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A treatment for autistic children with psychiatric problems that has never been tested is routinely used in France. Some psychiatrists say the technique has produced therapeutic results. But critics say that it is cruel, unproven, and potentially dangerous. Laura Spinney investigates. In France, autistic children who have psychiatric problems routinely undergo a treatment that has never been tested in a clinical trial and that many parents regard as cruel. Psychiatrists who use the technique claim that it produces positive results, but critics argue that it shows just how far France has fallen out of step with the international medical community in its understanding of the condition.

ARTICLES


International guidelines for management of septic shock recommend that dopamine or norepinephrine are preferable to epinephrine. However, no large comparative trial has yet been done. We aimed to compare the efficacy and safety of norepinephrine plus dobutamine (whenever needed) with those of epinephrine alone in septic shock. This prospective, multicentre, randomised, double-blind trial was done in 330 patients with septic shock admitted to one of 19 participating intensive care units in France. Participants were assigned to receive epinephrine (n=161) or norepinephrine plus dobutamine (n=169), which were titrated to maintain mean blood pressure at 70 mmHg or more. The primary outcome was 28-day all-cause mortality. Analyses were by intention to treat. There were no patients lost to follow-up; one patient withdrew consent after 3 days. At day 28, there were 64 (40%) deaths in the epinephrine group and 58 (34%) deaths in the norepinephrine plus dobutamine group (p=0·31; relative risk 0·86, 95% CI 0·65–1·14). There was no significant difference between the two groups in mortality rates at discharge from intensive care (75 [47%] deaths vs 75 [44%] deaths, p=0·69), at hospital discharge (58 [34%] deaths vs 58 [34%] deaths, p=0·97), and at 6-month follow-up (58 [34%] deaths vs 58 [34%] deaths, p=0·97).


A bungled corruption case against one of Poland’s leading cardiac surgeons has destroyed the conservative government’s credibility with the medical profession, helping inflame relations at a time when first doctors and now nurses have gone on strike. Jan Cienki reports from Warsaw. Mirosław Garlicki was a well regarded surgeon at Warsaw’s interior ministry hospital. In what the young and ambitious justice minister, Zbigniew Ziobro, hoped would be a coup in his attempt to root out corruption in Polish public life, Garlicki was arrested in February while at work, and led out in handcuffs past stunned co-workers.


This month, the UK’s High Court ruled in favour of the National Institute for Health and Clinical Excellence to limit access to drugs for Alzheimer’s disease. But the legal win is unlikely to stem the recent spate of controversies surrounding the institute. Richard Hoey reports. It was a legal ruling greeted with relief at the offices of the National Institute for Health and Clinical Excellence (NICE) but bitter disappointment among campaigners and the pharmaceutical industry. After 10 months of legal wrangles, a London court upheld the institute’s decision to restrict access to drugs for Alzheimer’s disease.


In Egypt, 15 people have died from avian influenza since the virus emerged in its poultry population last year. Controlling the infection in domestic birds—which are often undeclared—is proving to be one of the government’s biggest challenges. May Meleigy reports from Cairo. As avian influenza moved across Asia and into the Middle East in 2006, Egypt braced itself for a major outbreak in its country’s poultry. As expected, the highly pathogenic H5N1 avian influenza virus was first confirmed in Egypt in domestic poultry in February, 2006, and has since become deeply entrenched in this poultry population. From March, 2006, to August 3, 2007, there have been 15 human deaths from avian influenza out of 38 infections, ranking Egypt the worst affected region in the eastern Mediterranean.
discharge (84 [52%] vs 82 [49%], p=0·51), and by day 90 (84 [52%] vs 85 [50%], p=0·73), time to haemodynamic success (log-rank p=0·67), time to vasopressor withdrawal (log-rank p=0·09), and time course of SOFA score. Rates of serious adverse events were also similar. There is no evidence for a difference in efficacy and safety between epinephrine alone and norepinephrine plus dobutamine for the management of septic shock.


