Short cuts

What's new in the other general journals

Pain is different for men and women

It's been clear for a long time that men and women experience pain differently. Women get painful conditions such as fibromyalgia more often than men and are much more likely consult a doctor when they do, for example. Until recently, doctors tended to undertreat or even dismiss women's pain, putting women's complaining down to a lack of moral fibre or to emotion.

But a recent review of pain research finds mounting evidence that women feel pain differently from men because they have different neurophysiology (moderated by different receptors) and different neurochemicals. Scientists have already found one gene that modulates pain in women but not men—the melanocortin-1 receptor gene, which is linked to red hair and fair skin.

Experiments in functional brain imaging are also emerging, showing that pain activates different areas of the brain in men and women. This has knock-on effects on the system generating endogenous opioids.

These issues are not simply academic. One fifth of medical consultations are about pain, and a tenth of all sales of prescription drugs are for pain relief. The review argues that if scientists could unravel sex differences in pain processing, then the path would be clear for drug companies to develop analgesics specifically for men or women, improving pain relief.

Ann Intern Med 2006;144:461-4

Telithromycin implicated in life threatening liver failure

Doctors should think carefully before prescribing telithromycin, say authors from North Carolina who report three cases of massive hepatic necrosis in fit people taking the drug. Only one patient recovered spontaneously. A 26 year old man died of liver failure, and the remaining patient, a 51 year old woman, survived after a liver transplant operation.

Telithromycin is the first in a new class of antibiotic. It was developed to overcome macrolide resistance and is licensed in the US for common primary care infections such as sinusitis, exacerbations of chronic obstructive pulmonary disease, and community acquired pneumonia. It is active against *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*,

Mycoplasma pneumoniae, and *Chlamydophila pneumoniae*.

More than 11 million people have already taken telithromycin. A handful are known to have had hepatic side effects, but these authors say their cases are the most clear cut and among the most serious so far. No other reports of deaths or transplant operations have been directly linked to telithromycin.

Further post-marketing studies should help quantify the risk a little better. But in the meantime an editorial (pp 447-8) urges doctors to pause for thought before prescribing any antibiotic, and especially telithromycin.

Ann Intern Med 2006;144:415-20

When women recover from depression, their children recover too

Children with depressed mothers often have mental health problems. In one recent study, over a third of mothers with major depression had a child with a current mental health diagnosis, usually a behavioural disorder, depression, or anxiety. When the mothers were treated successfully with antidepressants in a separate randomised trial, their children also seemed to get better. When the treatment didn't work, the children did not improve either, and some got worse.

Participating mothers were moderately or severely depressed and had had an average of six previous depressive episodes. A third of them (38/114) went into remission less than three months after

starting treatment with citalopram. During the same period, the proportion of their children with a current psychiatric diagnosis fell from 35% (12/34) to 24% (8/34) ($P=0.03$).

Although the mothers who got better were richer and less depressed to start with than mothers who did not, the association between mothers' responses and children's mental health remained after the authors controlled for these differences. They estimate that mothers must get at least 50% better before a difference is detectable in their children.

Since this was an observational study, it's impossible to say for certain whether the children got better simply because their mothers got better. But that is one plausible interpretation, say the authors.

When citalopram fails in major depression, adding bupropion or buspirone, or switching antidepressants can still work.

JAMA 2006;295:1389-98

The children's mothers were originally recruited into trials comparing treatments for depressed men and women who fail to get better after treatment with the selective serotonin reuptake inhibitor citalopram. Two of these trials reported last week.

In the first, about a quarter of the 727 participants went into remission after switching from citalopram to either sertraline (up to 200 mg a day), bupropion sustained release (up to 400 mg), or venlafaxine extended release (up to 375 mg). The trial lasted 14 weeks and reported no differences between the various treatments, including side effects.

In the second report, participants added bupropion sustained release or buspirone (up to 60 mg) to their citalopram instead. Just under a third of both groups went into remission, although bupropion

caused fewer side effects and improved symptoms slightly more than buspirone.

An editorial (pp 1305-7) says these trials were well done, pragmatic, and likely to be generalisable to the real world of primary care and outpatient psychiatry. The findings show that when initial treatment fails, it is well worthwhile trying something else or adding something else. There were no clear winners in either of these trials, both of which were paid for by the US National Institutes of Health.

