RESEARCH

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RESEARCH NEWS All you need to read in the other general medical journals Kristina Fišter, associate editor, *BMJ* kfister@bmj.com

Staphylococcus aureus vaccination before heart surgery fails to deliver

Merck's V710 vaccine, developed to prevent infection with *Staphylococcus aureus* after heart surgery, failed to deliver. A trial done across 26 countries with more than 7000 participants was stopped early after a second preplanned interim analysis suggested the vaccine was ineffective and harmful.

Despite a good antibody response to the vaccine, it was no more effective than placebo in preventing the primary outcome—*S aureus* bacteraemia or deep sternal wound infection (including mediastinitis), or both, up to postoperative day 90. This outcome was seen in 22 of 3528 patients randomised to the vaccine (2.6/100 person years) versus 27 of 3517 given placebo (3.2/100 person years); relative risk 0.81, 95% CI 0.44 to 1.48. No effect was seen on secondary outcomes either, which included all *S aureus* surgical sites and invasive infections to day 90.

Adverse events were more common with the vaccine (30.8% *v* 21.8% with placebo), as were serious adverse events (1.7% *v* 1.3%); 31 multiorgan failure events were seen with the vaccine versus 17 with placebo (0.9 *v* 0.5 per 100 person years; P=0.04).

All cause mortality was similar in the two groups (5.7% *v* 5.0%), but people who developed staphylococcal infections after receiving the vaccine were more likely to die than those who received placebo (15/73 *v* 4/96; difference 18.8/100 person years).

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Low melatonin secretion is a risk factor for type 2 diabetes

The hormone melatonin is secreted by the pineal gland during the night and has receptors throughout the body, including the pancreatic islet cells. It is thought to play a role in energy metabolism and to affect the risk of type 2 diabetes, although no prospective studies have examined this until now.

In 2000, nearly 19 000 women in the Nurses Health Study provided blood and first morning urine samples, as well as filling in questionnaires. In the next 12 years, the 370 women who developed diabetes were matched by age, ethnicity, and timing of sample collection to 370 women without diabetes. Unsurprisingly, the onset of diabetes was linked with higher body mass index, less physical activity, worse quality diet, less sleep, personal history of hypertension, and family history of diabetes, as well as higher markers of inflammation and endothelial dysfunction.

But after accounting for all these factors, melatonin concentrations were still predictive of developing type 2 diabetes. When women were divided into thirds according to their morning urine levels of melatonin, those in the upper third (four times higher levels than in the bottom third) had half the risk of developing diabetes (incidence 4.3 *v* 9.3 cases/1000 person years). It remains to be seen how modifiable this risk factor may be.

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Treating cryptococcal meningitis in people with HIV

Guidelines recommend that cryptococcal meningitis is initially treated with combined amphotericin B deoxycholate and flucytosine, although evidence is limited. Guidelines also recommend substituting fluconazole in settings such as Asia or Africa, where flucytosine is unavailable and over half of people with the disease die despite receiving treatment. In the West, up to a quarter die.

In a three arm trial, 299 patients were randomised to receive high dose amphotericin B alone over four weeks, or combined with flucytosine or fluconazole over two weeks.

Flucytosine increased survival compared with amphotericin B alone, but the addition of fluconazole had no effect. At two weeks, 15 of the 100 people receiving combination treatment with flucytosine had died, as had 25 of the 99 people taking amphotericin B alone (hazard ratio 0.57, 95% CI 0.30 to 1.08). By day 70, the difference in deaths was 30 versus 44 (0.61, 0.39 to 0.97), confirming the importance of initial treatment on longer term prognosis. The addition of fluconazole had no effect on deaths at 14 or 70 days (0.78, 0.44 to 1.41 and 0.71, 0.45 to 1.11).

Flucytosine also increased rates of yeast clearance from cerebrospinal fluid, and fewer people receiving it had severe anaemia, compared with those taking amphotericin B alone (35% *v* 46%). However, serious neutropenia was seen in 9% of patients taking flucytosine versus 2% of those taking amphotericin B alone.

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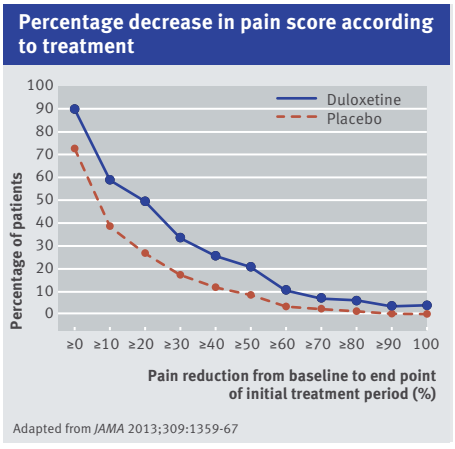
Duloxetine reduces chemotherapy induced peripheral neuropathy



Adapted from *JAMA* 2013;309:1359-67

The antidepressant duloxetine is the first drug shown to reduce pain in people with peripheral neuropathy after chemotherapy with taxanes or platinums. All participants in a placebo controlled crossover trial had moderate to severe pain for at least three months after chemotherapy, mostly paclitaxel or oxaliplatin. Of the 231 patients, 115 were randomised to duloxetine first and 116 to placebo first. The drug was given at 30 mg per day for a week, then 60 mg daily for a month.

After five weeks, the duloxetine group reported an average 10% lower pain score compared with baseline, just above the minimal clinically significant difference, whereas the placebo group reported a 3.4% lower score. Any decrease in pain was reported by 59% versus 38% of people taking duloxetine or placebo, respectively. A 30% pain reduction was twice as common with duloxetine and 50% pain reduction 2.4-fold more common with duloxetine than with placebo. The results also suggest that duloxetine is more effective in people treated with platinums rather than taxanes.

Favourable effects of duloxetine were also seen on secondary outcomes: pain interfering with daily functioning, quality of life, numbness and tingling in the feet, and use of analgesics.

More people in the duloxetine first group dropped out because of adverse events (11% *v* 1% after the first five weeks), but no serious adverse effects (grade 4 or 5) were seen. Most common with duloxetine were fatigue (7%), insomnia (5%), and nausea (5%).

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