

NEWS

Sex bias blights drug studies

The typical patient with chronic pain is a 55-year-old woman — the typical chronic-pain study subject is an 8-week-old male mouse. To pain researcher Jeffrey Mogil at McGill University in Montreal, Canada, that discrepancy is a telling example of the problem that he and other neuroscientists discussed last week at a workshop held in San Francisco, California: the serious under-representation of females in biomedical studies.

The lack of female participation, which extends from basic research in animals to clinical trials in humans, has obvious consequences for women, not least a paucity of effective drug treatments for diseases that predominantly affect them. But it also affects men, for example when drug candidates fail to get regulatory approval because they don't work in women in late-stage clinical trials, or have

severe side effects in women that are not seen in men. Such failures might be spotted earlier if more preclinical work was done in female model animals, according to researchers at the Workshop on Sex Differences and Implications for Translational Neuroscience

Research, convened on 8–9 March by the US Institute of Medicine's Forum on Neuroscience and Nervous System Disorders.

"This is an issue of enormous importance," says biologist Irving Zucker at the University of California, Berkeley. "In a

number of disciplines, researchers simply don't study females, and there is so much evidence for sex differences at all levels of biological organization that to only study males, and assume the results apply to females, is just wrong."

Many diseases disproportionately affect one sex: chronic pain, depression and autoimmune disease, for instance, more often affect women, with addiction and cardiovascular disease disproportionately affecting men. The NIH Revitalization Act of 1993 attempted to take account of this by requiring clinical trials funded by the National Institutes of Health to include adequate numbers of women to detect differing treatment effects.

The US Government Accountability Office reported in 2000 that participation of women

Diseases such as depression can disproportionately affect women.



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in NIH-funded trials had increased substantially (see www.gao.gov/archive/2000/he00096.pdf). The following year, it noted similar progress in late-stage drug trials overseen by the Food and Drug Administration (see www.gao.gov/new.items/d01754.pdf).

But data from clinical trials are often not analysed separately on the basis of sex. Such analyses could reveal whether a drug has different adverse effects in men and women, for example.

And the accountability office also noted in 2001 that although women made up more than half of full-scale safety and efficacy trials, they formed just 22% of the participants in initial, small-scale safety studies.

Back at the bench, lab animals are still predominantly male, even in studies of diseases that disproportionately affect women. Investigators tend to prefer male animals because it is thought that females might introduce variability through factors such as

their oestrous cycles. But Mogil has reported that in common tests used to measure responses to pain, data from female mice are no more variable than those from males (J. S. Mogil and M. L. Chanda *Pain* 117, 1–5; 2005).

The problem is particularly acute in neuroscience, in which the ratio of male- to female-only studies is 5.5 to 1. But under-representation of females occurs in most fields of basic research, according to an unpublished analysis by Zucker

and postdoctoral researcher Annaliese Beery. They investigated the use of female and male animals in research published during 2009 in 10 fields across 42 journals. They found that studies in eight of the fields used only male animals more often than only females, and that the data were often not analysed by sex. In two journals that the researchers investigated

back to 1909, the proportion of animal studies using only males had actually grown since the early twentieth century. The authors speculate that this is because oestrous cycles in guinea pigs, rats and mice were first clearly characterized only in the 1920s.

Researchers such as Karen Berkley of Florida State University in Tallahassee have been trying to boost female representation for decades, and Berkley feels that

some progress has been made, citing, for example, the launch of an online journal in the field, *Biology of Sex Differences*, and an overall growth in research on sex differences.

But at the workshop, Berkley and other scientists agreed that further steps were needed to address the problem. Many endorsed the idea that journals should require

their authors to report the sex of animals used in the research. The London-based National Centre for the Replacement, Refinement and Reduction of Animals in Research is developing a set of research reporting guidelines that will call for authors to disclose the sex of animals. Seán Murphy, chief editor of the *Journal of Neurochemistry*, says that there is "interest" in the guidelines among journal editors at its publisher, Wiley-Blackwell.

Researchers at the workshop said that funding agencies, too, could ask grant applicants to specify the sex of the animals they propose studying and justify their decision whenever they chose only male animals. Funders could also change the status quo, the researchers claimed, by supporting more work on sex differences, although the NIH would not comment on whether this was under consideration. ■
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