In-vitro and animal experiments have shown that the cyclo-oxygenase 2 inhibitor celecoxib can reduce formation of neointima within stents. We aimed to test whether celecoxib has similar effects in a clinical setting. In a randomised two-centre trial, we enrolled 274 patients who had angina pectoris or a positive stress test and who had native coronary artery lesions for which implantation of paclitaxel-eluting stents was feasible. All patients were given aspirin (100 mg daily) and clopidogrel (75 mg daily). 136 patients were randomly assigned to receive celecoxib (400 mg before the intervention, and 200 mg twice daily for 6 months after the procedure). The primary endpoint was late luminal loss on quantitative coronary angiography at 6 months after the intervention. Secondary endpoints were cardiac death, non-fatal myocardial infarction, and revascularisation of the target lesion. Analysis was done on a modified intention-to-treat basis. At 6 months, mean in-stent late luminal loss was lower in the celecoxib group (0.49 mm, SD 0.47) than in the control group (0.75 mm, 0.60) (absolute difference 0.26 mm; 95% CI 0.12–0.40). Frequency of secondary outcomes at 6 months was also lower in the celecoxib group, mainly because of a reduced need for revascularisation of the target lesion. These data suggest that the adjunctive use of celecoxib for 6 months after stent implantation in patients with coronary artery disease is safe and can reduce the need for revascularisation of the target lesion.


Whether remote ischaemic preconditioning, an intervention in which brief ischaemia of one tissue or organ protects remote organs from a sustained episode of ischaemia, is beneficial for patients undergoing coronary artery bypass graft surgery is unknown. We did a single-blinded randomised controlled study to establish whether remote ischaemic preconditioning reduces myocardial injury in these patients. 57 adult patients undergoing elective coronary artery bypass graft surgery were randomly assigned to either a remote ischaemic preconditioning group (n=27) or to a control group (n=30) after induction of anaesthesia. Remote ischaemic preconditioning consisted of three 5-min cycles of right upper limb ischaemia, induced by an automated cuff-inflator placed on the upper arm and inflated to 200 mmHg, with an intervening 5 min of reperfusion during which the cuff was deflated. Serum troponin-T concentration was measured before surgery and at 6, 12, 24, 48, and 72 h after surgery. Analysis was by intention to treat. Remote ischaemic preconditioning significantly reduced overall serum troponin-T release at 6, 12, 24, and 48 h after surgery. The total area under the curve was reduced by 43%, from 36-12 lg/L (SD 26-08) in the control group to 20-58 lg/L (9-58) in the remote ischaemic preconditioning group (mean difference 15·55 [SD 5·32]; 95% CI 4·88–26·21; p=0·005). We have shown that adult patients undergoing elective coronary artery bypass graft surgery at a single tertiary centre could benefit from remote ischaemic preconditioning, using transient upper limb ischaemia.
Antigen sparing is regarded as crucial for pandemic vaccine development because worldwide influenza vaccine production capacity is limited. Adjuvantation is an important antigen-sparing strategy. We assessed the safety and immunogenicity of a recombinant H5N1 split-virion vaccine formulated with a proprietary adjuvant system and investigated whether it can induce cross-reactive immunity. Two doses of an inactivated split A/Vietnam/1194/2004 NIBRG-14 (recombinant H5N1 engineered by reverse genetics) vaccine were administered 21 days apart to eight groups of 50 volunteers aged 18–60 years. We studied four antigen doses (3.8 μg, 7.5 μg, 15 μg, and 30 μg haemagglutinin) given with or without adjuvant. Blood samples were collected to analyse humoral immune response. Adverse events were recorded up through study day 51. Safety analyses were of the whole vaccinated cohort and immunogenicity analyses per protocol. All eight vaccine formulations had a good safety profile. No serious adverse events were reported. The adjuvanted vaccines induced more injection-site symptoms and general symptoms than did the non-adjuvanted vaccines, but most were mild to moderate in intensity and transient in nature. The adjuvanted formulations were significantly more immunogenic than the non-adjuvanted formulations at all antigen doses. At the lowest antigenic dose (3.8 μg), immune responses for the adjuvanted vaccine against the recombinant homologous vaccine strain (A/Vietnam/1194/2004 NIBRG-14, clade 1) met or exceeded all US Food and Drug Administration and European Union licensure criteria. Furthermore, 37 of 48 (77%) participants receiving 3.8 μg of the adjuvanted vaccine seroconverted for neutralising antibodies against a strain derived by reverse genetics from a drifted H5N1 isolate (A/Indonesia/5/2005, clade 2). Adjuvantation conferred significant antigen sparing that could increase the production capacity of pandemic influenza vaccine. Moreover, the cross-clade neutralising antibody responses recorded imply that such a vaccine could be deployed for immunisation before a pandemic.

