Short cuts

What's new in the other general journals

Normal doses of paracetamol can derange liver enzymes in healthy adults

Therapeutic doses of paracetamol (acetaminophen) are normally considered safe. But in a recent experiment, healthy young volunteers taking therapeutic doses of the drug developed abnormal liver function after only a few days.

The 145 volunteers took 4 g a day of paracetamol with or without an opioid (morphine, hydromorphone, or oxycodone), or a placebo. More than a third of the volunteers taking paracetamol had serum concentrations of alanine aminotransferase over three times the upper limit of normal at some point during the 14 day experiment. More than a fifth experienced peak concentrations over five times the upper limit of normal. The opioids seemed to make no difference either to peak concentrations of alanine aminotransferase or to the timing of the abnormal results, which persisted for 1-11 days after treatment was stopped and long after serum concentrations of paracetamol had fallen to subtherapeutic levels. Overall, peak values for alanine aminotransferase were two to three times higher in the paracetamol groups than the placebo group.

The researchers aren't sure why no one has noticed such a marked effect before and suggest that further work be done to find out who is most vulnerable. In this study, Hispanic volunteers seemed more likely than non-Hispanic Americans to develop abnormally high serum concentrations of alanine aminotransferase (relative risk 1.9; 95% CI 1.1 to 3.3).

JAMA 2006;296:87-93

Acupuncture and sham acupuncture both ease the pain of arthritis

In Germany, acupuncture is a popular treatment for chronic pain caused by osteoarthritis of the knee. Faced with a patchy and inconsistent evidence base, a consortium of social healthcare insurance organisations funded a large and well designed trial to find out if acupuncture adds anything to standard treatments based on anti-inflammatory drugs and physiotherapy.

All 1007 participants had up to six sessions of physiotherapy and anti-inflammatory drugs as required (rofecoxib or diclofenac). They also had either 10 consultations with a doctor, 10 sessions of real acupuncture, or 10 sessions of sham acupuncture over six weeks. The acupuncture and the sham acupuncture worked equally well, producing a clinically important improvement in over half the patients at 26 weeks (53% (173/326) for acupuncture and 51% (186/365) for sham acupuncture). Standard treatment alone produced the same response in only 29% (92/316) of patients, a significantly worse performance than either real or sham acupuncture ($P < 0.001$).

The authors were slightly surprised by these results, which suggest that acupuncture relieves the symptoms of arthritis in a way we don't yet understand. One possibility is that the patients who had either real or sham acupuncture benefited from more intensive interpersonal contact with their practitioner than the controls. Another, say the authors, is that needling, whether or not it's in the "right" places, might have real therapeutic effects.

Ann Intern Med 2006;145:12-20

New drug helps smokers to quit

Experts from the United States have given a cautious welcome to a new drug designed to help people quit smoking. Varenicline is a partial agonist at nicotinic acetylcholine receptors and is the first new agent in nearly a decade that does not contain nicotine. Three randomised trials (pp 47-55, 56-63, 64-71) suggest it can work better than a placebo and possibly better than sustained release bupropion, although the experts say that important limitations in all three trials mean that it probably won't work for everyone.

Even with the new drug, most trial participants failed to quit for long. About four fifths of participants taking varenicline

CONTINUOUS ABSTINENCE FROM SMOKING

had relapsed by the end of a year in two of the trials. In the third, 44% managed to stop smoking for a year, but this trial recruited only people who had shown they were willing and able to stop smoking for at least a week.

Three out of 10 people taking varenicline said it made them feel sick. Sleep disturbance was also relatively common.

These large trials show once again that most people find it difficult to stop smoking, even in the best possible conditions and even when they want to quit badly enough to volunteer for a randomised trial of a new treatment.

JAMA 2006;296:94-5

Mediterranean diets reduce cardiovascular risk after only three months

A team of Spanish investigators is running a large feeding trial to find out if Mediterranean diets really do protect people from cardiovascular disease. They won't have any data on cardiovascular events until at least 2010, but they recently reported some preliminary findings on the short term effects of Mediterranean diets on surrogate markers of cardiovascular risk such as blood pressure.

After only three months, a diet rich in either mixed nuts or virgin olive oil had a greater impact on glucose metabolism, systolic blood pressure, and plasma lipid profiles than a standard low fat diet among 772 older Spanish adults with a high risk of cardiovascular disease.

Participants prepared their own food during the three months but were advised by a dietitian how to make their diet more classically Mediterranean by eating more fish, fruit, vegetables, and vegetable fats and oils. They were also given a free supply of nuts or extra virgin olive oil. Compared with a low fat diet, the two Mediterranean diets reduced systolic blood pressure by 6 mm Hg (oil) and 7 mm Hg (nuts) and

reduced serum concentrations of glucose by 0.4 mmol/l and 0.3 mmol/l respectively.

