was assessed after three and seven days; by day three (the end of Coartem treatment) adherence was not significantly different between the treatment arms, but it then declined progressively in the quinine arm so that by day seven almost half (44%) of the children taking oral quinine were no longer adherent.

These findings show that a full seven day course of oral quinine is needed to cure malaria. The quinine content of the trial drug was not measured, although its source had been checked to the satisfaction of Ugandan authorities, so poor drug quality is an unlikely but possible alternative explanation. The key finding is that oral quinine was ineffective under conditions that closely resembled those in routine care.

Inadequately treated malaria carries a high risk of morbidity and mortality,[10] and World Health Organization guidelines (2006) do not recommend the use of unsupervised oral quinine as monotherapy. These guidelines recommend its use only in combination with clindamycin or a tetracycline (which are rarely available and tetracyclines are unsuitable for children or pregnant women) for the rare treatment failures that follow a course of artemisinin combination therapy or for uncomplicated malaria in the first trimester of pregnancy. Even then, the use of an alternative artemisinin combination is recommended before using quinine-clindamycin in children.[11] Unfortunately, these recommendations have not found their way into many national guidelines, and more than half of the national malaria control programmes in Africa still recommend monotherapy with oral quinine as second line treatment. In routine practice the use of oral quinine as a first line treatment seems to be widespread.

National guidelines need to be reviewed and updated, and health staff need to be made more aware that unsupervised oral quinine is not an effective treatment for malaria. Careful planning should prevent stock-outs (running out) of artemisinin combinations, and weak distribution networks need to be strengthened. Alternative artemisinin combinations also need to be stocked for the rare cases of treatment failure with a first line

combination; the choice of these should be directed by evidence from clinical trials. For the rare occasions when oral quinine must be used in children, the availability of a paediatric preparation with a less bitter taste would probably improve treatment adherence.

The much bigger question is what clinicians will do if artemisinin combinations cannot be relied on as a class of drugs? A strain of *P falciparum* with decreased susceptibility to artemisinin derivatives has been reported in southeast Asia.[12] If this resistance spreads to sub-Saharan Africa, there may be few alternatives to oral quinine. Because of the time needed to develop and license drugs, time and money must be spent now to develop alternative antimalarial drugs.

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Eating healthily and rising food prices

Implementing a rational food policy requires a political process that is transparent, documented, and accountable

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ANALYSIS, p 269

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Competing interests: None declared.
Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2009;339:b2527
doi: 10.1136/bmj.b2527

The linked analysis article by Lock and colleagues assesses the factors that contribute to rising food prices, the potential consequences for food security and public health, and policies that could help to secure an affordable and healthy global food supply.[1]

If the UK population ate a healthy diet, this would undoubtedly result in a considerable reduction in the burden of chronic disease, lower NHS costs, and increased workforce productivity. Furthermore, a consensus exists on what a healthy diet should look like. So what is the problem?

Firstly, we need to appreciate the current situation. The last national dietary survey, conducted in the United Kingdom in 2001, showed how many adults were meeting each of the government's dietary guidelines for fat, saturated fats, sugar, salt, and fruit and vegetables, but it did not perform a crucial piece of analysis: how many people were meeting all five targets at once? The answer is less than 1%—of the 1724 adults surveyed, just two men and eight women ate all round healthy diets.[2]

Next, we need to understand the nature of contemporary food supplies. After decades of government support for agricultural policies that invested heavily in meat and dairy production (and the grain to feed the livestock) and aimed to lower the costs of food supplies through mass production, the contemporary diet is remarkably rich in animal products, fats, oils, sugar, and starches, while remaining poor in foods with a short shelf life, such as fresh fruit, vegetables, and fish. The situation is fine for people who have the resources, but communities still exist in the UK where it is said to be easier to buy class A drugs than it is to buy apples.

Food prices have followed the investment process—the real price, after adjusting for general inflation, of fruits, vegetables, and fish has increased steeply over the past two decades whereas the price of soft drinks, snacks, and take away food has fallen. Vegetable oils, starches, and sugar have remained relatively cheap on global markets, even as overall food prices have risen. As Lock and colleagues show the trends are towards greater provision of less healthy foodstuffs, which implies that the most nutritious foods may soon sit only on the tables of the rich.

