HEALTH

Why the drugs don't work for women and what to do about it

Whether you are male or female can make a significant difference to the safety and effectiveness of your medication

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Many of the drugs we commonly use have been trialled almost exclusively on men
ALAMY

To observe that men and women are biologically different might sound like an exercise in stating the obvious. Yet for decades medicine has worked on the basis that we are fundamentally the same. Remarkably, many of the drugs we commonly use have been trialled almost exclusively on males.

The male bias is particularly pervasive in early animal testing because male animals are supposedly more reliable for research — they are not subject to the hormonal fluctuations of females, so standardising results is easier. However, there's another reason that medical research is dominated by males. Just as the age of rigorous, evidence-based medicine began in the early Sixties, the thalidomide scandal and other pregnancy drug disasters hit. The resulting ethical guidelines effectively classed women and children as too vulnerable to be subjected to medical testing and so clinical trials of new drugs became dominated by male patients. As a result, it is their response to drugs that has been charted for the past half-century. A 2010 study found that only a quarter of those involved in coronary artery disease trials are women.

The consequences of this have only started to become clear. A 2001 official audit of medicines withdrawn from the American market for safety reasons revealed that 80 per cent were a greater risk to women than men. Among them were appetite suppressants that caused heart valve problems, antihistamines that caused a potentially fatal irregular heartbeat, a diabetes drug that caused liver failure and a drug for irritable bowel syndrome that caused intestinal inflammation.

At about the same time, worrying reports began to emerge about the sleeping pill Ambien. There were stories of driving accidents, particularly among women, the morning after taking the tablets. Research confirmed that women were indeed more likely than men to have daytime drowsiness and in 2013 America's drug regulating agency declared the dose recommended on the packet was double what it should be for women.

Trials leading to the drug's launch in 1992 had not separated out data for men and women, so it had taken two decades of potentially lethal side-effects for authorities to recognise that it took women a much longer time to get Ambien out of their systems.

Since then, our understanding of how women and men respond to drugs differently has grown. "We know for example that women have more fat tissue than men, and some drugs tend to linger in fat tissue," says Dr Cara Tannenbaum, the scientific director of the Institute of Gender and Health for the Canadian Institutes of Health Research. "We also have less muscle in our bodies and our kidneys are typically smaller, so we tend to eliminate the drugs slower than males."

Indeed, it can take women twice as long as men to digest food and medication. There

are many other medical differences too. Women have a faster and stronger immune response. They are significantly more likely to have autoimmune diseases such as rheumatoid arthritis. They display different symptoms in heart attack, bipolar disorder and Alzheimer's disease. And women experience pain in a different way.

"We know that more women develop chronic pain syndrome," says Professor Lesley Colvin, who holds the chair of pain medicine at the University of Dundee. "Basic science now indicates that some of the underlying pain system, the neurobiology, is different."

According to Carole Torsney, a senior lecturer at Edinburgh University's Centre for Discovery Brain Sciences, the timing of pain signals delivered to the spinal cord differs between men and women. This may influence how pain information is integrated, processed and ultimately experienced by the brain. She has also found that the way that pain signals are transmitted after injury also differ. "There's strong clinical and preclinical evidence that there are differences in pain sensitivity and possibly sensitivity to analgesic medications as well," she says.

The drug industry is beginning to face facts revealed by academic research. Recent guidance from the drug regulating authorities in the United States and Europe requires pharmaceutical companies to make sure that their trials reflect the gender prevalence of the condition studied. According to the European Medicines Agency (EMA), women are no longer routinely excluded from drug trials, successive reviews suggesting that "women are adequately represented in pivotal trial populations".

But many believe that much more could be done — because simply combining the results from men and women does nothing to illuminate any potential differences in how drugs work.

"If you're just mixing the results they won't be applicable to either men or women," says Alyson McGregor, an associate professor of emergency medicine at Brown University in the US and a leading campaigner in what has become known as "gender medicine". "Some studies have shown that a drug has a positive effect on men and a negative effect on women. But if we just combine the results we will never discover those differences and will have lost important clinical meaning."

She wants data for women and men gathered and presented separately in every trial

for every new treatment, and for funding agencies to make this a condition of their support. With other experts in gender medicine she believes there is a moral obligation to do this — not just because it will benefit women, but men too.

“There’s certainly a push on pharmaceutical companies to recruit more women into trials,” Tannenbaum says. “This is a good start because you need sufficient sample sizes to look for statistically significant differences in efficacy and toxicity. There’s some push-back that it’s too expensive. My answer to that is that the societal cost of deaths and side-effects is worth it.”

Awareness of the issue is low in Europe, particularly in the UK. While the American Food and Drug Administration has an Office of Women’s Health and publishes user-friendly information on the gender demographics of every drug trial, the EMA has no equivalents. A spokesman said the agency had opted to work in a way that would “ensure expertise around women’s health is considered across all medicines development and evaluation support in the agency”.

Hildrun Sundseth, the president of the European Institute of Women’s Health, a non-governmental organisation based in Ireland that promotes gender equity in public health and research across Europe, says it’s time for a change. Authorities, drug companies and medicine generally need to be making gender a priority.

“I fail to understand how scientists and society could have been ignoring such a basic difference for so long,” she says. “I am surprised that even robust researchers are not interested and women themselves have not organised to fight this battle.”

WHAT YOU NEED TO KNOW

Antidepressants
Studies suggest that women respond better to serotonin reuptake inhibitors (SSRIs) than men, while tricyclic antidepressants such as imipramine suit men better. There is clear evidence that women absorb, distribute and eliminate antidepressants differently.

Painkillers
Evidence suggests that morphine is better at killing pain in women than in men, although several studies suggest that women require larger doses.

Statins

Most clinical trials of cholesterol-busting statin drugs have involved many more men that women. However, studies indicate that women can suffer different side-effects, experiencing more muscle aches and pains.

Fluid-regulating drugs

Women are recommended to take half the dose of the drug desmopressin, which regulates kidney function and can control the amount we urinate. Research suggests that women are more sensitive to the drug, so larger doses are more likely to cause low sodium levels, leading to dizziness and even seizures.

Heart and stroke drugs

Research suggests that low-dose aspirin lowers the risk of heart attacks in healthy men, but less so in healthy women. On the other hand, aspirin is more effective at preventing strokes in women than in men.

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