5-2023

A History of the Representation of Women in Clinical Trial: Implications for Modern Health Care

Madison Gulizia
University of Nebraska - Lincoln

A History of the Representation of Women in Clinical Trial: Implications for Modern Health Care

An Undergraduate Honors Thesis
Submitted in Partial Fulfillment of
University Honors Program Requirements
University of Nebraska-Lincoln

by
Madison Gulizia, BS
Biological Sciences
College of Arts and Sciences

March 27, 2023

Faculty Mentors:
Kim Hansen, PhD, Physiology
Kathryn Holland, PhD, Psychology & Women's Studies

Abstract

The male body is the medical baseline for all things regarding health care. Whether it is education or an actual trip to the doctor's office, female bodies are still viewed as the "smaller male body." The physiological differences in the male and female body range from the cellular level to whole body systems. These differences can mean millions of different things, depending on what avenue of discussion is taken. There are differences in the ways genes are expressed, leading to a variety in metabolic pathways, the digestive system, and the nervous system. A specific area that requires attention is the way in which medication is effective in the human body. Unfortunately for many years, and still ongoing, medications were tested in regards to only the male body. Having biologically female research participants was not required for funding from major institutions until 1993. This has left women out of the history of medicine and research in drastic ways. The implications of this exclusion are enormous due to the fact that it negatively impacts women's health today. Many medications created and approved before this benchmark are still on the shelves today and are commonly taken by the American population. By finding the biological differences between men and women, analyzing the inclusion of women in clinical trial research, diving into issues with common medications and looking for ways to improve, the climate of women's health today can be better understood. This understanding can hopefully lead to a world where "women's health" does not need a separate classification to be considered "health."

Key Words: Women's Health, Clinical Trials, Pharmacokinetics, Gender Medicine

Appreciation

I would like to express my appreciation for the support I received during this project from the College of Arts and Sciences, the University Honors Program, Dr. Hansen, and Dr. Holland. I would also like to thank my peers who supported me through this process. Thank you for directing, encouraging, and validating my passion for this important topic.

Disclaimer of Gender and Sex

Due to the nature of the topic and the vocabulary associated with it, making the distinction between sex and gender is important. The American Medical Association Journal of Ethics provides definitions to differentiate between these two terms. The AMA states, “Sex refers to the biological differences between males and females. Gender refers to the continuum of complex psychosocial self-perceptions, attitudes, and expectations people have about members of both sexes” (Tseng, 2008). In this paper ‘female/male’ is used to refer to the sex of a person, but ‘women/men’ are used interchangeably to refer to both the biological differences of sex and the socially-defined construct of gender identity. The author recognizes the differences between sex and gender but uses both sets of terms for lexical purposes, not for definitional difference. Acknowledging the differentiation between these terms can hopefully lead to a period of health care where both physiology and expression are considered in the treatment of a patient.

A History of the Representation of Women in Clinical Trial:

Implications for Modern Health Care

From the beginning of modern medical education, the male body has been the model. Textbooks, as well as posters at the doctor's office are all complete with images of the male body (Morgan et al., 2013, 352). The reason for this one-sided coin of representation lies in the way research has been, and in some cases is still currently being, conducted. Medical research, especially studies relating to medications, require clinical trials and a research testing population. Until 30 years ago, it was very common to have a research population that consisted of only male research participants, the majority of them being white. There are multiple reasons as to why women were excluded from clinical trial research. For one thing, it was the law, beginning in 1977, that most women of "childbearing potential" were not allowed as members of clinical trial populations (*Policy of Inclusion of Women in Clinical Trials*, 2020). This law was put in place in order to protect women's fertility and potential fetuses from teratogens. Although there are traces of good intention, this was detrimental to the research done for women's health in this time period. Women were also excluded from clinical trials because of the fluctuation of hormones throughout a menstrual cycle (Mazure & Jones, 2015, 5). Monitoring medications and results over a month-long period is more costly and time consuming than having a non-menstruating population. In 1993, the National Institute of Health Revitalization law was passed requiring women be included as part of the research population in clinical trials that receive funding from the National Institute of Health (Mazure & Jones, 2015, 1-9). Although this was a huge step forward in women's health history, there was still a lot of lost time and ground to cover in order to catch up. Medicine and research in the present day are still attempting to catch up. These years

of lost time serve to be dangerous and even fatal for women seeking health care or taking medication. Many medications approved before 1993 are still taken by women even though these drugs have never been tested or approved for the female body. When women are prescribed medication, or even buy them over the counter, the dose is just a modified dose from what was tested on men. The dose is often adjusted for height and weight, but these are not the only differences in the male and female body that dictate a medication's influence (Rosen, 2023).

