GENDER EQUALITY TOOLBOX

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# CASE STUDY IN GENDER INTEGRATION

## Sex Differences in the Effects of Pharmaceutical Products

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# ACKNOWLEDGEMENTS

This case study was prepared for the Global Health Discovery and Translational Sciences team and the Gender Equality team of the Bill & Melinda Gates Foundation by Julie Becker, Executive Vice President, and Saroj Sedalia, Vice President, at Rabin Martin. Valuable technical review and inputs were provided by Sandra Laney, Rebekah Neal, Jessica Jones, Jennifer McCleary-Sills, Peter Dull and Graham Snead (the Bill & Melinda Gates Foundation).

# OVERVIEW

At the time this case study was written in 2017, Zolpidem (Ambien) was the only drug on the market with different dosing for men and women. The FDA's post-approval decision to introduce sex-specific dosing provided a public example of the possibility of sex differences in drug efficacy and raised questions as to whether the drug development industry has adequately explored sex differences in clinical trials.[1]

Zolpidem is a sleep aid, approved by the FDA in 1992. At that time, differences in rates of absorption of the drug between men and women were noted, but no action was taken related to those findings. In the early 2000s, both men and women using Ambien and its lower dose form, Intermezzo, began increasingly experiencing hypnotic effects, such as "sleep-driving". Additional pharmacokinetic studies of zolpidem, Ambien's active ingredient, conducted in 2011 showed differences between men and women in the rate and extent of absorption (45% higher in women than men for immediate-release zolpidem and 50-70% higher for controlled-release zolpidem).[2] For this reason, zolpidem stays in women's systems longer than in men's.

These findings of sex differences, paired with the increased reporting of side effects among men and women, led the FDA to reconsider zolpidem drug dosing. In 2011, the FDA cut Intermezzo (low-dose zolpidem) dosing for women in half and introduced a lower "bedtime dose" for both sexes. In 2013, they released public statements recommending reduced Ambien (another zolpidem product) dosing for women.[3] The FDA suggested that all patients understand risks related to use of zolpidem products, but also stated that women appear to be more susceptible to the risk because they tend to eliminate zolpidem from their bodies more slowly than men.[4]

This case study documents the story of Ambien and its role in stimulating public and professional discourse about sex differences in product development. It is one of four case studies developed for the Bill & Melinda Gates Foundation Internal Gender Challenge: Gender Considerations in Clinical Trials.

This case study is part of the Bill & Melinda Gates Foundation's Gender Equality Toolbox, which includes a series of case studies and other resources for supporting Program Officers in applying a gender lens to their investments. Note that not all of these case studies are foundation-funded programs and a program's inclusion in this series does not indicate an endorsement by the foundation.

# DOSING CHANGES

In 1992, FDA reviews of zolpidem, a sleep aid, noted a 45% difference in absorption rates between men and women. That review did not result in sex differences in dosing. The FDA reviewer reported that it was not possible to make a clear interpretation of the 45% difference due to a "lack of specific details such as study design and individual data".

Once the drug was released publicly, reports of harmful side effects caused the FDA to reconsider dosing for men and women. In 2007, the FDA instructed pharmaceutical companies producing products with zolpidem to issue flier warnings describing the dangers of sleep driving and sleep eating while using zolpidem. These reports led scientists to return to the 1992 data and reconsider dosing based on sex. The earlier data on pharmacokinetic differences was reinterpreted, and additional data from driving simulations led scientists to conclude that dosing should be reduced for women.[5,6]

Four years later, in 2011, the FDA approved sex-differential dosing of Intermezzo and began to retrospectively review recommendations for all zolpidem containing drugs.[7] In 2013, the FDA issued a statement (see appendix for full text) acknowledging the dangerous side-effects of zolpidem (Ambien), particularly for women and recommended differential reductions in the dosage. The original 10mg recommendation was halved to 5mg for women.[8]

# PUBLIC RESPONSE

The "Ambien story" was picked up by media outlets worldwide, including New York Times,[9] Newsweek,[10] and The Guardian.[11] On February 9, 2014, the CBS program 60 Minutes aired an episode entitled "Sex Matters: Drugs Can Affect Sexes Differently," in which many of the researchers interviewed reconsidered their 1992 position that pharmacokinetic differences were not significant enough to merit sex-differential dosing. Some reported that they simply did not look as critically at sex differences at that time. Media outlets subsequently questioned why the FDA missed the difference in efficacy and whether sex-differences in other products were being overlooked. The FDA released several statements to reassure the public of its rigor in looking for sex differences, such as a blog[12] on its commitment to determining sex differences in how drugs work. They also released guidance[13] for pharmaceutical industry and FDA staff on evaluation of sex-specific data in medical device clinical studies.

