



Gender Disparities in Clinical Trials

October 12, 2021

Thalidomide

- Application filed to the Food and Drug Administration (FDA) in 1960
 - Used to treat morning sickness for pregnant women
 - Frances Oldham Kelsey
- Caused severe birth defects
- FDA did not have the authority to require proof of efficacy of drugs
- Kefauver-Harris Drug Amendments were signed into law on October 10, 1962
 - Drug companies must provide proof of both safety and efficacy of their products before approval

FDA Guidelines Through Time

- Clinical Trial Phases
 1. Safety and dosage
 2. Efficacy and side effects
 3. Efficacy and monitoring of adverse reactions
- “General Considerations for the Clinical Evaluation of Drugs” in 1977
 - Women with “childbearing potential” are inappropriate subjects for phase 1 and 2 clinical trials
- Female hormone fluctuations make it difficult to include women in clinical trials
 - Also applied to animals in pre-clinical research
- Belief that studies of men apply to women
 - Most drugs (even today) are prescribed to women and men at the same dose

FDA Guidelines Through Time

- US Public Health Service Task Force on Women's Health Issues in 1985
 - "Historical lack of research focus on women's health concerns has compromised the quality of health information available to women as well as the health care they receive."
- General Accounting Office (GAO) report in 1992
 - Fewer women were represented in drug trials than the number of women in the population with the disease of interest for >60% of the drugs
 - Pharmaceutical manufacturers often did not analyze data for sex and gender differences.
- National Institutes of Health (NIH) Revitalization Act of 1993
 - Mandated enrollment of women in federally supported phase 3 clinical trials
 - Lifted the 1977 restriction on the inclusion of women of childbearing potential in early clinical trials
 - Called for data to be analyzed to assess gender effect

Disparities in Drug Effects

- Women are twice as likely to exhibit side effects across all drug classes
- Women are significantly more likely to be hospitalized
- Among 668 drugs of the 20 most frequent treatment regimens in the USA, 307 (46%) report significant sex differences in side effects
- Given the same drug dose as the men, women had higher concentrations of the drug in their blood, and it took longer for the drug to be eliminated from their bodies
- The sex disparity in side effects is not related to body mass differences

Ambien (Zolpidem): A Case Study

- Sleep medication approved in 1993
- Trials and FDA monitoring indicated that blood zolpidem levels were 25–33% higher in women than in men the morning after taking the drug
- Increased blood levels caused: next-morning drowsiness, substantial cognitive impairment, and increased traffic accidents
- The FDA halved the recommended dosage prescribed to women in 2013

Recent Developments

- In 2016, the NIH mandated that grant applicants would be required to recruit male and female participants in their protocols.
- A 2018 review of 107 NIH funded randomized control trials that enrolled both men and women found that 72% did not include sex in their analyses

Sources

- Brazil, R. (2020, May 28). Why we need to talk about sex and clinical trials. *The Pharmaceutical Journal*. <https://pharmaceutical-journal.com/article/feature/why-we-need-to-talk-about-sex-and-clinical-trials>
- Carey, J. L., Nader, N., Chai, P. R., Carreiro, S., Griswold, M. K., & Boyle, K. L. (2017). Drugs and Medical Devices: Adverse Events and the Impact on Women's Health. *Clinical Therapeutics*, 39(1), 10–22. <https://doi.org/10.1016/j.clinthera.2016.12.009>
- FDA. (2019). Step 3: Clinical Research. FDA. <https://www.fda.gov/patients/drug-development-process/step-3-clinical-research>
- FDA. (2020). Gender Studies in Product Development: Historical Overview. FDA. <https://www.fda.gov/science-research/womens-health-research/gender-studies-product-development-historical-overview>
- Mastroianni, A. C., Faden, R., & Federman, D. (1994). Women and health research: A report from the Institute of Medicine. *Kennedy Institute of Ethics Journal*, 4(1), 55–62. <https://doi.org/10.1353/ken.0.0121>
- University of California - Berkeley. (2020, August 12). Lack of females in drug dose trials leads to overmedicated women: Gender gap leaves women experiencing adverse drug reactions nearly twice as often as men, study shows. *ScienceDaily*. <https://www.sciencedaily.com/releases/2020/08/200812161318.htm>
- Zucker, I., & Prendergast, B. J. (2020). Sex differences in pharmacokinetics predict adverse drug reactions in women. *Biology of Sex Differences*, 11(1), 32. <https://doi.org/10.1186/s13293-020-00308-5>