Short cuts

What's new in the other general journals

Pregnancy does not protect women from depression

Women are often advised to stop taking antidepressants around the time of conception, partly to protect the early fetus but also because the received wisdom is that pregnancy will protect them from depression. In a US cohort of 201 pregnant women, 86 had a relapse of major depression. Discontinuing treatment was associated with a 68% (44/65) risk of relapse. The 82 women who maintained their treatment unchanged throughout pregnancy had a relapse rate of only 26% (21/82). Women who decreased their medication had a risk somewhere between the two (35%; 12/34).

All these women had a longstanding history of major depression before they became pregnant. Nearly half (44%) had had more than five episodes, and 53% had other psychiatric problems, such as anxiety or an eating disorder. They were taking a range of antidepressants—mostly fluoxetine, sertraline, venlafaxine, or paroxetine.

Since the women in this cohort had fairly severe mental illness, these findings may not apply to the majority of young women taking antidepressants, but they could be a useful starting point for discussions about the risks and benefits of antidepressants during pregnancy. It looks as though pregnancy hormones are not as protective as previously thought.

JAMA 2006;295:499-507

Stem cell transplantation could help patient with life threatening SLE

There have been no new treatments for severe systemic lupus erythematosus (SLE) for years, so research activity has focused on minimising the toxicity, and maximising the effectiveness, of existing treatments—specifically the immunosuppressant cyclophosphamide.

In a preliminary open label study, researchers gave high doses of the drug to 50 patients with severe lupus, along with an autologous stem cell transplant. All the patients had tried standard treatment regimens and some had tried experimental treatments, without success, and now had life threatening disease involving visceral organs. Although one patient died from the treatment, overall five year survival was 84% and disease free survival at five years was 50%. In general, scores on a disease activity index improved. A previous European study reported similar benefits, but greater treatment related risks.

The authors, and an editorial (pp 557-8), say it's now time to test this treatment against more traditional standards of care in a randomised trial. Only then will we know whether the dangers of intensive treatment (severe cytopenia, infections, increased risk of relapse) are offset by longer survival and better disease control in this group of very sick patients.

JAMA 2006;295:527-35

First available treatment for infant botulism reduces hospital stay by three weeks

Drugs for rare diseases are designated orphan drugs and given special patent protection to encourage pharmaceutical companies to develop them. Without regulatory incentives, few of these often lifesaving drugs would ever get to market: they are expensive to develop, difficult to evaluate, and don't return a profit for many years after approval. It took researchers five years to find enough infants with botulism for a randomised trial of human antitoxin, for example. It took another six years to find 382 more for an open label study to establish safety. The trial recruited from 90 Californian hospitals, and the researchers had to seek ethical approval from 62 institutional review boards.

The human immune globulin worked, according to a recent report of the study, halving the time that infants had to spend in hospital and reducing their stay on the intensive care unit by three weeks. Infants treated with the antitoxin were weaned off ventilators and tube feeding significantly faster than controls, saving \$88 600 per patient in hospital costs. Human botulism immune globulin (BIG-IV) was finally approved by the US Food and Drug Administration in 2003. It is the first and only drug treatment for botulism in infants.

N Engl J Med 2006;354:462-71

Adding risperidone to clozapine does not improve symptoms of severe schizophrenia

Despite many trials, it is still hard to pin down the best therapeutic option for people with schizophrenia who do not respond to their primary treatment. Mood stabilisers, antidepressants, and other antipsychotics have all been tried as add-on treatments, without much success. A trial that evaluated risperidone added to primary treatment with clozapine does little to clarify things, according to a linked editorial (pp 518-20). The well designed randomised trial, which included 68 patients, found that additional treatment with risperidone worked no better than a placebo for patients who failed to respond adequately to clozapine. At the end of eight weeks, less than a quarter of patients had improved enough to be classified as responders. The placebo group and the treatment group did equally badly, in direct contrast to the findings of two previous trials.

These conflicting results could be due to the recruitment of sicker patients, the use of a lower dose of risperidone, or

sponsorship—the latest trial was independent, the two previous trials were sponsored by industry. Whatever the reason, the effectiveness of this treatment strategy is still in doubt, and more trials are needed. In the meantime, the editorial advises psychiatrists to carry on doing what they have always done: weighing up risks and benefits, trying different treatments, and tailoring therapy to individual patients. *N Engl J Med* 2006;354:472-82

New type of vaccine protects mice against bird flu

Scientists in the US have genetically engineered a vaccine against bird flu and successfully tested it in mice. Unlike conventional vaccines prepared from viruses grown in eggs, the new vaccine is manufactured by a genetically engineered adenovirus.