A mixture of excluding women from research, and disregarding deeper physiological differences has led to both the overmedication and undermedication of women today (Lerner, 2020). The sized down doses found from the male-dominated research can lead to women taking far more medication than the actual efficacious dose. This can lead to an excessive amount of adverse drug reactions compared to male populations taking the same medication. The undermedication aspect comes from not understanding the female body and dismissing the pain and symptoms of women in clinical health care settings. It is not entirely uncommon for women to leave the doctor's office without medication or effective treatment. There is a growing importance for women to learn how to be their own advocate at the doctor's office in order to receive the help they require. Today, there are many physicians and educators passionate about the topic of women's health and women's health research. The topic of 'gender medicine' is becoming more and more popular. This concept of incorporating women's health education into modern medical education instead of keeping it an isolated topic is one aspect of gender medicine. The other aspect is taking deeper consideration of the biological differences between the male and female body when assessing a female patient. This could factor into their prescriptions, their treatments, and even lead to a better prognosis (Colville, 2017).

Ignoring the current state of women's health would be doing a disservice to half of the population. This very broad, yet very complex topic is one that simply demands more attention in order to achieve significant progress.

Why are Men Considered the Default Medical Model?

Sex specific medicine is founded on a gross misunderstanding. This being that the default body is the male body and the female body is simply a smaller version. This belief has posed a threat to women for many years, although it defies physiological basics. When in the womb the default sex of every fetus is in fact female and not male. Every developing fetus has a gland called a gonad. Hormones throughout the pregnancy can influence a gonad to develop into different anatomical structures. If left completely alone, the gonad would begin to develop into the female reproductive organs. There is a very specific requirement for the male reproductive organs to develop, and that is the presence of the SRY gene ("Sex Begins in the Womb," 2001, 45). The SRY gene is only found on the Y chromosome which is a chromosome unique to only males. The SRY gene functions as a transcription factor, which means it has specific control over the expression of certain genes, such as the genes that code for the development of sex organs in the fetus. When the SRY gene is present on the Y chromosome, hormones are released, mainly testosterone, which triggers the development of the gonad into male sex organs. If no additional genes were present, estrogen would be released automatically, prompting the gonad to develop into female sex organs (Wu, 2016).

A deeper dive into physiology can show the anatomical differences happening within a developing fetus. At roughly nine weeks gestation, there are two ducts present in the embryo. There is a Wolffian duct, also known as the mesonephric duct, and the Müllerian duct, also

known as the paramesonephric duct (*Difference Between Müllerian Duct and Wolffian Duct*, 2023). The Müllerian duct is what develops to form the female genitalia. This duct, unless influenced otherwise, will form the cervix, uterus, both fallopian tubes, and upper third of the vagina. The Wolffian duct is what develops to form parts of the male genitalia, specifically the seminal vesicles, epididymis, and vas deferens. The SRY gene of course is responsible for the production of male sex organs, such as the testes. The testes, once they begin to develop, will release a group of hormones called androgens. One specific hormone is called Anti-Müllerian hormone (AMH). At this point in time, if there were any developments in the Müllerian ducts, this would cease and the Müllerian ducts would begin to break down and degenerate. If the SRY gene is not present, testes will not begin to form, and androgens will not be produced. The lack of this hormonal mixture will cause the Wolffian ducts to degenerate, resulting in the development of the female reproductive organs. In short, the female sex organs begin development in every fetus, but an additional set of hormones are required to stop the female production and begin the male production (*Difference Between Müllerian Duct and Wolffian Duct*, 2023). This is evidence on the cellular level that the male body is not actually the baseline of development and all things physiology. In recent years there has been an abundance of evidence indicating vast differences between the male and female body.

