



CLINICAL RESEARCH

Inequality in medicine

Regulators have been calling for equal representation of men and women in health research for nearly 25 years. So why are women still underrepresented?

BY ANNA NOWOGRODZKI

All drugs pose some risk to everyone who takes them. But women face more danger than men and have a lower likelihood that a therapy will work. Between 2004 and 2013, for instance, women in the United States suffered more than 2 million drug-related adverse events, compared with just 1.3 million for men, according to the US Food and Drug Administration (FDA).

A special report from the US General Accounting Office found that, of the ten drugs removed from the US market between 1997 and 2000, eight were withdrawn because of side effects that occurred only, or mainly, in women. Four of them were drugs that are prescribed more to women than men, but they also included the antihistamine Seldane and the anti-heartburn drug Propulsid. “They were withdrawn from the market because they caused heart disturbances, many of them fatal,” and mostly in women, says Cara Tannenbaum, scientific director of the Institute of Gender and Health at the Canadian Institutes of Health Research (CIHR), who is based in Montreal.

One of the main reasons women fare worse is that they are underrepresented in studies of disease mechanisms and treatment.

When women are ignored, researchers might miss differences in the way the female body responds to therapies, giving doctors little guidance about how to prescribe drugs for each sex.

Researchers and policymakers are working on several fronts to remedy this, although there is still resistance and progress is slow. Those who are pushing for more women to be included in research argue that it should not be viewed as an inconvenience but as an opportunity for better science. “You could miss important discoveries if you don’t include both sexes,” Tannenbaum warns.

MORE THAN JUST A PHASE

The underrepresentation of women in medical research is deeply rooted. Many studies include no women at all. But even studies that do include women often fail to report or analyse the data by sex. Only one-third of cardiovascular clinical-trial subjects are women, and of those trials that do include women, just 31% report their results by sex, according to a report by Brigham and Women’s Hospital in Boston, Massachusetts.

If women are represented, they are most likely to appear in phase III clinical trials, which enrol large numbers of participants.

Many phase I and phase II trials — the stages where researchers identify safe and effective doses — include only men. “That’s problematic,” says Kathryn Sandberg, who studies hypertension at Georgetown University in Washington DC, because the omission can leave women in phase III trials languishing on ineffective doses, and it can also waste time and money. “If there’s an efficacy problem that’s sex specific, you’re not going to find out until you’ve enrolled a whole lot of women.”

The bias against women in clinical trials stems in part from a 1977 decision by the FDA that barred women of reproductive age from participating in phase I and early phase II studies unless they relate to life-threatening illnesses. The FDA reversed the ban at around the same time that the US National Institutes of Health (NIH) Revitalization Act of 1993 required that women and minorities be included in any government-funded clinical health research. The act has made a difference but, for various reasons, a design approved by the NIH in a grant proposal does not necessarily match the final protocol used or the results that are reported.

Females are neglected long before drug trials enlist their human subjects, however, because preclinical animal tests are also biased towards

males. Fewer than 45% of animal studies on depression or anxiety include females, for example. An examination of the major journals covering kidney disease reveals, for instance, that five studies using solely male subjects are typically published for every one that includes females. One journal even reached a ratio of 16:1, says Sandberg. "You're biasing the whole drug pipeline toward what is optimal in the male," she says.

Animal research on both sexes is important because, without females, scientists do not know if they have valid grounds for testing a drug in women, says Tannenbaum. "I don't even know if it's ethical to tell women, 'Yes, you should be in this trial to test this new drug, but actually we've never tested it in a female vertebrate,'" she says.

Historically, male animals have been used more than females because, lacking monthly hormonal cycles, they were thought to be less variable. But a meta-analysis in 2014 found that male mice have as much variation as female mice, and sometimes more. It's not clear why the males' hormone levels vary so much, although researchers found that keeping them in group cages increased the effect.

Since January 2016, the NIH has demanded that grant proposals in vertebrate research include both sexes and promise to analyse results by sex — or convincingly explain why including both sexes is not relevant. Nevertheless, the imbalanced history continues to disadvantage researchers who conduct preclinical studies using female animals. "They're charting new territory in the females and they're not building on a background of knowledge," says Gillian Einstein, a neuroscientist at the University of Toronto in Canada.

