Short cuts

What's new in the other general journals

Fluoxetine does not prevent relapse of anorexia nervosa

Antidepressants such as fluoxetine are a common treatment for anorexia nervosa, even though there's no evidence that they help with weight gain. A new trial has found that fluoxetine doesn't prevent relapses either, a disappointing result given the high rate of relapse and the high risk of all cause mortality associated with this common mental illness. The trial was relatively small ($n = 93$) but well done, and a linked editorial (pp 2659-60) describes it as convincingly negative. Compared with placebo, fluoxetine did not prolong remission in women aged 16-45 who had recovered after initial treatment. Time to relapse was similar in both groups, and only 26.5% of the women taking fluoxetine and 31.5% of those taking a placebo managed to continue with treatment and keep their body mass index above 18.5 during the trial, which lasted one year. All the participants had cognitive behaviour therapy.

As expected, dropout rates were high. Only 40 of the 93 women completed their course of treatment. They were equally likely to drop out of placebo and treatment groups.

The editorial says this trial leaves doctors with few if any drug options for young women with anorexia, partly because the research effort so far has not matched the importance of this disease. Anorexia is associated with a higher risk of suicide than any other mental illness.

JAMA 2006;295:2605-12

New treatment for rotavirus looks promising

Nitazoxanide is an antidiarrhoeal agent already licensed in the United States to treat diarrhoea caused by *Cryptosporidium* spp and *Giardia* spp. It also seems to work

against rotavirus, the commonest cause of life threatening diarrhoea in children worldwide. In a small randomised trial sponsored by the drug's manufacturer, nitazoxanide halved the time it took for Egyptian children to get better after being admitted to hospital with severe rotavirus infection. The 38 children who took part had had watery diarrhoea for a median of seven days before being admitted to hospital, where they were treated with standard rehydration and metabolic management, as well as nitazoxanide or a placebo. Most were under 2 years old. Children given three days of nitazoxanide got completely better in a median of 31 hours. Children treated with placebo took a median of 75 hours, a substantial and significant difference ($P = 0.014$). There were no drug related side effects.

No drug treatments are currently licensed for rotavirus, an infection that kills half a million children worldwide every year and costs the US economy alone an estimated \$1bn (£0.54bn; €0.79bn). So these researchers say their results are encouraging, despite the small size of their trial. Bigger, more definitive trials are on the way.

Lancet 2006 doi 10.1016/S0140-6736(06)68852-1

Meta-analysis questions safety of long acting β agonists

Long acting β agonists are a controversial treatment for asthma. Last year, the US Food and Drug Administration issued a "black box" warning, clearly stating that these drugs are associated with an increased risk of poor outcomes, including death. US researchers now argue that the FDA should consider taking long acting β agonists off the market after their meta-analysis of 19 placebo controlled trials found that salmeterol and formoterol significantly increased the risk of admission to hospital (odds ratio 2.6 (95% CI 1.6 to 4.3)), life threatening exacerbation

(1.8 (1.1 to 2.9)), and death (3.5 (1.3 to 9.3)). Admissions were increased in both adults and children.

The absolute increased risk of death was small—about one extra death for every 1000 patients using these drugs for a year. But salmeterol is so widely prescribed, the researchers say, that this drug alone could be responsible for 4000 of the 5000 asthma related deaths in the US each year.

What should doctors do? The author of a linked editorial (pp 936-7) writes that these findings are not as clear cut as they look, and the weight of evidence still favours leaving doctors the option of long acting β agonists when all other strategies, including escalating doses of inhaled steroids, have failed. Current guidelines recommend they are never used as a first line treatment.

Ann Intern Med 2006;144:904-12

US prisoner monitored with EEG during execution

Mounting pressure on some US states to make executions more "humane" has led to at least one prisoner being monitored with electroencephalography to prevent awareness while being put to death by lethal injection. Willie Brown Jr was executed by the state of North Carolina earlier this year, using a new technology that translates electroencephalograms into a simple numerical index indicating depth of anaesthesia.

Use of the device is highly controversial, writes one commentator. There's no evidence that the device, when used alone, is accurate enough to monitor awareness, even in surgical patients. Its performance in

prisoners being executed by lethal injections of thiopental, pancuronium, and potassium is completely unknown.

The manufacturers do not want their device used in executions and were unaware of its intended use when they sold one to a prison official from North Carolina 10 days before Brown's execution. They have since insisted that any prison wanting to buy one—for example, for its hospital—must sign a declaration that it will not use it to monitor executions. It may be too late. The monitors can be bought on eBay.