Differences in Male and Female Body - Gender Medicine

A study from 2017 finds that one third of all genes are expressed differently according to sex (*In Sickness and in Health | Differences in Male Vs. Female Gene Expression Drive Infertility*, 2017). Because genes carry the genetic code that make individuals unique, there are bound to be some large differences between the male and female body. These differences boil

down to the basic bodily functions. Some examples are the way food is digested, the way blood flows through the body, or the way medications are metabolized. These differences extend to disease prevalence and prognosis as well. Heart diseases, lung diseases, autoimmune and gastrointestinal disorders, mental health disorders, and orthopedic injuries all differ in nature of disease depending on the sex of the patient (Colville, 2017). In terms of lung disease, women who have never smoked are twice as likely to develop lung cancer than men who have never smoked. In regards to heart disease, the number one cause of death in the United States today, women show entirely different symptoms than men. These symptoms can present as shortness of breath, fatigue, or jaw and back pain. Although these are the common symptoms for heart attacks in women, these are considered the "atypical" symptoms of a heart attack, meaning the typical symptoms are those that men commonly experience. It was not until after research of women's heart disease picked up in the 1980s that incidence of women's heart attacks was known. It is now known that women die of heart disease at a higher rate than men, are less likely to be prescribed the best medications to prevent future heart attacks, and are less likely to be referred to a cardiac rehabilitation program. A shocking statistics states that when comparing heart attack survivors five years later, 50 percent of women die, compared to 36 percent of men (Rosen, 2023). Statistics like these are unfortunately to be expected when the fundamental differences between the male and female body go unobserved.

There are two major issues that extend from this overwhelming amount of information. The first is that the differences in the male and female bodies that extend beyond size and reproductive systems are being grossly overlooked. The second issue being that the answer to why these conditions affect men and women differently is often still a question mark. Addressing these issues follows the idea of "gender medicine." Gender medicine essentially means that the

differences between men and women need to be considered on all levels as a part of the diagnosis and treatment processes. Gender medicine is being stressed in all stages of the health care system, starting in the classrooms of medical schools all the way to gender competence classes that professionals can teach to further educate themselves (Colville, 2017).

Gender medicine is a critical step in the right direction for health care because the overall goal is to debunk the myth of the female body being a smaller version of a male's body. As stated earlier, there are many genetic and embryonic pieces of evidence that highlight the differences determined by sex, but that does mean they are taken into account in clinical practice. The main area that this poses a threat to women is in the game of taking medication. The University of Chicago and the University of California Berkeley conducted research that found women being prescribed more medication, were prescribed too high of a dose, and experiencing more adverse side effects resulting from the unfair comparison to the male body (Lerner, 2020). Women are being prescribed either the same amount of medication as men with the same dosage, or just a downsized version based on their weight or height (Zucker & Prendergast, 2020, 2). This is extremely dangerous and can be as serious as life or death for some female patients. As mentioned earlier, one of the main differences in the male and female bodies is metabolism. Female patients will metabolize drugs in a much different, and often slower, way than male patients will. These drugs are staying in their systems for longer which is what is causing the adverse side effects and potentially damaging internal organs and tissues (Lerner, 2020). The real question is, with all of these proven differences between the male and female body, why have the correct doses of mediation been discovered for men and only modified for women. The answer to this question is that most drugs, when going through the clinical trial phase were never tested on women at all. Large institutions that play pivotal roles in the creation, production, and

approval of medications in the United States, such as the National Institute of Health (NIH) and the Food and Drug Administration (FDA) did not require drugs to be tested on women before approval until very recently. Taking a closer look at the timeline of the involvement of women in these institutions, demonstrates how late medications for women were actually being tested on women along with their biologically unequal counterparts.

Table I. Timeline of the Inclusion of Women in Clinical Trial Research in Terms of Policies from the NIH and FDA (Mazure & Jones, 2015, 1-9)

1990	The NIH Office of Research on Women's Health was formed in response to congressional concern about the inclusion of women in NIH-supported clinical trials.
1991	NIH announced the start of the Women's Health Initiative (WHI)
June 10, 1993	The NIH Revitalization Act was signed into law. This required clinical trials (phase 3) funded by the NIH to include women in the human research population.
1993	The NIH Revitalization Act also established the NIH Office for Research on Women's Health by law.
July 1993	FDA Guidance for Industry: Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs. - This changed the guideline from 1977 which excluded women of childbearing potential from early clinical studies.
1998	U.S. FDA Final Rule: Investigational New Drug Applications. - Drug approval applications require statistics of effectiveness and safety data for demographic subgroups including gender, age, and race. Discussion and analysis of this data was not required.
2000	Building Interdisciplinary Research Careers in Women's Health (BIRCWH) began to train junior faculty in interdisciplinary research on women's health and sex differences
2001	U.S. General Accounting Office Report- Women Sufficiently Represented in New Drug Testing, but FDA Oversight Needs Improvement.