Scientists deliberately avoided any process involving eggs, which they surmised would be in short supply during a bird flu pandemic. The new process is completely egg free and produces a protein component of the H5N1 virus called haemagglutinin subtype 5. Mice inoculated with the protein seem protected against H5N1 viruses isolated from sick humans, mainly because the protein stimulates the cellular arm of the immune system. In a laboratory experiment, intramuscular inoculation worked better than intranasal. Importantly, vaccination by either route protected the mice against three different strains of H5N1. The authors say this type of vaccine could be a useful weapon against the genetic drift that characterises H5N1 viruses—but they

are careful to point out that experiments in a handful of laboratory mice tell us nothing about the effects, particularly the safety, of these vaccines in people.

Lancet 2006 doi:10.1016/S0140-6736(06)68076-B

Aggressive treatment with insulin does not prolong survival for medical patients needing intensive care

Tight glycaemic control has been shown to prolong survival among surgical patients on intensive care units. The same kind of approach did not work so well for medical patients in a randomised trial by the same authors. The 595 patients treated aggressively with insulin to maintain serum concentration of glucose below 6.1 mmol/l were just as likely to die in hospital as the 605 patients treated only when their serum concentration of glucose rose above 12 mmol/l (37% v 40%).

All the patients were expected to need intensive care for at least three days. Subgroup analysis showed that those staying at least that long got some survival benefit from aggressive treatment with insulin (43% mortality v 53%; $P = 0.009$). It had the opposite effect, however, on the subgroup discharged earlier. Among the 433 patients who stayed less than three days, more patients in the aggressive treatment group died (56 deaths v 42). Since it's impossible to know at the outset how long a patient will need intensive care, these findings are not particularly helpful for intensivists or anyone else making treatment decisions.

So what should doctors do, pending more definitive evidence? An editorial (pp 516-8) suggests a compromise. Aim for a serum concentration of glucose below 8.3 mmol/l (150 mg/dl) for the first three days, then tighten control to achieve normoglycaemia for patients staying longer. *N Engl J Med* 2006;354:449-61

South Africa abandons race as a surrogate for HIV risk in blood donors

In 1999 the South African blood transfusion service introduced new measures to stem the rising prevalence of HIV in donated blood, which peaked at 0.26% in 1998 (1:385 donations). The measures included closing down donation centres in high risk areas, educating and interviewing donors about risky behaviour, and, most controversially, triaging blood products according to a risk assessment based on race.

A before and after study shows that the new measures worked. But they effectively excluded the majority black population from donating blood. President Mbeki's own donation was famously discarded under these rules. They reduced the prevalence of HIV in donated blood but dismayed black employees of the blood transfusion service and stigmatised this population in general, according to an editorial (pp 519-26).

The policy was abandoned last year, replaced by a more equitable, less discriminatory system that relies on repeated donations combined with sophisticated screening for transmissible diseases. First time donations are quarantined, and used only after a second donation is cleared as safe. This costs a little more, but is on much safer ground ethically and morally than a policy that uses race as a surrogate for risk of HIV infection. *JAMA* 2006;295:557-8

Self monitoring can work well for people taking anticoagulants

People taking anticoagulants who can monitor their own blood clotting have fewer thromboembolic events, fewer serious bleeding complications, and a lower overall mortality than people who rely on health professionals to do it for them, according to a meta-analysis. If they can adjust their own treatment, they may do even better, although greater reductions in thromboembolic events and mortality were offset in this group by a smaller reduction in bleeding complications.

Researchers found 14 randomised trials including more than 3000 adults taking anticoagulants, usually warfarin, for any reason. Most trials were of long term treatment, and all were from high income countries. The conclusions were broadly in line with several previous systematic reviews: people who monitor themselves at home do it more often, keep tighter control of their INR (international normalised ratio), reduce the harm associated with warfarin (odds ratio for major haemorrhage 0.65; 95% CI 0.42 to 0.99), enhance the benefits (odds ratio for thromboembolic events 0.45; 0.3 to 0.68), and ultimately live longer (odds ratio for all cause mortality 0.61; 0.38 to 0.98) than controls monitored by primary care doctors, specialists, or anticoagulant clinics.

The down side is that not everyone can do it. In these trials, between 31% and 88% of potential recruits were excluded because they couldn't or wouldn't self monitor. A further fifth dropped out of trials for the same reason. The rest needed extensive education, a monitoring device, and lots of very expensive test strips.

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