The NIH also took note of the FDA's decision to change zolpidem dosing. As the FDA made changes around Ambien and public response increased, the NIH began more publicly disseminating its view[14] that looking for sex differences during clinical trials is an important step for product development that serves both men and women. This included a blog,[15] a policy on including male and female cells or animals in pre-clinical studies,[16] and a public commitment to participating in public discourse on the issue of sex in clinical trials.

## THE TIP OF THE ICEBERG?

Beyond Ambien, other drugs have been found to have different effects in men and women. For example, there are sex differences in adverse drug reactions to cardiovascular drugs.[17] A U.S. FDA data-base with reports of adverse events from 2004-2013 shows that adverse reactions are reported more frequently among women than men. In another review, eight out of ten of the drugs withdrawn from the market between 1997 and 2001 had greater risks for women, though for four of them this was likely due to greater prescribing among women. In one study, women were 1.5-1.7 times more likely to experience and report adverse drug reactions. Another study showed that aspirin reduces men's risk of heart attack, but not stroke. Conversely, it can reduce the risk of stroke in women, but not the risk of heart attack.[18] Women are more likely to wake up from anesthesia faster and experience side effects from anesthetic drugs.[19,20] The high blood pressure drug Verapamil appears to be more effective in women than men.[21,22] These examples demonstrate the real possibility that sex differences matter for understanding drug efficacy and appropriate dosing.

## CONCLUSION

The case of Ambien demonstrates the importance of looking for sex differences in product effects. While this story successfully generated public interest in sex differences, limited action followed, and it is still unclear whether sex differences are adequately examined in the product development process. In 2014, zolpidem and another sleep aid, flurazepam[23] were the only drugs on the market with different dosage recommendations for men and women.[24]

As recently as 1990, women were excluded from early phase clinical trials due to concerns over reproductive toxicity or teratogenicity, which is the potential harm to the embryo or fetus. Protectionist policies of the '60s and '70s emerged in response to events in clinical research, including birth defects caused by Thalidomide and DES, that led to the development of policies to protect "vulnerable populations," which includes pregnant women.[25-27] Although these policies focused on phase I and II trials, they inadvertently led to systematic exclusion of women from phase III drug trials and trials for those with life-threatening diseases.[28]

Without clear donor guidelines and monitoring of adherence to guidelines and regulations, it remains uncertain whether researchers will adequately capture sex differences.

**This is not just about Ambien — that's just the tip of the iceberg.**

Dr. Janine Clayton, director for the Office of Research on Women's Health at the National Institutes of Health, New York Times Article: The Drug-Dose Gender Gap

# APPENDIX A: 2013 FDA STATEMENT REGARDING AMBIEN DOSING

**The FDA released the following statement in 2013:**

The U.S. Food and Drug Administration (FDA) is notifying the public of new information about zolpidem, a widely prescribed insomnia drug. FDA recommends that the bedtime dose be lowered because new data show that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving. Today's announcement focuses on zolpidem products approved for bedtime use, which are marketed as generics and under the brand names Ambien, Ambien CR, Edluar, and Zolpimist.

FDA is also reminding the public that all drugs taken for insomnia can impair driving and activities that require alertness the morning after use. Drowsiness is already listed as a common side effect in the drug labels of all insomnia drugs, along with warnings that patients may still feel drowsy the day after taking these products. Patients who take insomnia drugs can experience impairment of mental alertness the morning after use, even if they feel fully awake.

FDA urges health care professionals to caution all patients (men and women) who use these zolpidem products about the risks of next-morning impairment for activities that require complete mental alertness, including driving. For zolpidem products, data show the risk for next-morning impairment is highest for patients taking the extended-release forms of these drugs (Ambien CR and generics). Women appear to be more susceptible to this risk because they eliminate zolpidem from their bodies more slowly than men.

Because use of lower doses of zolpidem will result in lower blood levels in the morning, FDA is requiring the manufacturers of Ambien, Ambien CR, Edluar, and Zolpimist to lower the recommended dose. FDA has informed the manufacturers that the recommended dose of zolpidem for women should be lowered from 10 mg to 5 mg for immediate-release products (Ambien, Edluar, and Zolpimist) and from 12.5 mg to 6.25 mg for extended-release products (Ambien CR). FDA also informed the manufacturers that, for men, the labeling should recommend that health care professionals consider prescribing the lower dosesÐ5 mg for immediate-release products and 6.25 mg for extended-release products.[29]

# ENDNOTES


1. Based on a desk review conducted by the Stanford Global Center for Gender Equality in July 2020, other drugs also consider differential dosing: NOCDURNA recommends different doses to men and women. NIASPAN, ZOMACTON, BELSOMRA, and Fluvoxamine have sex-differential dosing considerations where dosing recommendations involve titration on an individual basis. PROZAC and ZYPREXA have gender considerations when prescribed in combination for bipolar disorder.
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