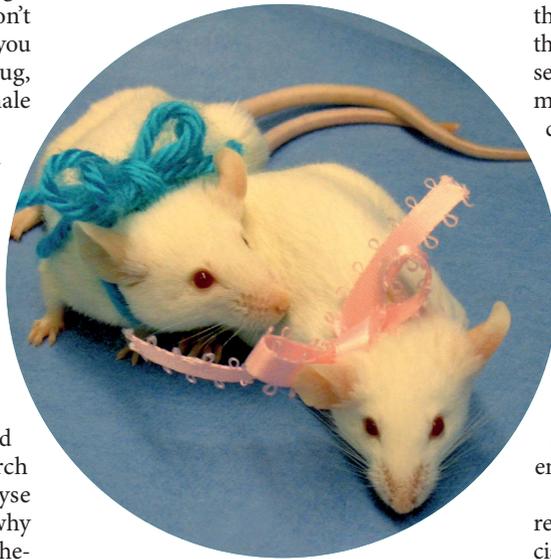
But perhaps the greatest obstacles to the increased study of females are mind-set and misinformation, says Margaret McCarthy, a developmental neuroscientist at the University of Maryland in Baltimore. McCarthy says that many researchers who study very young mice or rats tell her it is impossible to tell the sexes apart at that age. She explains to them that it can be done: she does it in her own research. "I spend a lot of time at meetings drawing little pictures of mouse and rat butts," she says, to show people how to tell them apart.

DRUG PROBLEMS

Research that has included females underscores the value of comparing the sexes. Since the NIH Revitalization Act of 1993 was passed, many fields of biomedical research have identified differences in the sexes that influence drug responsiveness. Animal experiments have revealed differences in the way the two sexes process pain. And *APOE4*, a genetic risk factor for late-onset Alzheimer's disease, confers greater risk in women than in men, so any drugs that target it might be expected to be more effective in females. The idea that a

low dose of aspirin reduces the risk of heart attack came from a study done only in men. When researchers looked at the risk in women, they found that aspirin reduced the incidence of strokes but not of heart attacks.

Women also process the sleeping pill Ambien (zolpidem) more slowly than men do. Unfortunately, it took more than 20 years and many reports of incidents, such as women driving while almost asleep, before the FDA changed its dosing recommendations. Since 2013, women have been advised to take a lower



Male and female mice exhibit a wide range of physiological differences.

dose of the drug than men. But for most drugs, doctors have little information about whether to prescribe differently for men and women, says Tannenbaum.

Many groups have now called for the equal inclusion of women and men — and male and female lab animals — in research, and for the analysis of any sex differences. In 2016 — the year the NIH issued its mandate for including females in vertebrate studies — the gender policy committee of the European Association of Science Editors issued the Sex And Gender Equity in Research guidelines, which recommend that journal editors should ask all authors to report their results separated by sex and gender. And, the UK National Centre for the Replacement, Refinement and Reduction of Animals in Research has issued guidelines calling for basic research to always report the sex of lab animals.

FURTHER EDUCATION

Another way to address the need for more studies to include women is to educate medical students, says Larry Cahill, a neuroscientist at the University of California, Irvine. "They overwhelmingly are not taught about this and want to be," he says. A 2016 survey of five US medical-student associations found that 94% of respondents think that sex and gender

differences should be taught in the curriculum, but only 59% said their medical education covered this topic.

It is also important to improve education about the realities of including females in research. Many researchers have a misconception that they need to double the size of their study if they are to show whether a drug is effective in both males and females. But McCarthy and Marcia Stefanick, a hormone researcher at Stanford University in California, say that scientists need to add only a small number of subjects to determine whether there are adverse events in one sex. Showing that there is a statistical difference between the sexes would have required the larger numbers: more subjects are needed to show a statistical difference than to show that something is true in each of the two groups.

Funding can be a big lever for change. The CIHR expects applicants for its research grants to include sex and gender in their experimental designs where appropriate. Tannenbaum points out that the CIHR offers supplement grants that specifically provide extra money for researchers to include both sexes in their studies. Sandberg says that if the NIH issued a request for proposals on sex differences, researchers would follow the money.

Tannenbaum views journal editors and reviewers as the ultimate gatekeepers, especially as studies do not always end up including the female subjects specified in grant proposals. Journals, she argues, should require papers to meet basic standards of reporting and analysis of sex differences before publication. *Nature*, for example, has a list of methodological details that authors should report in life-sciences articles, but the list does not even include the word 'sex'.

Many journals ask reviewers to tick boxes if features such as the statistics are sound, and this checklist could easily be extended to include whether the paper reports the sex of research subjects and analyses data by sex. "How hard would it be to put a check box?" asks Tannenbaum. "If you want to be a part of the solution, when you review an article for publication you should be asking yourself — and the author — whether they disaggregated the results by sex," she says. "It's really the journal editors and the journal reviewers who need to hold researchers accountable." If editors stopped accepting papers for publication unless the results are segregated by sex and gender, the problem would disappear very quickly, she argues.

Including both sexes in research is too important to ignore. "We really have to get past this idea that it's just about women or that it's too complicated to do," says Einstein. "Fundamentally it's an issue of better science." ■

Anna Nowogrodzki is a freelance science writer based in Cambridge, Massachusetts.