Using electroencephalography gives a spurious clinical appearance to executions, writes the commentator: "the concept of a humane execution could be considered an oxymoron. An execution is not a clinical procedure, and capital punishment is not the practice of medicine."

N Engl J Med 2006;354:2525-7

Tight control of fluids benefits patients with acute lung injury

Patients with acute lung injury may do better when managed with a conservative, rather than liberal, fluid regimen, according to a large trial from the United States. The researchers compared two fluid strategies—both defined by strict and detailed protocols—in nearly 1000 patients with established acute lung injury. The conservative strategy aimed for lower intravascular pressures than the liberal strategy and resulted in an overall fluid balance of −136 ml over the seven days it was in force. After a month, these patients had spent less time ventilated and less time in the intensive care unit and had better lung and brain function than patients treated with the liberal protocol, who had a positive fluid balance of nearly 7 litres at the end of the first week.

Being careful with fluids did not save lives—25.5% of the "conservative" group and 28.4% of the "liberal" group ($P=0.30$) died within 60 days—but the researchers still think the benefits are clear enough to support a change in practice. Restricting fluids made no measurable difference to the risk of renal failure or shock in this trial. But the patients were relatively young (mean age 50) and relatively fit before their acute lung injury. In most patients, the original insult was caused by pneumonia, sepsis, or aspiration.

N Engl J Med 2006;354:2564-75

Fish oil is poor prophylactic against life threatening arrhythmias

There's some evidence that fish oil prevents sudden cardiac death, so it makes sense to test it in patients with implantable cardioverter defibrillators. Two trials have already reported mixed results. A third (with 546 participants) does little to clarify the situation. Compared with placebo, the fish oil (at a dose equivalent to two or three meals of salmon or mackerel a week) did not prevent ventricular arrhythmia or death in men and women with implantable cardioverter defibrillators. About a third of the patients in each group had an event during the trial, which lasted a year (81/273, 30% v 90/273, 33%; hazard ratio 0.86 (95% CI 0.64 to 1.16)). The researchers found no significant benefit to any subgroup, although they found

a non-significant trend towards benefit for men and women with a history of heart attack.

Negative results are always harder to interpret than positive ones because the reliability of the results depends critically on the size and power of the trial. This one was powered to detect a difference of 33% or more in the primary outcome—death, or an arrhythmia successfully treated by the patient's implantable device. It's still possible that fish oil reduces the risk by less than 33%. It's also possible that fish oil works best for people with a history of heart attack. This trial wasn't powerful enough for a conclusive result in this subgroup.

JAMA 2006;295:2613-9

Delayed cord clamping reduces anaemia in infants

A large trial from Mexico City has shown once again that waiting for two minutes before clamping a baby's umbilical cord gives them a valuable transfusion of iron. The researchers chose a delay of two minutes because that's roughly how long it takes for the cord to stop pulsating, giving birth attendants a visible cue when stopwatches or the staff to deploy them are not available.

The 358 infants in this study were all born at term and had a normal birth weight. The benefits of a perinatal transfusion of cord blood lasted for at least six months, when researchers found that infants in the delayed clamping group had significantly more body iron than control infants, whose cord was cut within 10 seconds of delivery. They also had bigger red blood cells and were less likely than control babies to be iron deficient or anaemic. Breast fed babies, smaller babies (birth weight 2500-3000 g), and those born to mothers with a low serum concentration of ferritin benefited most. The two biggest fears associated with delayed cord clamping—polycythaemia and jaundice—were not a problem in this trial.

Up to half of infants born in developing countries become iron deficient by the age of 1 year. Prevention is a priority, and delayed cord clamping is a relatively simple way to achieve this, write the authors.

Lancet 2006;367:1997-2004

Enhanced feedback helps GPs order fewer tests

Primary care doctors are requesting more and more laboratory tests. Requests to UK laboratories went up by over 80% between 2000 and 2004, and there's a growing concern that a substantial minority are inappropriate. Tests for thyroid stimulating hormone, ferritin, cancer markers such as CA125, and *Helicobacter pylori* serology are popular but often add little to the management of patients in primary care. So researchers tried to reduce requests for these and other selected laboratory tests in a clinical trial of education and feedback. Both seemed to work, reducing test requests by about a fifth overall when used together.

The trial included all 85 general practices in one region of Scotland, a total of 370 doctors. They received quarterly feedback (a booklet of graphs comparing their practice's request rates with the region as a whole plus helpful tips about the tests), education (the same helpful hints added to test results), both, or neither for a year. The education and feedback worked better on some tests than others, but across the board they worked better together than alone. The authors say this is encouraging, and consistent with a large body of research outside primary care.

Lancet 2006;367:1990-6

Alison Tonks associate editor
atonks@bmj.com