The goal of healthy diets for all faces a further challenge. Food supplies are crucially affected by fluctuations in weather, and rational action is needed to ensure survival through periods of shortage. The earliest recorded food policy makes exactly this point, with Joseph's advice to the Pharaoh to store the surplus from seven good harvests to allow for seven lean ones. Now the predictions for global warming are indicating that within 50 years the United States may cease to be a major grain producer, whereas Canada might grow grain around the Hudson Bay towards the Arctic Circle. Floods and droughts may also affect the UK, with Scotland potentially replacing East Anglia and Kent as the nation's main provider of horticulture.

These predictions get the UK government's attention far more readily than predictions of widespread obesity or diabetes in India, or the overwhelming of health services in Brazil. And although some economists may argue that free markets can deal with emerging health problems, no-one expects free markets to produce

sustainable environments without major government intervention.

And so the intriguing question becomes one of integrating dietary health with environmental sustainability and the production of food. The ideal is an agricultural policy which is both environmentally sustainable and able to provide the types of food that can ensure health for all. Quite an ambition.

The conclusion of Lock and colleagues' article notes the need to tackle the problem internationally, and to consider both the controls on supply—such as tariffs and trading terms and local value chains—and controls on demand—such as marketing restrictions, labelling requirements, and standards for food composition.

These are indeed important considerations, and to its credit the UK government has put some resources into exploring them in more detail. Its Foresight Research Project on Global Food and Farming will report in October 2010 on current and predicted trends, the drivers of change, and the types of policies needed.[3] Just this spring, the Biotechnology and Biological Sciences Research Council launched a consultation on the research requirements for future food security as part of a cross research council response to food supply concerns highlighted in the 2008 Cabinet Office Strategy Unit report *Food Matters*.[4]

But while these research endeavours continue the crisis can be expected to worsen. Little may be done to follow through Lock and colleagues' concerns for better controls on food supply and demand factors. Why? Because behind these issues lies a deeper more intractable set of problems—namely, the power relationships that determine how the trading controls are framed and implemented. The heart of global food policy is found in the dealings between highly financed corporations on the one side and the governmental agencies such as the United Nations Food and Agriculture Organization, the World Health Organization, and the World Trade Organization on the other.

These dealings occur mostly out of view, go unreported, and involve a small number of people. To make worthwhile changes they need to become transparent, routinely documented, and exposed to challenge and accountability. Again, to its credit, the UK has opened the workings of government to more critical view, by providing diaries of meetings, records of decisions, and even lists of expenses incurred by its legislators. These principles need to be applied at international level if food policies are to be truly democratised and rationalised.

This may seem a long way from people's daily diets, but public health was never a localised problem, and achieving health for all is fundamentally a matter of politics. Only by opening up the political process will we have a chance to implement a rational food policy, and thereby design a food supply that allows us all to eat a healthy diet.

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Making information about clinical trials publicly available

Open access to information on the EudraCT database will improve transparency

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Competing interests: None declared.
Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2009;338:b2473
doi: 10.1136/bmj.b2473

Recognition of the commercial and non-commercial benefits of greater transparency within clinical research has increased in the past decade. Public dissemination of the conduct and outcome of all clinical trials, including those performed as part of marketing authorisation applications, will ensure that professionals and patients have more information about how the safety and effectiveness of drugs has been evaluated. This will also prevent unnecessary duplication of research and, by encouraging greater scrutiny of clinical trials, will ensure that their ethical and scientific quality is improved. Wider dissemination of knowledge will also drive innovation and the conduct of further, more relevant, research.

This effort was considerably enhanced in 2004, when the International Committee of Medical Journal Editors (ICMJE) announced that an essential criterion for publication of a trial in one of their journals was that the details of the trial should be publicly available in a clinical trials register.[1 2] These requirements have been an important factor in driving public registration of clinical trials and the development of registers that provide free access to information about the research question, methodology, intervention, funding, and sponsorship. These registers include those of the World Health Organization (www.who.int/ictrp/en/), the US National Library of Medicine (http://clinicaltrials.gov/), the International Standard Randomised Controlled Trials Registry (http://isrctn.org/), and many others.

