
Susan Kendig

Women in clinical trials: FDA Office of Women's Health efforts

By Susan Kendig, JD, MSN, WHNP-BC, FAANP

During the fall of 2015, NPWH CEO Gay Johnson and I attended an FDA Office of Women's Health (FDA OWH) meeting regarding the exciting work being done to foster inclusion of diverse populations of women in clinical trials. The FDA OWH campaign, to be launched in 2016, aims to encourage women to make a difference for themselves and others through participation in clinical trials.[1]

Why do we need more women in clinical trials?

Although the drug development process routinely includes an analysis of sex differences in terms of drug safety and efficacy, this was not always the case. Prior to 1993, male physiology was presumed to be the norm for scientific research. For the most part, restrictive FDA guidelines excluded women of childbearing potential from the early phases of clinical trials—except in situations involving life-threatening conditions.

In 1992, the General Accounting Office (GAO) issued a report stating that women were indeed under-represented in drug development trials and that there was a need for increased study of gender differences in prescription drug testing.[2] The GAO report was followed by development of a Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs (Gender Guideline), which set the stage for the creation of the FDA OWH.[3] After the Gender Guideline was issued, women's participation in clinical trials improved. A 2001 GAO report showed that women comprised a majority—52%—of the clinical trial participants in studies conducted for the 36 new drug applications approved between August 1998 and December 2000.[4] A 2013 FDA report showed that women were adequately represented in most of the clinical trials used as the basis for safety and effectiveness decisions about FDA-approved products.[5]

Women's participation in clinical trials is important because the same dose of the same drug may have different pharmacokinetics and/or pharmacodynamics in women versus men. Such differences in drug disposition can manifest as differences in drug safety and efficacy.[6] For example, women are almost twice as likely as men to experience an adverse drug reaction. Sex differences have been reported across all phases of drug disposition, and may be related to body weight, body makeup, interactions with endogenous sex steroid hormones, physiologic changes in pregnancy, and other factors. The FDA OWH plays an important role in increasing understanding of sex differences in therapeutic interventions, which can in turn lead to more precise dosing regimens, greater efficacy, decreased side effects, and fewer adverse drug events for *both* women and men.[6]

A refresher on the FDA OWH

The FDA OWH was created in 1994 to provide leadership and policy direction for the FDA with regard to women's health issues. The Office's purpose is to protect and advance the health of women through policy, science, and outreach; advocate for inclusion of women in clinical trials; and foster appropriate analysis of sex and gender effects.[3] Since its inception, the FDA OWH has established a science program for women's health research to inform sound policy and regulation development, and has provided support for multiple women's health research studies covering a broad range of topics that affect women throughout the lifespan.

Research funded by the FDA OWH focuses on topics or issues with regulatory impact, thereby providing a mechanism for science to inform policy. Funding mechanisms include intramural grants to support research within the FDA targeting gaps in knowledge, special funding initiatives to support FDA scientists in studying pressing women's health needs, and extramural contracts providing an avenue to convene with outside experts to answer regulatory research questions.[3] These examples demonstrate how FDA OWH-funded research has contributed to knowledge regarding the effects of sex differences on disease presentation and response to interventions, and its subsequent effect on health policy and regulation:

- Shaping policy regarding inclusion of women in clinical trials is a core FDA OWH commitment. Following release of the 1993 Gender Guideline, the newly created FDA OWH further clarified the effect of the Gender Guideline by funding a study reviewing protocol criteria for sex-based exclusions. Since this time, the FDA OWH has continued to monitor trends related to gender analysis and inclusion of women in clinical trials.
- The FDA OWH science and policy planning function has contributed significantly to improved understanding of gender differences in clinical presentation and therapeutic interventions. Early research supported by the FDA OWH elucidated (1) the effect of longer corrected QT intervals in women, (2) the effect of sex hormones on this phenomenon, and (3) the risks to women's health that are related to the effect of certain drugs on women's QT intervals. This information has led to regulatory requirements regarding relevant black box warnings, relabeling of approved drugs, and development of draft guidance to protect women's health.[3]
- Drug/dietary supplement interactions can lead to altered drug or hormone metabolism. FDA-funded studies have suggested a relationship between the use of the over-the-counter dietary supplement St. John's wort and decreased efficacy of oral contraceptives. Similarly, FDA-funded studies have shown the effect of Echinacea in compromising the safety and efficacy of drugs such as warfarin that have narrow therapeutic windows.[3]

FDA OWH and FDA resources for providers and patients

Healthcare providers (HCPs) can access the **FDA OWH website**[A] for basic information and links to additional resources. To help HCPs understand sex and gender differences with regard to disease conditions and therapeutic interventions, the FDA OWH and the NIH offer a **three-course series**[B] on sex- and gender-related differences. The series provides information regarding physiologic differences and their influence on health and disease; behavior; and disease manifestation, treatment, and outcome.

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On the FDA's **Women in Clinical Trials page**[C], patients can find links to a fact sheet, videos, and other resources designed to help them understand the role of clinical trials in protecting and promoting women's health. And on the FDA's **For Women page**[D], patients can find various gender-focused patient information tools related to chronic disease conditions and other women's health issues.

Conclusion

Women's health research provides valuable insights as to how sex differences can affect women's health outcomes. Likewise, inclusion of more diverse populations of women in clinical trials will better inform HCPs as to the potential of the effect of ethnicity overlaid with gender in the efficacy of therapeutic interventions. During 2016, the FDA OWH and NIH Office

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ment, and completed the CCS within a 2-month time frame (28%; 95% CI, 19%-39%). Of the 25 patients, 22 responded to the first invitation (mean response time, 5.7 days) and 3 to the second invitation (mean response time, 1 day), which met the endpoint criterion of making a response within 14 days. The remaining 63 patients (72%) did not meet the endpoint criteria of opening and/or responding to the invitation within 14 days and/or making and completing a CCS appointment within 2 months of receiving the invitation via the patient portal (95% CI, 61%-81%).

Limitations

This family medicine department lacked a standardized method of follow-up of patients who were overdue for CCS. As a consequence, there was no way to perform a cohort study for comparison of the web portal notification method with another CCS reminder method.

Implications for women's health

Cervical cancer may be preventable if recommended screenings are completed according to evidence-based guidelines. Technological advances provide various effective modes of notifying and scheduling patient screenings. A patient web portal may be successful if utilized routinely and efficiently by provider and patient.

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Web resource

A. npwomenshealthcare.com/author-instructions/

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of Research on Women's Health are focused on inclusion of diverse population of women in clinical trials. The links provided in this column can help nurse practitioners working in women's health to better inform their patients about opportunities for participation in studies that can "Make a Difference" in finding optimal, targeted assessment and intervention strategies to promote and protect the health of all women.

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Web resources

A. fda.gov/AboutFDA/CentersOffices/OC/OfficeofWomensHealth/default.htm

B. sexandgendercourse.od.nih.gov

C. fda.gov/forconsumers/byaudience/forwomen/ucm118508.htm

D. fda.gov/ForConsumers/ByAudience/ForWomen/