

## More evidence that hormone replacement therapy causes incontinence in postmenopausal women

**Research question** Does combined hormone replacement therapy increase the risk of incontinence in postmenopausal women with heart disease?

**Answer** Yes. In a large clinical trial, women taking hormone therapy were more likely to develop incontinence than women taking a placebo.

**Why did the authors do the study?** Evidence is mounting that hormone replacement therapy increases the risk of urinary incontinence in postmenopausal women. A re-analysis of one large randomised controlled trial, the women's health initiative, is already persuasive. These authors wanted to confirm the link using data from a second large trial, the heart and estrogen-progestin replacement study (HERS), which compared hormone replacement therapy with placebo in 2763 postmenopausal women with heart disease.

**What did they do?** The authors re-analysed data from 1208 women enrolled in the study who had reported no incontinence in the week before the start of the trial. Of these, 597 (49%) had been randomly assigned to daily hormone therapy with oestrogen (0.625 mg) and medroxyprogesterone acetate (2.5 mg) and 611 (51%) to an identical placebo. They were asked about stress and urge incontinence at baseline, after four months, then once a year for four years. Women who had leaked urine at least once in the previous week were classified as incontinent. Using intention to treat analysis, the authors compared the proportion of women in each group classified as incontinent at least once during four years of follow-up. The trial was double blind. All the women were under 80.

**What did they find?** During four years of treatment, 64% (382/597) of the women taking hormone therapy and 49% (302/611) of the women taking placebo were classified as incontinent at least once (odds ratio 1.6, 95% CI 1.3 to 1.9;  $P < 0.001$ ), giving an excess risk of 15% or a number needed to harm of 6.9. Urge and stress incontinence were both more common among women taking hormone therapy (48% *v* 36% and 54% *v* 38%,  $P < 0.001$  for both comparisons). Numbers needed to harm for urge and stress incontinence were 8.6 and 5.9 respectively.

The difference between the groups appeared after only four months and persisted throughout the trial. If anything, the adverse effect of hormone therapy got worse as the trial progressed ( $P = 0.03$  for linear trend).

**What does it mean?** It's now fairly clear that hormone replacement therapy increases the risk of incontinence in postmenopausal women. This trial found a clear link between combined therapy and incontinence that was evident soon after the start of treatment and lasted for at least four years. The findings confirm reports from the other large trial of hormone therapy, the women's health initiative, which found an increased risk of new incontinence among women taking combined hormone therapy or oestrogen alone. Other analyses from both trials show that hormone therapy makes existing incontinence worse.

Researchers are still debating why it happens. Whatever the reason, women considering hormone replacement therapy for even a short time should be warned about incontinence.

*Obstetrics and Gynecology* 2005;106:940-5

This summarises a paper that has been selected by bmjupdates. To register for bmjupdates (free email alerts about high quality new papers in your favourite subjects) go to <http://bmjupdates.com/>

## Editor's choice

### Disentangling separate effects

A cartoon by the American cartoonist Sidney Harris has one white-coated researcher saying to another: "Find out who set up this experiment. It seems that half of the patients were given a placebo and the other half were given a different placebo." In this week's *BMJ* we bring you that experiment.

On p 391 Ted Kaptchuk and colleagues report their randomised trial of two "placebo treatments." They wanted to see whether a sham acupuncture needle had a greater placebo effect than an inert pill in patients with persistent arm pain. The patients were randomised to a two week run-in period with either the sham device or a placebo pill. The patients were then re-randomised (those on sham acupuncture to continue the sham acupuncture or to real acupuncture and those on the placebo pill to continue the placebo or to amitriptyline). During the run-in period pain decreased about equally in both placebo groups, but during the subsequent treatment periods pain fell more in the sham acupuncture group than in the placebo pill group. The types of side effects were different between the two placebo groups, and, say the authors, "clearly mimicked the information given at informed consent." They admit that it's a limitation that they did not include a group who had no treatment at all.

This paper is one of several this week where authors try to disentangle separate effects. For example, Ann Oakley and colleagues describe how process evaluation can improve the interpretation of randomised trials of complex interventions (p 413). Their illustration is a cluster randomised trial of peer led sex education among schoolchildren, in which process evaluation aimed to document how the interventions were implemented, compare the processes in the two arms, assess the experience of taking part, and study school contexts. They could then see whether outcomes varied with the quality of implementation and whether subgroups of students differed in their responses. For example, they found that when the education was participative the peer led teaching was most effective but that when it wasn't teacher led education was more effective. The authors agree that their methods challenge traditional thinking about clinical trials but argue that they fit with other methodological developments, such as piloting and taking account of context.

Finally, there's a cautionary tale for those who want to speed up patients' access to new treatments. Three months after the US Food and Drug Administration had given natalizumab accelerated approval for treating relapsing multiple sclerosis its makers withdrew it after two patients developed progressive multifocal leucoencephalopathy. On p 416 Abhijit Chaudhuri dissects what went wrong: cumulative safety data weren't available, the trials' end points were dubious, natalizumab's mechanism of action was always risky, and the animal model was not suitable. His message is that what happened with natalizumab should be "a signal to change the way we treat this disease."

Jane Smith *deputy editor* ([jsmith@bmj.com](mailto:jsmith@bmj.com))