Short cuts

What's new in the other general journals

A few weeks' treatment with an opioid can help relieve neuropathic pain

During 15 years of research on the impact of opioids on neuropathic pain, only 607 patients have been randomised in comparative trials of reasonable quality, the longest of which lasted only eight weeks. That's not much to go on but, according to this meta-analysis, it's enough to show fairly conclusively that opioids such as morphine and oxycodone can relieve chronic neuropathic pain if taken regularly for several weeks. Short term treatments such as with fentanyl or intravenous morphine looked less effective, but it's impossible to say for certain because the trials were so small (median 13 patients) and hard to combine in any meaningful way.

Most of the 403 patients in the longer trials had post-herpetic neuralgia, diabetic neuropathy, or phantom pain. Taking opioids for a few weeks reduced their pain by a mean of 14 points on a scale of 1-100 compared with placebo—a 20-30% improvement, which the authors think is clinically meaningful and similar to the pain relief these patients get from other effective treatments such as gabapentin. The commonest side effects were nausea (number needed to harm 3.6), constipation (4.6), drowsiness (5.3), vomiting (6.2), and dizziness (6.7).

None of the trials in this review mentioned or measured the risk of addiction or misuse, possibly because in most of them the treatment period was too short for addiction to be a problem. Bigger, better, and longer trials are urgently needed to find out if opioids work long term for these patients, if the risks are acceptable, and if the moderate pain relief reported in this review translates to a better quality of life for patients.

JAMA 2005;293:3043-52

Death from idiopathic pulmonary fibrosis is often preceded by rapid and unpredictable decline

Pulmonary fibrosis is one of the commonest idiopathic interstitial pneumonias, but we know little about it beyond the fact that prognosis is generally poor. Studying patients in the placebo arms of randomised trials is one way to find out more. In one such study, lasting 76 weeks, 38 of 168 patients (23%) were hospitalised at least once for respiratory problems, and 36 (21%) died despite starting the study with only mild or moderate disease. What surprised researchers most, however, was that nearly half of the deaths from pulmonary fibrosis (15/32) were preceded by an acute worsening of symptoms, precipitating a terminal illness that lasted no more than a month.

Acute exacerbations of idiopathic pulmonary fibrosis are not new, but this study suggests they are substantially more common than previously reported, and possibly more lethal. Patients with this enigmatic disease should be monitored more closely and more often than they are now, say the authors. More importantly, they should be worked up for a possible lung transplant operation much earlier.

Annals of Internal Medicine 2005;142:963-7

New vaccine boosts immunity against whooping cough in adolescents and adults

Adolescents and adults now account for nearly two thirds of all cases of whooping cough in the United States, a proportion that has increased steadily over the past 30 years. A booster vaccine might help, but none is currently licensed in the US for adolescents or adults. Manufacturers Sanofi Pasteur have a new compound vaccine under evaluation, and their latest phase III trial shows that it produces a brisk and effective immune response in people aged 11-64 years.

The vaccine is similar to their existing compound vaccine against diphtheria and tetanus, which is already licensed for adults, with the addition of an acellular pertussis vaccine made of five different components—pertussis toxoid, filamentous haemagglutinin, pertactin, and fimbriae types 2 and 3. In a randomised trial, single intramuscular doses of both the new and existing vaccines induced a protective

immune response against diphtheria and tetanus within 28 days in over 90% of the 4480 participants. The new vaccine also induced an antibody response against pertussis antigens that was between two and five times bigger than the response produced by a similar vaccine known to be effective in infants. New and existing vaccines caused a similar number and type of side effects, mostly mild.

JAMA 2005;293:3003-11

Oral capecitabine is safer than fluorouracil for stage III colon cancer

Intravenous fluorouracil is a well established adjuvant treatment for patients with colorectal cancer. It works, but, like many chemotherapeutic agents, it causes serious side effects, including neutropenia, alopecia, diarrhoea, stomatitis, sickness, and hand-foot syndrome. A recent randomised trial shows that capecitabine, an oral prodrug that converts to fluorouracil at the cellular level, works just as well and is substantially less toxic.

The trial included 1987 adults with resected stage III (lymph node positive) colon cancer, who received 24 weeks of adjuvant chemotherapy with oral capecitabine or intravenous fluorouracil plus leucovorin given as a bolus. Three years later, disease-free survival was 60.6% in the fluorouracil group and 64.2% in the capecitabine group (hazard ratio 0.87; 95%

confidence interval 0.75 to 1.00, $P=0.12$), a difference that shows the two treatments are at least equivalent. Results for overall survival were similar. Patients who took capecitabine, however, had significantly fewer serious side effects than control patients, particularly neutropenia (2% *v* 26%, $P<0.001$). Hand-foot syndrome was the commonest side effect associated with capecitabine (17%).

For patients who need only one drug, capecitabine now looks like the better option, says a commentator (pp 2746-8). Other patients will have to wait for ongoing trials to report on the place of capecitabine in multidrug regimens.

