

## ***The Gender Gap in Pharmaceutical Research***

Elisabeth Armstrong

### ABSTRACT

Women had been overdosing on Ambien for more than 20 years – leaving them at greater risk for everything from impaired driving to addled decision-making. As it turns out, the FDA and makers of Ambien, Sanofi-Aventis, were aware of the issue. These attitudes produced a nexus of issues now referred to as the “gender gap.” The significant lack of data on how various drugs affect women leads to serious complications for patients to whom those drugs are prescribed. Solutions include adequate female participation and sex-stratified findings should be mandated with an emphasis on female inclusion. Objections to these solutions may be gender bias, arguments on the basis of sexual differences between men and women. Bioethical considerations such as the Belmont report is a valuable resource to overcome these objections.

Keywords: women’s health, pharmaceuticals, research

### INTRODUCTION

“I did what?!” That’s the question more than 1,350 people asked<sup>1</sup> when reporting adverse effects of Ambien.<sup>2</sup> The accounts became increasingly bizarre – sleep-eating, sleep-walking, sleep-driving. Ultimately, these resulted in enough serious accidents, prompting court cases and sparking “The Ambien Defense” as a response to everything from violent crimes to DUIs, even a sex offense.<sup>3</sup> A *Lexis Nexis* search in December of 2011 turned up more than 25 relevant legal cases in which this defense<sup>4</sup> was used.<sup>5</sup> Strikingly, the majority of these cases involved women, with adverse effects resulting in ER visits almost twice as often for women than men. However, no research into the discrepancy was pursued.<sup>6</sup> It took until 2013 for the FDA to address the issue – halving the recommended dose for women, after discovering that men and women metabolize the active ingredient in Ambien, Zolpidem, very differently.<sup>7</sup>

### I. TODAY’S PROBLEMS

Women had been overdosing on Ambien for more than 20 years – leaving them at greater risk for everything from impaired driving to addled decision-making. As it turns out, the FDA and makers of Ambien, Sanofi-Aventis, were aware of the issue.<sup>8</sup> In the original 1992 FDA review of Ambien, a researcher observed drug levels in the bloodstream were, “almost 45% higher in females than in males.” Larry Cahill, a neuroscientist at UC Irvine, told 60 Minutes, “It appears to say that they found a significant difference in how this drug is being processed in the body. And then the question is, ‘What did they do with that?’ and the answer appears to be, ‘Eh.’ They rationalized it away”.<sup>9</sup>

\* Elisabeth Armstrong, MS

Even as recently as the early 1990's, the term "women's health" was relegated to "bikini medicine" – breast and ovarian cancer, pregnancy, and menstrual cycles.<sup>10</sup> For the body parts that men and women shared, most of the studies were conducted on men. Researchers often viewed women as either smaller versions of men, or as too complicated because of their hormones.<sup>11</sup> In either case, researchers considered incorporating women into studies as difficult and superfluous.<sup>12</sup> This mentality was transferred to every class of researchers and physicians who studied the archetypal "70 kilogram man"<sup>13</sup> in biology and pharmacology courses.

These attitudes produced a nexus of issues now referred to as the "gender gap." While researchers may cite logistical issues, the benefits of including women in research and improving female health outcomes overwhelmingly outweigh any concerns, and could help eliminate some of these health disparities between the sexes.

After the FDA halved the recommended dose of Ambien for women, researchers began to understand the scope of the "gender gap" issue. Dr. Janine Clayton, director for the Office of Research on Women's Health at the National Institute of Health highlighted that "This is not just about Ambien – that's just the tip of the iceberg... There are a lot of sex differences for a lot of drugs, some of which are well known and some that are not well recognized".<sup>14</sup> Part of the issue is the lack of female inclusion in clinical trials. Another problem many emphasize is the lack of sex-based analysis of each drug, resulting in both an ignorance of adverse effects and a lack of sex-specific dosage recommendations.