	- ⅓ of drug applications to the FDA fail to meet the 1998 regulation that requires the presentation of safety and efficacy data by demographic subgroups.
2001-2014	Many studies done and research articles published differentiating diseases and conditions by sex and the discrepancies in the outcomes.
May 15, 2014	NIH announced a change in research policy, calling for the balancing of sex in cell and animal studies. The guidelines from 1993 only specified phase 3 clinical trials, but the cellular and animal testing was done on mostly male cells and subjects.

History of the Inclusion of Women in Clinical Trial

Prior to 1993, it was mostly men who made up the research population for clinical trials. Before the clinical trials even took place the research was being conducted on male cells, male mice, or other male animals (Mazure & Jones, 2015, 7). There were multiple reasons why women were not included in clinical trial research that all circle back to the belief that men are considered the medical model. The first reason is that women did not have to be included in order to receive funding by the NIH to conduct research. This was the purpose of the guidelines revised in 1993. Research could go on being conducted without women as part of the studied population with no financial setbacks. In fact, it was considered a financial setback if women were included due to concerns of hormone fluctuation, pregnancy, and menstrual cycles. A man's response to an experimental drug can be checked in the course of one day seeing as his hormones fluctuate in the 24 hour circadian rhythm he experiences. A woman's response to experimental drugs would need to be monitored over the course of her menstrual cycle. This time period of multiple weeks would be necessary due to a woman's hormone fluctuation throughout the infradian rhythm she experiences (Crompton, 2019). As far as pregnancy goes, the whole process and everything surrounding it is much better understood than it was in the origins of clinical trials. It was originally the belief that premenopausal women should be excluded from clinical

trials if they were not pregnant (Mazure & Jones, 2015, 4). In 1977, the FDA had a specific guideline which excluded women of childbearing potential from clinical trials (Mazure & Jones, 2015, 3). This guideline was implemented with the intention being the concern of the safety of a woman's reproduction capacity. They believed that including them in trials for experimental medication could cause developing fetuses harm in pregnant women, or damage the childbearing potential of women who were not pregnant. However, as pregnancy became better understood and science progressed overall, there was pressure from the government, specifically the Government Accountability Office, to fix the inclusion issue in clinical trial research.

This concern led to the NIH Revitalization Act, which was eventually signed into law on June 10, 1993. This law required investigators to include women and minority groups in phase three clinical trials if they were to continue to receive funding from the NIH. The NIH also made it clear that cost was not an acceptable reason for the exclusion of women and minorities. (Mazure & Jones, 2015, 3). The FDA followed suit in the same year by requiring that results of clinical trials be reported with differences by demographic. This data was necessary to apply to the FDA to get the drug approved. There was a downfall however to these guidelines and laws passed in 1993: although the data of the differences between men and women was strongly suggested that it was collected, there was no enforcement on whether it needed to be discussed, analyzed, or even reported in published work (Mazure & Jones, 2015, 3). Essentially, including women in the trials was just a box being checked to receive funding at this point, not because investigators were concerned and invested about the potential outcomes and side effects for women taking their future medications. As time went on after these regulations changed, more and more trials, reports, and findings were coming out with major differences between men and women which acted as sparks to the flame of gendered medicine.

What does this situation look like 30 years later? The short answer is better, but not by much. The medication that serves as the star example for this topic is a drug developed to treat female sexual dysfunction, Addyi. A significant part of the studies being done on Addyi were set to understand the effects of mixing the medication with alcohol. Surprisingly, this study was conducted on a research population of 92% men, regardless of the intended audience (Harrison & Violante, 2016). This was published more than 20 years after the inclusion of women in clinical trials became law and regulation. In a study done in 2015, it was found that of 868 ongoing clinical trials, the intent to analyze the results by gender was reported in less than 1% (Mazure, 2015). In a study done in 2018, there was a review done of 107 NIH funded control trial studies that enrolled both men and women and 72% did not include sex in their analyses (Zucker & Prendergast, 2020, 6). The question situations like these raise is what are the consequences or backlash for not including women in research and analyzing the sex differentiated results?