Individuals with diabetes are at higher risk of myocardial infarction than non-diabetics. However, much less is known about the incidence of, and risk factors for, development of diabetes and impaired fasting glucose in patients who have had a myocardial infarction. We set out to estimate this incidence and investigate whether lifestyle factors such as dietary habits might alter this risk. We used prospectively obtained data for 8291 Italian patients with a myocardial infarction within the previous 3 months, who were free of diabetes (determined by medication use, a physician-reported diagnosis, or fasting glucose =7 mmol/L) at baseline. Incidence of new-onset diabetes (new diabetes medication or fasting glucose =7 mmol/ L) and impaired fasting glucose (fasting glucose =6.1 mmol/L and <7 mmol/L) were assessed at follow-up at 0.5, 1.0, 1.5, 2.5, and 3.5 years. Baseline data for body-mass index (BMI), other risk factors, dietary habits, and medications were updated during follow-up. A Mediterranean diet score was assigned according to consumption of cooked and raw vegetables, fruit, fish, and olive oil. Associations of demographic, clinical, and lifestyle risk-factors with incidence of diabetes and impaired fasting glucose were assessed with multivariable Cox proportional hazards. During 26,795 person-years (mean follow-up 3.2 years [SD 0.9]), 998 individuals (12%) developed new-onset diabetes (incidence 37 cases per 1000 person-years). Of the 7533 without impaired fasting glucose at baseline, 2514 (33%) developed new-onset impaired fasting glucose or diabetes (incidence 123 cases per 1000 person-years), rising to 3859 (62%) of 6229 with the lower cutoff for impaired fasting glucose at baseline. Incidence of new-onset impaired fasting glucose (fasting glucose =6.1 mmol/L and <7 mmol/L) were assessed at follow-up at 0.5, 1.0, 1.5, 2.5, and 3.5 years. Baseline data for body-mass index (BMI), other risk factors, dietary habits, and medications were updated during follow-up. A Mediterranean diet score was assigned according to consumption of cooked and raw vegetables, fruit, fish, and olive oil. Associations of demographic, clinical, and lifestyle risk-factors with incidence of diabetes and impaired fasting glucose were assessed with multivariable Cox proportional hazards. During 26,795 person-years (mean follow-up 3.2 years [SD 0.9]), 998 individuals (12%) developed new-onset diabetes (incidence 37 cases per 1000 person-years). Of the 7533 without impaired fasting glucose at baseline, 2514 (33%) developed new-onset impaired fasting glucose or diabetes (incidence 123 cases per 1000 person-years), rising to 3859 (62%) of 6229 with the lower cutoff for impaired fasting glucose of 5.6 mmol/L (incidence 321 cases per 1000 person-years). Independent risk factors for new-onset diabetes or impaired fasting glucose included older age, hypertension, use of beta-blockers, lipid-lowering medications (protective), and diuretic use. Independent lifestyle risk-factors included higher BMI, greater BMI gain during follow-up, current smoking, a lower Mediterranean dietary score, and wine consumption of more than 1 L/day. Data for physical activity were unavailable, but inability to perform exercise testing was associated with higher incidence of diabetes and impaired fasting glucose. Compared with population-based cohorts, patients with a recent myocardial infarction had a higher
annual incidence rate of impaired fasting glucose (1.8 vs 27.5% in our study) and diabetes (0.8–1.6% compared with 3.7%) in this study. Thus, our results indicate that myocardial infarction could be a prediabetes risk equivalent. Smoking cessation, prevention of weight gain, and consumption of typical Mediterranean foods might lower this risk, which emphasises the need for guidance on diet and other lifestyle factors for patients who have had a myocardial infarction.

**Tang, BMP, Guy D Eslick, Caryl Nowson, Caroline Smith, and Alan Bensoussan. (2007). Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. The Lancet, 370(9588), 657-666.**

Whether calcium supplementation can reduce osteoporotic fractures is uncertain. We did a meta-analysis to include all the randomised trials in which calcium, or calcium in combination with vitamin D, was used to prevent fracture and osteoporotic bone loss. We identified 29 randomised trials (n=637897) using electronic databases, supplemented by a hand-search of reference lists, review articles, and conference abstracts. All randomised trials that recruited people aged 50 years or older were eligible. The main outcomes were fractures of all types and percentage change of bone-mineral density from baseline. Data were pooled by use of a random-effect model. In trials that reported fracture as an outcome (17 trials, n=527625), treatment was associated with a 12% risk reduction in fractures of all types (risk ratio 0.88, 95% CI 0.83–0.95; p=0.0004). In trials that reported bone-mineral density as an outcome (23 trials, n=417419), the treatment was associated with a reduced rate of bone loss of 0.54% (0.35–0.73; p<0.0001) at the hip and 1.19% (0.76–1.61%; p<0.0001) in the spine. The fracture risk reduction was significantly greater (24%) in trials in which the compliance rate was high (p<0.0001). The treatment effect was better with calcium doses of 1200 mg or more than with doses less than 1200 mg (0.80 vs 0.94; p=0.006), and with vitamin D doses of 800 IU or more than with doses less than 800 IU (0.84 vs 0.87; p=0.03). Evidence supports the use of calcium, or calcium in combination with vitamin D supplementation, in the preventive treatment of osteoporosis in people aged 50 years or older. For best therapeutic effect, we recommend minimum doses of 1200 mg of calcium, and 800 IU of vitamin D (for combined calcium plus vitamin D supplementation).