Another major driver in Europe has come from an initiative in a previously neglected area. The European regulation on better medicines for children became law in January 2007.[3] This legislation comprehensively deals with the unsatisfactory situation whereby a high proportion of drugs are used for children outside the approved conditions of their product licence, because they have not undergone clinical studies of safety and efficacy in that age group. The new legislation requires companies that wish to obtain a licence for their product in Europe to develop a paediatric investigation plan, unless the drug would never be used in children. It was also clear, however, that some companies had conducted studies in children during development programmes to market drugs and had decided not to market the drug for use in children. This may have been because the studies had not shown that the benefits outweighed the risks in this age group. Nevertheless, information from these studies was

not available either in the summary of product characteristics or any publicly accessible form.

This suppression of information was widely publicised when Eliot Spitzer, New York state's attorney general, accused GlaxoSmithKline (GSK), makers of the selective serotonin reuptake inhibitor paroxetine, of suppressing data from studies in adolescents, which either showed no benefit over placebo or a slight increase in self harm.[4] Spitzer's main complaint was that trials of paroxetine to treat major depressive disorder in childhood, as well as the safety outcomes of other trials, had been hidden from doctors by the manufacturer, and that GSK therefore deprived doctors of the information needed to evaluate the risks and benefits of prescribing paroxetine for children and adolescents with this disorder.[5] The law suit was settled, and in June 2004 GSK announced a GSK clinical trial register that would provide summaries of trial protocols and results for GSK sponsored trials of marketed drugs. The company stated that this move was to restore trust in research undertaken by the drugs industry. Other companies followed suit, and it seemed that the drugs industry recognised that the benefits of more openness greatly outweighed the risks.

The European paediatric legislation made it a requirement that information about clinical trials of investigational medicinal products being conducted in Europe with children should be made publicly available on the EudraCT database, and, following a consultation, the European Commission has recently published a guideline about the data fields for which information should be provided.[6] In addition, the results of clinical studies should be made available "without delay." For studies intended for marketing authorisation this means within six months of completion of the study; sponsors of non-commercial studies can extend this to one year, if they provide a scientifically justified reason.

With the implementation of the paediatric regulation, the incongruity of the position whereby the EudraCT database provided public access to information about clinical trials with children, but not adults, became untenable. In February 2009, the European Commission published the list of data fields to be made public from the EudraCT database for all trials, and these were similar to those for children.[6] The commission hopes that data about the protocols of ongoing trials will be available later this year, and the results of trials will be included about a year after this. The transatlantic position is also being harmonised. In the United States, the Food and Drug Administration Amendments Act (2007) made provision for the results of trials registered in the clinicaltrials.gov database to be made available no later than 12 months after data from the last participant were received.

Clinical research is undergoing a huge transformation. The availability of these rich and comprehensive datasets will provide important material for those who review, appraise, and synthesise information to inform drug regulation, patient care, and future research. Most importantly, it will provide reassurance to the public that information from studies, made possible by the generosity and support of patients, is being used for the benefit of all.

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Photodynamic therapy and cancer

Promising results need to be followed by development of more selective drugs

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Competing interests: SBB works for and holds shares in Photopharmica Ltd, a private company involved in early development of new drugs for photodynamic therapy, although not currently in the cancer field.
Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2009;339:b2459
doi: 10.1136/bmj.b2459

Photodynamic therapy uses visible light, molecular oxygen (normally present in most tissues at adequate concentration), and an otherwise innocuous drug to destroy tumours.[1] All three components are needed for the cytotoxic effect. Photodynamic therapy is licensed for the treatment of several cancers[1] and age related macular degeneration[2]; it is also being developed for the treatment of infections.[3] Photosensitising drugs may be given systemically or locally, but because the primary targeting is through precise direction of visible light from a laser or other source, the ultimate effect is local rather than systemic. This is important because, although it means that photodynamic therapy cannot cure disseminated disease, it underpins the selective targeting of this treatment and lack of generalised toxicity.

The photosensitising drug is given first, and after a time interval of between a few hours and four days—to allow the maximum concentration differential to develop between the tumour and surrounding healthy tissue—light is applied either from a laser for internal treatment or a light emitting diode or similar source for topical treatment. The tumour localised photosensitiser absorbs light of the appropriate wavelength and transfers the light derived energy to molecular oxygen. This creates cytotoxic activated oxygen species (mainly singlet oxygen), which destroy tumour cells directly through apoptosis or necrosis or indirectly through damage to tumour vasculature, thus starving tumour cells of oxygen.[1]

Relatively low cost lasers, light emitting diodes, and other light sources are routinely available for photodynamic therapy in the clinical setting, and light can now be accurately targeted to most internal and external parts of the body. Many photosensitisers have been tested in the laboratory, but few have


DAVID PARKER/SPL

progressed as far as clinical studies, and even fewer have been licensed as drugs.