Taken from the NIH Grants Policy Statement: "If a recipient has failed to comply with the terms and conditions of award, NIH may take one or more enforcement actions which include disallowing costs, withholding of further awards, or wholly or partly suspending the grant, pending corrective action" (*8.5.2 Remedies for Noncompliance or Enforcement Actions: Suspension, Termination, and Withholding of Support*, 2023). Besides removing funding there is really not much else that is done in terms of violating NIH rules and regulations. This is not essentially effective however due to the influence and wealth of the U.S. pharmaceutical industry. The United States pharmaceutical industry spends roughly $50 billion a year on research and development according to an article published in 2018. Medication research that has been funded by pharmaceutical companies does not have to become part of the scientific

commons, unlike NIH funded research (Skerrett et al., 2018). This information goes to show that there can be many drug productions a year that really do not have guidelines or any checks and balances telling them who needs to be involved in clinical research and what results should be reported. Next there is the FDA to take into consideration. The FDA has approved over 20,000 drugs for marketing. However, anyone can submit drugs for approval to the FDA and there are plenty of drugs on the market that are not FDA approved (*Unapproved Drugs*, 2021). The FDA also has removed drugs that were developed before 1993 for the way that women and minorities were experiencing side effects, but this has only happened for a limited number of medications. Thousands still remain on the market (Lerner, 2020).

Common Medication that Affect Male and Female Bodies Differently

A study in pharmacokinetics was published in 2020 discussing how adverse drug reactions (ADRs) present differently in men and women taking the same medications. According the National Cancer Institute, "The study of pharmacokinetics (PKs) is the activity of drugs in the body over a period of time, including the processes by which drugs are absorbed, distributed in the body, localized in the tissues, and excreted" (*Definition of Pharmacokinetics - NCI Dictionary of Cancer Terms - NCI*, 2023). The findings from this study in which 86 drugs were tested, show that 59 of them had clinically recognizable ADRs. When considering sex-biased PKs, 88% of all cases were found to have sex-biased ADRs. Female-biased PKs had an ADR association rate of 96%, while male-biased PKs only had an association rate of 29% (Zucker & Prendergast, 2020, 1). There are sex differences in the metabolization of drugs at every stage that the drug works in the body and it is estimated that there is a 40% difference in PKs overall between men and women (Regitz-Zagrosek, 2012, 267).

A medication that typically comes up in this conversation is Zolpidem, which is a sleep aid that goes by the common name of Ambien. The FDA approved Ambien as a sleep aid safe for men and women, then 21 years later, cut the dose for women in half. This was due to the differences in drug metabolism by women. Ambien was causing serious and dangerous side effects such as sleep walking, sleep eating, and even sleep driving (Harrison & Violante, 2016).

Another day to day medication class for most people are NSAIDs, which are common painkillers like aspirin, Advil, ibuprofen, etc. When the body is injured, one of the first immune responses is swelling at the site of injury, and NSAIDs can be taken to control swelling in most situations. The problem with NSAIDs being so generic is that women have a more active immune system than men so swelling, and other symptoms that NSAIDs typically combat, happens differently. In addition to differences in immune systems, a study published in 2021 found a direct correlation between NSAID exposure and liver injury in women but not in men. This study also found that the analgesic effects of ibuprofen work more effectively in men. The interesting thing about this class of medications is that there have not been any PK discrepancies found between men and women for NSAIDs. This means that the answer to why these effects happen is still unknown even though these are of the most common day to day medications (Farkouh et al., 2021, 1441). There are many studies and treatments for cardiovascular disease that involve NSAIDs, specifically aspirin in hopes of prevention. In 1989 a study of 22,071 men and 0 women was conducted concluding that the risk of heart attack and stroke was increased in men aged 50+ with the use of aspirin. When *The New England Journal of Medicine* chose to replicate the study in 2005, which included almost 40,000 women, it was found that the use of aspirin lowered the risk of stroke in women aged 65+, which is the opposite result of the trial for

men (Mazure & Jones, 2015, 2-12). For 16 years women could have lowered their risk of stroke by taking aspirin, had they been included in the original study.