Most FDA-funded studies and Institutional Review Boards (IRBs) require inclusion of female participants; however, this requirement is often perfunctory and inadequate. This is particularly pronounced in research surrounding cardiovascular disease - the number one killer of women. Cardiovascular disease affects men and women differently on every level - including symptoms - yet just one third of trial participants are women. Furthermore, just 31% of cardiovascular clinical trials that include women report results by sex.<sup>15</sup>

The significant lack of data on how various drugs affect women leads to serious complications for patients to whom those drugs are prescribed. For example, problems arose with the cardiovascular medication Posicor, the antihistamines Hismnal and Seldane, the gastrointestinals Propulsid and Lotronex, the appetite suppressants Pondimin and Redux, and the diabetic Rezulin, which were all ultimately pulled off the market after resulting in serious side effects and even deaths in female patients.<sup>16</sup> A Government Accountability Office Study found that most of these drugs carried a major health risk for Torsades de Pointes and Valvular Heart Disease in females.<sup>17</sup> Sex-specific data analysis could have minimized the frequency of these adverse reactions.

Yet evidence suggests that many drugs currently on the market may cause arrhythmia, including certain "antiarrhythmics, gastrokinetics, antipsychotics, antihistamines and antibacterials"<sup>18</sup>. One study found a greater propensity for adverse events in twelve of 31 pharmaceuticals analyzed, concluding that "Women are more prone to experiencing drug-induced adverse effects. Some of the reasons for this are the greater degree of polypharmacy, the increased bioavailability of drugs and a greater sensitivity of their target organs".<sup>19</sup> Their recommendations stated that "study of gender specificity should also be a goal of preclinical and clinical development of drugs potentially prolonging the QT interval",<sup>20</sup> highlighting the need for sex-specific data analysis during clinical trials. Even today, none of these drugs have sex-specific dosage recommendations or warnings<sup>3</sup>.

Researchers have furthermore long suspected even over-the-counter drugs like acetaminophen carry higher risks for women. Some researchers have hypothesized that women's bodies break down

acetaminophen's toxic by-product more slowly, which might explain why 74% of those hospitalized with acetaminophen-related acute liver failure were women.<sup>21</sup> At this point, the dosage recommendations for women and men remain the same – particularly important, as studies have shown that women take more of these drugs than men.<sup>22</sup>

A final issue that many researchers fail to account for is that drugs will produce different reactions at different points of a female's life. Prior to 1993, women of childbearing age were excluded from the trials of new drugs.<sup>23</sup> Following the FDA's decision to lift that ban, scientists were unsure if aspirin, for example, would be effective for women in preventing heart disease or stroke, as they had not been included in any studies. Today, puberty, pregnancy, and menopause are often ignored as factors in disease or considerations for drugs. Their role in depression or Alzheimer's, for instance, is not considered in current research: a recent report from Brigham and Women's Hospital found that just 45% of animal studies include female lab animals.<sup>24</sup>

## II. POSSIBLE SOLUTIONS

In "Sex-Specific Medical Research: Why Women's Health Can't Wait," researchers from Brigham and Women's Hospital highlight several ways to address the "Gender Gap." While Congress required that all federally funded clinical studies include women in the 1993 NIH Revitalization Act, there are no specifications for how many subjects must be women, or requiring an analysis of differences between the sexes. It is imperative that the spirit of this policy be respected and enforced through an expansion of this act: adequate female participation and sex-stratified findings should be mandated (where relevant) in proposals and prior to labelling of approved drugs.<sup>25</sup> Proposals that include a robust plan for inclusion and reporting should be fast-tracked for approval or funding.<sup>26</sup> For drugs already on the market, labels should be included for products that were not adequately tested on female subjects/female animals.<sup>27</sup> Extra consideration should be given to the inclusion of minority females.