**SEMINAR**

**Messerli, F.H., Bryan Williams, and Eberhard Ritz. (2007). Essential hypertension. The Lancet; 370(9587), 591-603.**

Essential hypertension can be defined as a rise in blood pressure of unknown cause that increases risk for cerebral, cardiac, and renal events. In industrialised countries, the risk of becoming hypertensive (blood pressure >140/90 mm Hg) during a lifetime exceeds 90%. Essential hypertension usually clusters with other cardiovascular risk factors such as ageing, being overweight, insulin resistance, diabetes, and hyperlipidaemia. Subtle target-organ damage such as left-ventricular hypertrophy, microalbuminuria, and cognitive dysfunction takes place early in the course of hypertensive cardiovascular disease, although catastrophic events such as stroke, heart attack, renal failure, and dementia usually happen after long periods of uncontrolled hypertension only. All antihypertensive drugs lower blood pressure (by definition) and this decline is the best determinant of cardiovascular risk reduction. However, differences between drugs exist with respect to reduction of target-organ disease and prevention of major cardiovascular events. Most hypertensive patients need two or more drugs for blood-pressure control and concomitant statin treatment for risk factor reduction. Despite the availability of effective and safe antihypertensive drugs, hypertension and its concomitant risk factors remain uncontrolled in most patients.

**REVIEW**


Atrial fibrillation is the most common sustained cardiac rhythm disorder, and confers a substantial mortality and morbidity from stroke, thromboembolism, heart failure, and impaired quality of life. With the increasingly elderly population in the developed world, as well as improvements in the management of myocardial infarction and heart failure, the prevalence of atrial fibrillation is increasing, resulting in a major public-health problem. This Review aims to provide an overview on the modern management of atrial fibrillation, with particular emphasis on pharmacological and non-pharmacological approaches. Irrespective of a rate-control or rhythm-control strategy, stroke prevention with appropriate thromboprophylaxis still remains central to the management of this common arrhythmia.
SERIES, Health and Human Rights


Neglected diseases remain one of the largest causes of disease and mortality. In addition to the difficulties in provision of appropriate drugs for specific diseases, many other factors contribute to the prevalence of such diseases and the difficulties in reducing their burden. We address the role that poor governance and politically motivated oppression have on the epidemiology of neglected diseases. We give case examples including filariasis in eastern Burma and vector-borne diseases (Chagas’ disease, leishmaniasis, and yellow fever) in Colombia, we show the links between systematic human rights violations and the effects of infectious disease on health. We also discuss the role of researchers in advocating for and researching within oppressed populations.


For humanitarian health-care practitioners bearing witness to violations of human dignity has become synonymous with denunciations, human rights advocacy, or lobbying for political change. A strict reliance on legal interpretations of humanitarianism and human rights is inadequate for fully understanding the problems inherent in political change. With examples from the HIV/AIDS epidemic in the USA, the Rwandan genocide, and physician-led political activism in Nepal, we describe three cases in which health practitioners bearing witness to humanitarian and human-rights issues have had imperfect outcomes. However these acts of bearing witness have been central to the promotion of humanitarianism and human rights, to the pursuit of justice that they have inevitably and implicitly endorsed, and thus to the politics that have or might yet address these issues.

SEMINAR


Polycystic ovary syndrome is a heterogeneous endocrine disorder that affects about one in 15 women worldwide. The major endocrine disruption is excessive androgen secretion or activity, and a large proportion of women also have abnormal insulin activity. Many body systems are affected in polycystic ovary syndrome, resulting in several health complications, including menstrual dysfunction, infertility, hirsutism, acne, obesity, and metabolic syndrome. Women with this disorder have an established increased risk of developing type 2 diabetes and a still debated increased risk of cardiovascular disease. The diagnostic traits of polycystic ovary syndrome are hyperandrogenism, chronic anovulation, and polycystic ovaries, after exclusion of other conditions that cause these same features. A conclusive definition of the disorder and the importance of the three diagnostic criteria relative to each other remain controversial. The cause of polycystic ovary syndrome is unknown, but studies suggest a strong genetic component that is affected by gestational environment, lifestyle factors, or both.