Mental health is a topic of medicine that is gaining more awareness and consideration by the day. There are many people who combat their mental health diagnoses or symptoms with medications. Two common medications used to mitigate depression and anxiety are Sertraline (Zoloft) and Imipramine (Tofranil). Zoloft is an example of an SSRI medication and Imipramine is a tricyclic antidepressant. In 2000 a study was conducted which included both men and women taking both of these medications. The results show that women who took Zoloft responded much better than women who took Tofranil and the opposite was true for men. A key part of this study is that it was analyzed between pre and postmenopausal women as well. Postmenopausal women and men showed no significant difference in their reaction to the medications. This suggests that female sex hormones may enhance response to SSRIs or inhibit responses to tricyclic antidepressants (Kornstein et al., 2000, 1445-1450). There have been many other studies that indicate women have a more positive response to SSRIs than men, but it is unclear why. Although sex hormones seem to be a highly regarded topic of investigation.

When it comes to sex-differences in medication, the complexities of anesthesiology must be held with high regard. The importance of anesthesiology today with the amount of surgery and procedure that is performed is insurmountable. Regardless, women and men react differently to anesthesia and the reason why is still to be determined. In 2009 there were findings published in *Anesthesia and Intensive Care* saying that women awake faster than men and have potentially less sensitivity to hypnotic effects. Women have slower recovery from anesthetic drugs and higher rates of complications from general anesthesia. The results of this study also took menopause into account. Premenopausal women had worse recovery experiences than

postmenopausal women. This study contained 253 men and 247 women (Mazure & Jones, 2015, 9-10). Another study regarding sensitivity to anesthesia was conducted in 2015. This study found that women are less sensitive to propofol, a drug used in general anesthetic settings. However women were found to be more sensitive to neuromuscular blocking agents and opioid receptor agonists than men. The sensitivity to opioid receptor agonists means women are more likely to experience respiratory depression and more ADRs if given the same amount of opioids as men. The sensitivity to neuromuscular blocks resulted in adverse allergic reactions in 70% of women and only 30% of men. These findings can be tied to the way lipid-soluble drugs, like propofol and opioids, or water-soluble drugs, like muscle relaxants, metabolize differently in men and women (Regitz-Zagrosek, 2012, 272). When looking at more broad scope results, these are all side effects that can happen before the procedure even takes place, creating a longer or harder recovery for women in comparison to men.

These were just a few of the common medications that are used in procedures, over the counter, or prescribed by a physician. There is no aspect of pharmacology that goes untouched by the sex-differences in medication usage. As Dr. Carolyn Mazure from Yale School of Medicine said, “If we don’t finish the work begun 25 years ago, we will all suffer from a lack of important data and potentially misguided medical decisions” (Mazure, 2015). This quote was in reference to the requirement of women in clinical trials in the first place, and as it has been demonstrated there is still quite a bit of room for improvement.

Areas for Improvement

One way to improve the current situation is to focus on the implementation of gender medicine at every stage in the health care system. This starts with education. The male model has

been proven false time and time again, but is still prevalent within courses such as anatomy. A study published in 2013 shows that outside of urogenital images, only 11% of the images in a select group of anatomy textbooks were discernibly female (Morgan et al., 2013, 352). This creates underlying biases and over-generalizations in many areas of medicine. A leading example of how to change education is Dr. Kelsey Martin. Dr. Martin is the new Associate Director for Medical Education in Women's Health. She is passionate about integrating women's health data, beyond reproductive health, and the role of sex and gender into the preclinical curriculum and Yale Medical School, where she teaches. Dr. Martin discusses the "health equity thread" which weaves women's health aspects into the current curriculum. Making women's health classes completely separate would defeat the purpose and be detrimental to the goals of breaking down stereotypes about the medical model to begin with, so the health equity thread is a large step in the right direction (Steffen & DeCarlo, 2022).

As stated previously, a reason for excluding women and minorities from research was cost. Funding the right areas will always help situations such as these. Places like the University of Nebraska Medical Center are setting the standard for the attention women's health research deserves. In April of 2022 the creation of the Nebraska Center for Women's Health Research at UNMC was approved. The center will be a hub for research, trials, and collaboration with leading physicians and investigators in the field. Dr. Carl Smith, the chair of the UNMC Department of OB/GYN had a powerful message regarding the approval of the new center: "Many of the studies that have been conducted in the U.S., on areas such as medication use, have systematically excluded women from participation because of concerns related to pregnancy. Thus, we have medications that have been approved for use without ever having been adequately studied in women. The Center for Women's Health Research will allow for the organization of

research activities such as these" (Keenan, 2022). The creation and funding of centers like these will allow the forward progression of women in clinical research, and even filling the gaps of knowledge from the past.