The participants experienced few side effects. But up to 13% of those eating extra nuts said the bits got stuck between their teeth.

Ann Intern Med 2006;145:1-11

Perioperative chemotherapy prolongs survival for people with gastric cancer

Patients with resectable gastric and lower oesophageal cancers need surgery. They may also benefit from perioperative chemotherapy, according to an international clinical trial that found a clear survival advantage for a regimen based on three cycles of epirubicin, cisplatin, and fluorouracil before surgery and another three cycles starting up to six weeks after surgery.

The trial included 503 patients with an adenocarcinoma of the stomach or lower oesophagus that had penetrated the submucosa. All had a gastrectomy. Two hundred and fifty were also offered perioperative chemotherapy, although less than half completed all six cycles. Those assigned to chemotherapy had a five year survival of 36%, significantly higher than the 23% survival among controls.

Progression-free survival was also longer in the chemotherapy group (hazard ratio for progression 0.66 (95% CI 0.53 to 0.81); $P < 0.001$). Of the 209 patients who completed their chemotherapy before surgery, fewer than half completed the treatment afterwards.

As expected, substantial side effects were associated with chemotherapy, including severe granulocytopenia, which affected about a quarter of patients. The authors hope that newer agents will prove less toxic. But in the meantime, patients with these dangerous tumours should be given the option of a treatment that increases their chances of surviving for five years by 25%.

N Engl J Med 2006;355:11-20

Recently released prisoners have high risk of suicide

Men and women prisoners are more likely to kill themselves than men and women on the outside. Being released can be equally hazardous, according to a data linkage study of men and women released from prisons in England and Wales. During the first year, men were eight times (95% CI 7.5 to 9.3) more likely to die by suicide than men of the same age in the general population. For women, the suicide rate was a striking 36 (25 to 50) times higher than expected.

Among men, the comparative risk of suicide increased roughly linearly with age, being highest in the over 50s. In other populations, suicide is commoner among the young. All released prisoners seemed most vulnerable during the first month of freedom, when about a fifth of the suicides occurred. Overall, the researchers identified 382 suicides in recently released prisoners over a two year period, a rate of 156 per 100 000 person years. The risk of suicide among recently released prisoners in this study approached the risk recorded among patients released from psychiatric hospitals.

There are many plausible explanations for these dismal findings, write the study authors, including mental illness, poverty, poor housing, unemployment, and fractured social and family networks. In 2002 a third of the prisoners released in England and Wales had no homes to go to, three quarters had no jobs, and half had no family.

Lancet 2006;368:119-23

Childhood influenza is common, underdiagnosed, and undertreated

US authorities recommend a yearly influenza vaccination for toddlers aged between 6 months and 2 years. The recommendation was driven by high rates of hospitalisation among young children with influenza. But the real problem is out there in the community, according to a report from an active surveillance network operating in three US states. For every 1000 children under 5 years old, the network recorded 95 visits to outpatient clinics and 27 visits to emergency departments during the 2003-4 season alone. That's a burden of illness in outpatient visits between 10 and 250 times greater than the burden in hospitalisations in the same states.

During active surveillance, nurses tested all children under 5 presenting to selected hospitals, clinics, and emergency departments with upper respiratory tract symptoms or a fever. Of all those tested as outpatients, 16% (274/1742) had laboratory confirmed influenza. The commonest symptoms were fever (95%), cough (96%), and a runny nose (96%). Doctors recognised the infection in only a minority of children—28% of inpatients and 17% of outpatients. Very few got any kind of antiviral treatment.

A linked editorial (pp 79-81) says this represents a substantial missed opportunity. Early treatment can help prevent complications and control spread to contacts.

N Engl J Med 2006;355:31-40

Particulate pollution probably reduces lung function in healthy children

Air pollution from traffic is damaging children's lungs. Researchers from the United Kingdom have found a clear link between carbon particles in children's lung macrophages and poor performance in lung function tests. The carbon they found had come from local traffic near where the children lived in Leicester, one of the UK's largest cities.

The link between inhaled pollution and lung function was dose dependent such that each increase of 1.0 µm² in the carbon content of lung macrophages was associated with a reduction of 17% (95% CI 5.6% to 28.4%) in forced expiratory volume in one second, a 13% (0.9% to 24.8%) reduction in forced vital capacity, and a 34.7% (11.3% to 58.1%) reduction in forced expiratory flow between 25% and 75% of the forced vital capacity.

The children who took part were all healthy volunteers from local schools and aged between 8 and 15 years. Researchers isolated macrophages from their sputum to look for carbon and also modelled the volume of particulate pollution in the ambient air around their home address. Every extra 1.0 µg per cubic metre of particulate pollution in the atmosphere was associated with an extra 0.10 µm² of carbon in the children's airways.

N Engl J Med 2006;355:21-30

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