N Engl J Med 2006;354:1231-42 and 1243-52

Aspirin suppresses platelet aggregation equally well in women and men

Low dose aspirin is better at preventing heart attacks in men than in women. To try and find out why, researchers tested the impact of aspirin on platelet aggregation in 571 men and 711 women from high risk families.

Fourteen daily doses of 81 mg aspirin had similar effects in men and women, substantially reducing platelet aggregation by the direct COX-1 and other pathways. If anything, women's platelets responded more briskly to aspirin. It disabled their COX-1 dependent platelet aggregation almost completely. Women had more reactive platelets to start with, however, so in some tests at least, they were left with slightly more reactive platelets after treatment. Overall, any differences between men and women were small.

Age and sex hormones, whether endogenous (in premenopausal women) or exogenous (contraceptive pills or hormone replacement therapy), had little effect on the findings, except that women taking contraceptive pills had slightly shorter platelet closure times than other women, suggesting slightly more reactive platelets.

Since aspirin is thought to protect against heart attack largely because it inhibits the direct COX-1 pathway to platelet aggregation, the authors say women should be just as well protected as men. There must be some other reason why they are not.

JAMA 2006;295:1448-50

The long wait for atheroma busting drugs gets longer

The long search for a safe drug that shrinks atheromatous plaques in diseased arteries encountered a setback when the drug industry's most promising compound failed to work. In a placebo controlled trial, the compound—an enzyme inhibitor that alters cholesterol transport in macrophages—had little effect on atheromatous plaques in 408 patients with coronary heart disease who were treated for 18 months. It may even have made the plaques worse.

The results were a disappointment to the manufacturers, who funded the trial, and to hopeful doctors, academics, and regulatory agencies, who must now wait even longer for their atheroma busting drug. This one, called Pactimibe, has been withdrawn from any further clinical testing, and the trial's authors warn anyone testing other compounds in the same class to proceed with extreme caution.

Pactimibe inhibits the enzyme that esterifies cholesterol inside plaque macrophages. Scientists thought this would stop macrophages turning into moribund foam cells stuffed with cholesteryl ester, and so would slow the plaque's growth. An editorial (pp 1307-9) reflects on why it didn't. Firstly, Pactimibe and similar compounds increase intracellular concentrations of free cholesterol, which is cytotoxic. Secondly, they seem to have no effect on plasma lipids. Finally, they have the "dubious privilege" of being the only drugs known to reduce the effectiveness of statins.

N Engl J Med 2006;354:1253-63

One quarter of women who smoke heavily die in middle age

We already know that smoking is lethal. The best way to find out exactly how lethal is to follow up large populations of smokers and non-smokers for many decades. We already have precise data on men, from a 50 year old cohort of British doctors. Equally precise data on women are now available too, thanks to a cohort study from Norway that began in 1974 and included 24 505 middle aged women.

Among women who continued to smoke heavily during follow-up, one quarter (26%) died in middle age, which the authors defined as between 40 and 70 years old. The death rate among women who never smoked was only 9%. The corresponding figures for men were substantially worse: 41% of men who continued to smoke a packet a day or more died before they reached 70.

Smoking, then, seems to be more lethal for men than for women. The authors estimate that overall, heavy smoking costs women 1.4 years of middle life but costs men 2.7 years, the main reason being that women are less likely than men to die from

smoking related heart disease. Rates of lung cancer were similar in both sexes—41 deaths per 1000 in women who were heavy smokers and 43 deaths per 1000 in men who were heavy smokers.

Ann Intern Med 2006;144:381-9

Mental illness is common in the Lebanon and much remains untreated

In 2000, the World Health Organization launched an initiative to survey the burden of mental health in all its regions. Data from the Middle East are particularly scarce, and WHO chose to start by surveying the Lebanon, an Arab country with a troubled history, but one that has been at peace for more than 10 years.

After interviewing 2857 adults, researchers found that the overall prevalence of mental illness in the Lebanon was in line with the prevalence in western Europe. Seventeen per cent of the men and women they questioned had at least one diagnosable mental health problem. Major depression was the commonest mood disorder, with a prevalence of 5%, and a specific phobia was the commonest anxiety disorder, with a prevalence of 8%. The response rate was 70%.

Nearly half of respondents had been traumatised by war. More than a third had been displaced by sectarian violence, and nearly a fifth had seen someone being killed or seen the body. One in 10 people had lost a loved one. Experience of war was directly associated with high rates of mental illness in this survey, particularly mood disorders and anxiety. The most striking finding, however, was that only one in 10 people with a mental illness had received any treatment.

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