Holding institutions like the NIH and the FDA accountable will also play a large role in the improvement of women's health research and medication approval. There are still clinical trials that happen today that meet the requirements for NIH funding but are not analyzing their results in an effective matter. An update to the NIH guidelines and FDA application process may be necessary for all researchers to take sex-determined differences seriously in their studies. Authors in pharmacokinetics research have begun calling on the FDA to post the gender breakdown of study participants and to label drugs that are already known to have sex differences (Lerner, 2020).

Inclusivity is something that is in constant need of improvement regardless of the area of profession or education. Scientific research is by no means an exception to this. A study done in May of 2013 found that of the 277 treatment trials and 27 prevention trials included in the report, more than 80% of participants were white and 59.8% were male (Kwiatkowski MPH et al., 2013, 2958). In the gathering of information for this article, there was some sort of disclaimer in almost every article and journal that I read regarding the topic at hand. Pretty much every source had added in their conclusion that it is well past time to start paying attention to sex and gender differences in men and women and that more personalized medicine is on the horizon. However, I have been seeing these messages in articles published as early as 2000 and it is now 23 years later, and 30 years since the passage of the NIH Revitalization Act. It is no longer enough to say we need to start paying attention and reporting the findings that are necessary to obtain in order to receive funding. Deeper changes need to be implemented.

Tips for Self-Advocating at the Doctor's Office

There is both an overwhelming and underwhelming amount of knowledge regarding women's health. Due to this it is not uncommon for women's symptoms to be ignored or blown out of proportion in the clinical setting. There are countless examples of women's pain being ignored or undermined in appointments, as well as the stated over medication. Because of the current state of women's health, it is important that women are self-advocates in the doctor's chair. Listed are a few tips on how to be an advocate for yourself at doctor's appointments.

1. Spend time finding a doctor who listens to you and your concerns, who does not rush your visits, and takes you seriously. If you have the time and resources to find a new doctor, do so until you find the one who is right for you.
2. Prepare for your doctor and your appointments like you prepare for your accountant (Rosen, 2023). Keep your own copies of medical records, full lists of medications and supplements, test and lab results, detailed family history, and a calendar of menstrual cycle and symptoms.
3. Write down questions you have before you go to visits or appointments, this way you can avoid forgetting what you want to ask due to being flustered or overwhelmed. Bringing a friend or trusted family member can sometimes be a good idea so there is an extra set of ears and eyes in the room. This reduces the risk of forgetting or misunderstanding what your doctor has said. However, you should still be assertive in asking for explanations of topics, symptoms, diagnoses, prescriptions, or prognoses you do not understand.

4. Look up any medications or prescriptions in the National Drug Code (NDC) directory. This can provide you with details about the dates and participants of clinical trials, and more information about the medication in general.

References

Colville, D. (2017, August 6). *Medicine's gender revolution: how women stopped being treated as 'small men'*. The Conversation. Retrieved March 18, 2023, from https://theconversation.com/medicines-gender-revolution-how-women-stopped-being-treated-as-small-men-77171

Crompton, S. (2019, May 1). *Gender medicine: Should men and women be prescribed differently?* BBC Science Focus. Retrieved March 19, 2023, from https://www.sciencefocus.com/the-human-body/should-medicine-be-gendered/

Definition of pharmacokinetics - NCI Dictionary of Cancer Terms - NCI. (2023). National Cancer Institute. Retrieved March 19, 2023, from https://www.cancer.gov/publications/dictionaries/cancer-terms/def/pharmacokinetics

Difference between Müllerian Duct and Wolffian Duct. (2023). Byju's. Retrieved March 18, 2023, from https://byjus.com/biology/difference-between-mullerian-duct-and-wolffian-duct/

8.5.2 Remedies for Noncompliance or Enforcement Actions: Suspension, Termination, and Withholding of Support. (2023). NIH Grants and Funding. Retrieved March 19, 2023, from https://grants.nih.gov/grants/policy/nihgps/html5/section_8/8.5.2_remedies_for_noncomp

liance_or_enforcement_actions-_suspension__termination__and_withholding_of_support.htm