The treatment can be applied systemically or topically.[1] Systemic administration of photosensitisers followed by laser light delivery endoscopically or interstitially is mainly used palliatively, but it can been used curatively when surgery is contraindicated.[1] Randomised controlled trials have led to the licensing of porfimer sodium (Photofrin), a mixture of porphyrins, for patients with completely or partially obstructing oesophageal cancer,[1] for palliation of symptoms in patients with completely or partially obstructing non-small cell lung cancer,[4] and for the ablation of high grade dysplasia associated with Barrett's oesophagus.[5] Temoporfin (Foscan), a porphyrin derivative known as a chlorin, is licensed for the treatment of head and neck cancer.[6] These treatments are available in a relatively small number of specialised centres in Europe, North America, and Japan.

In contrast, photodynamic therapy is much more widely used as a curative topical treatment for non-melanoma skin cancer and precancerous changes. Instead of using a photosensitiser directly, these topical treatments use the pro-drugs 5-aminolevulinate (licensed as Levulan in the United States) or its methyl ester (licensed as Metvix in Europe), which are naturally metabolised via the haem biosynthetic pathway to protoporphyrin IX, a powerful photosensitiser.

More than 150 dermatology centres offer treatment with Metvix in the United Kingdom and Ireland alone. Relative selectivity of protoporphyrin IX formation is seen in tumour cells, which helps target diseased tissue. Photodynamic therapy is increasingly used to treat superficial basal cell carcinoma, carcinoma in situ (Bowen's disease), and actinic keratosis. Multicentre randomised controlled trials have shown high efficacy (>80%) for clearance of superficial actinic keratosis of the face and scalp, Bowen's disease, and superficial basal cell carcinoma, with a recurrence of about 20% at five years of follow-up (but no recurrence after three years).[7] These response rates are at least equivalent to conventional treatments such as cryotherapy or 5-fluorouracil, but photodynamic therapy is better tolerated, produces superior healing and cosmetic outcome, and is preferred by patients. The British Photodermatology Group has published guidelines for the use of topical photodynamic therapy, and these are supported by a European international consensus and guidelines from the National Institute for Health and Clinical Excellence.[7-10]

Superior healing and cosmetic outcome are important advantages, particularly for superficial, large, or multiple lesions, as indicated in the NICE guidance. Photodynamic therapy may also have a role in treating immunosuppressed patients, such as those who have received an organ transplant, who are at increased risk of skin cancer.[7 11] Treatment is carried out on an outpatient basis, can be repeated, and is generally well tolerated, although the irradiation procedure is often painful. Topical photodynamic therapy is not indicated for melanoma or invasive squamous cell carcinoma, and it is not currently the treatment of choice for nodular basal cell carcinoma because it is less effective than surgery, although it may be considered when surgery is contraindicated.

Future developments in topical photodynamic therapy include refining the parameters for treatment with the photosensitiser and irradiation, and increasing the availability of treatment. Availability could be improved by the development of ambulatory home photodynamic therapy based on low irradiance light delivery, which seems to reduce the pain associated with this treatment. The future of photodynamic therapy for internal cancers is less certain, although the Department of Health has highlighted this treatment as one that should be more widely used by 2012. Such guidance has recently enabled not only dermatology departments, but also ear, nose and throat departments; plastic surgery units; and maxillofacial units to secure funding for photodynamic therapy services.

Systemic photodynamic therapy can be highly effective in certain cancers; for example, it can preserve speech in laryngeal cancer when surgery would lead to a substantial speech deficit. However, both Photofrin and Foscan are associated with long treatment times and prolonged skin photosensitivity. Drugs with higher tumour selectivity and little or no residual photosensitivity are needed, along with more controlled trials to confirm initially promising results—for example in pancreatic cancer and cholangiocarcinoma,[12] where photodynamic therapy has the potential to meet a currently unmet medical need.

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