New England Journal of Medicine
2005;352:2696-704

Daclizumab reduces rejections but not mortality after heart transplant

Daclizumab, a monoclonal antibody directed against activated lymphocytes, reduced the risk of graft rejection in a randomised trial to assess this treatment in patients with a heart transplant (55/216 (25%) *v* 90/218 (41%) with placebo). But its effects on mortality were much less clear: six months after treatment 6.5% of those given daclizumab had died compared with 3.2% of those given a placebo. All patients received standard triple therapy (ciclosporin, mycophenolate mofetil, and corticosteroids) for immunosuppression. The difference in mortality was not statistically significant but worried one transplant cardiologist: he commented (pp 2749-50) that he would not trade the lower rate of rejection in this trial for even a small increased risk of death.

By dissecting their results further, the trial's authors found that the excess deaths were mostly among patients who had received other cytolytic treatments in addition to daclizumab and outside the trial's protocol. Of the 21 patients who died in the daclizumab group, eight had received two cytolytic treatments and six of these had died of infection. The authors (supported by the drug manufacturers) say the problem could be solved by avoiding other cytolytic therapies in patients given daclizumab; others may need more convincing.

New England Journal of Medicine
2005;352:2705-13

Endovascular repair: lower mortality from aneurysms is offset by higher rate of complications

Endovascular repair of abdominal aortic aneurysm was developed as a less invasive alternative to open repair. Early results from ongoing trials show that it's safer in the short term, reducing operative mortality by about two thirds for patients with aneurysms 5.5 cm or more in diameter. In a

midterm report from the UK trial, aneurysm related mortality remained lower in the endovascular repair group than in the open repair group four years later (4% *v* 7%; hazard ratio 0.55, 95% CI 0.31 to 0.96), even though patients who had had endovascular repair had significantly more complications (41% *v* 9%; hazard ratio 4.9, 3.5 to 6.8) and needed significantly more reinterventions. All cause mortality was about the same in both groups (28%), as was quality of life one year after the initial repair. Overall, endovascular repair cost a third more than open repair, because of all the extra hospital costs associated with follow-up.

All 1082 patients in this trial were relatively fit. In a sister trial, however, of patients who were too unfit for open surgery (pp 2187-92), endovascular repair was no better than doing nothing: 9% of patients died within a month after the operation, and 64% of the patients in both groups were dead four years later.

What does all this mean for patients with an aneurysm? An accompanying editorial (pp 2156-8) says that young fit patients with low operative risk and a long life expectancy should probably stick with open repair, at least for now. Patients with a higher operative risk and suitable anatomy should be considered for endovascular repair, and patients with a very high operative risk should be managed conservatively.

Lancet 2005;365:2179-86

Sexually transmitted infections fuel the HIV epidemic in Moscow

The Russian Federation is in the middle of the world's fastest growing epidemic of HIV infection, fuelled by an explosive mix of sexually transmitted infections, sex work, and injecting drug use among vulnerable

populations in Moscow, according to a recent survey. The survey included 1066 teenagers and adults living in a juvenile detention centre, a remand centre, or facilities for the homeless in Moscow.

Around 2% of all participants were HIV positive (1.9%, 2.8%, 1.8%, respectively). Over half the teenage girls in the detention centre (58%; 97/167) had one or more sexually transmitted bacterial infections, including syphilis, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis*, a rate of infection 3-31 times higher than the rate among teenage boys in the same centre. Infection rates were even higher among homeless women: three quarters (133/178; 75%) had a sexually transmitted infection, half had syphilis (91/178; 51%), and four of the 165 with test results were HIV positive. Rates of all infections, except HIV, were higher among women than men in that facility. Women and girls who reported trading sex for money, drugs, or other commodities had double the risk of sexually transmitted infection compared with the others, and 5-11% of them also injected drugs. Most of the women and girls with HIV were sex workers.

Lancet 2005;366:57-60

Cholera vaccines protect the herd

Cholera vaccines have been available for decades, but not even the most vulnerable countries have mass vaccination programmes, partly because of doubts about how well they work. A new look at a 20 year old study from Bangladesh shows that herd immunity can augment the direct effects of a killed cholera vaccine, reducing the risk of infection by about three quarters among unvaccinated people.

The original study, a randomised trial comparing two killed whole cell vaccines with placebo, recruited 124 035 women and children from rural Bangladesh living in extended family units called baris. Coverage in the baris varied between 4% and 65%. During the first year of the study, the incidence of cholera among unvaccinated participants was four times higher in baris with low coverage than in baris with high coverage (7.01 cases per 1000 *v* 1.47 cases per 1000, $P<0.0001$). The incidence of cholera among vaccinated participants was also slightly lower in baris with high coverage.

This substantial herd protection should be factored in to any discussions about the overall benefits to public health of killed cholera vaccines, say the authors. Previous analyses that ignored herd protection may have seriously underestimated the protective potential of mass vaccination against cholera.

Lancet 2005;266:44-99

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