In emphasizing female inclusion, it is also imperative that researchers improve both recruitment and retention – ensuring that women who work, are the primary caregivers for their families, and those who do both are included in a study's design. Minimizing time and safety concerns can have a significant effect on increasing female participation<sup>28</sup>. Researchers can also boost participation by opening study sites on evenings/weekends, providing childcare, and ensuring a safe waiting area.<sup>29</sup>

Beyond new mandates, a cultural shift is also necessary for improving research. Academic journals requiring sex-stratified data and analysis for publication, IRBs assessing the study requirements surrounding inclusion and reporting for institutional approval, and medical colleges prioritizing education surrounding women's health in research, are all viable way for establishments to effect change.

## IV. POSSIBLE OBJECTIONS

### A. Women's Research Comes at the Expense of Men

In "Sex & Gender: The Politics, Policy, and Practice of Medical Research," Sarah Keitt points out that some researchers viewed the NIH Revitalization Act's mandate of female subjects as a prioritization of women's health over men's. A 2000 study by Curtis Meinert indicated that women had

not been excluded from clinical trials prior to 1993, prompting vocal opponents to decry the new policies as promoting a female agenda.<sup>30</sup>

While the findings in Meinert's studies are refuted by a plethora of other research highlighting a bias against the inclusion of women,<sup>31</sup> it is important to highlight that equity in research is essential for quality outcomes and value. As public investment in healthcare increases, it is imperative that research on sex and gender differences becomes a priority.<sup>32</sup> Without that commitment, there is a strain on the healthcare system: treatments are never explored for women, perpetuating poor health and ineffective or dangerous drugs that produce adverse reactions, prompting the need for further treatment. Each of these outcomes induces inefficient use of resources, and the value of public investment is not met. Emphasizing women in research marks advancement in healthcare for all. To put it another way, "A rising tide lifts all boats."

## B. Differences and Politics

There are many examples of sex differences beyond the reproductive system, including differences in immune function, cardiovascular disease, response to toxins, brain organization, metabolism, and psychiatric disorders.<sup>33</sup> In fact, at a cellular level, the difference between males and females "[exists] within every cell of their [bodies]".<sup>34</sup> Yet in some circles, suggesting that there are significant biological differences between men and women is considered taboo.<sup>35</sup> Some researchers point out that highlighting these differences could make a political statement and result in decreased funding. While sex and gender-identity issues and their consequences for medicine are important, their conflation with the lack of female representation in research is illogical. If one accepts sex differences for research purposes, it does not follow that there is an immediate implication for any political or social issue. It's important that the medical community does not ignore women's health issues out of fear of making an unconnected statement.

## C. Bioethical Considerations

The Belmont Report - written by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research - summarizes core ethical principles for research: respect for autonomy, beneficence (non-maleficence), and justice. Working to minimize the gender gap is in accordance with these bioethical norms. The principle of *autonomy* calls for researchers and healthcare providers to respect an individual's rule of self. It's imperative that patients have the ability to make meaningful decisions with full understanding of the risks and benefits of a course of action. To respect their autonomy, women must have accurate information about a treatment's effects in order to make the best choice for themselves. The principle of *beneficence* entails acting in the best interests of a patient; this entails having accessible/attainable information about how a drug will interact with a woman's body in order to promote the best possible health outcome. On the flipside, the principle of *non-maleficence* necessitates avoiding an adverse event due to a lack of data. Lastly, the principle of *justice* demands acknowledging the historical dismissal of women's health, and working to alleviate that from today's research.

## CONCLUSION

Continuing to exclude women from research – when there is overwhelming evidence to support the necessity of their inclusion – is an implicit rejection of bioethical principles. Biological, economic, and ethical considerations further compel inclusion of women in research.

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<sup>4</sup> Occasionally, drugs work more effectively in women than in men. Some pharmaceuticals like the ARB Verapamil or antibiotic Erythromycin have been shown to be more successful in treating certain conditions in females [34]. These drugs also lack sex-specific dosage recommendations.

<sup>5</sup> Ibid.

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<sup>9</sup> Ibid.

<sup>10</sup> Ibid.

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<sup>25</sup> Ibid.

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