Farkouh, A., Baumgartel, C., Gottardi, R., Hemetsberger, M., Czejka, M., & Kautzy-Willer, A. (2021, April 1). Sex-Related Differences in Drugs with Anti-Inflammatory Properties. *Journal of Clinical Medicine*, *10*(7), 1441. 10.3390/jcm10071441

Harrison, R., & Violante, C. R. (2016, January 14). *A Drug for Women, Tested on Men < Yale School of Medicine*. Yale School of Medicine. Retrieved March 19, 2023, from https://medicine.yale.edu/news-article/a-drug-for-women-tested-on-men/

In sickness and in health | Differences in male vs. female gene expression drive infertility. (2017, May 9). Weizmann Institute of Science. Retrieved March 19, 2023, from https://www.weizmann.ac.il/WeizmannCompass/sections/briefs/in-sickness-and-in-health

Keenan, J. (2022, April 11). *Research center to focus on women's health | Newsroom*. University of Nebraska Medical Center. Retrieved March 19, 2023, from https://www.unmc.edu/newsroom/2022/04/11/research-center-to-focus-on-womens-health/

Kornstein, S. G., Schatzberg, A. F., Thase, M. E., Yonkers, K. A., McCullough, J. P., Keitner, G. I., Gelenberg, A. J., Davis, S. M., Harrison, W. M., & Keller, M. B. (2000, September). Gender differences in treatment response to sertraline versus imipramine in chronic depression. *The American Journal of Psychiatry*, *157*(9), 1445-1452. 10.1176/appi.ajp.157.9.1445

Kwiatkowski MPH, K., Coe PhD, K., Bailar MD, J. C., & Swanson PhD, MPH, G. M. (2013, May 14). Inclusion of minorities and women in cancer clinical trials, a decade later: Have

we improved? *American Cancer Society*, *119*(16), 2956-2963. https://doi.org/10.1002/cncr.28168

Lerner, L. (2020, June 22). *Women are overmedicated because drug dosage trials are done on men, study finds*. UChicago News. Retrieved March 18, 2023, from https://news.uchicago.edu/story/women-are-overmedicated-because-drug-dosage-trials-are-done-men-study-finds

Mazure, C. M. (2015, October 27). *Home*. YouTube. Retrieved March 19, 2023, from https://medicine.yale.edu/whr/news-article/what-we-still-dont-know-about-womens-health/

Mazure, C. M., & Jones, D. P. (2015, October 26). Twenty years and still counting: including women as participants in studying sex and gender in biomedical research. *BMC Women's Health*, *15*(94), 1-16. https://doi.org/10.1186/s12905-015-0251-9

Morgan, S., Plaisant, O., Lignier, B., & Moxham, B. J. (2013, June 19). Sexism and anatomy, as discerned in textbooks and as perceived by medical students at Cardiff University and University of Paris Descartes. *Journal of Anatomy*, *224*(3), 352-365. 10.1111/joa.12070

Policy of inclusion of women in clinical trials. (2020, December 17). Office on Women's Health. Retrieved March 22, 2023, from https://www.womenshealth.gov/30-achievements/04

Regitz-Zagrosek, V. (2012). Sex and Gender Differences in Pharmacology (V. Regitz-Zagrosek, Ed.). In (pp. 265-278). Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-642-30726-3_13

Rosen, S. E. (2023). *When the standard of care is treating women like little men*. Northwell Health. Retrieved March 18, 2023, from

https://www.northwell.edu/katz-institute-for-womens-health/articles/standard-of-care-treating-women-like-little-men

Sex Begins in the Womb. (2001). In M.-L. Pardue & T. M. Wizemann (Eds.), *Exploring the Biological Contributions to Human Health: Does Sex Matter?* (pp. 45-46). National Academies Press. https://www.ncbi.nlm.nih.gov/books/NBK222286/#:~:text=During%20early%20development%20the%20gonads,the%20development%20of%20the%20testes.

Skerrett, P., Bluestone, J. A., Beier, D., & Glimcher, L. H. (2018, January 3). *The NIH is in danger of losing its edge in creating biomedical innovations*. STAT News. Retrieved March 19, 2023, from https://www.statnews.com/2018/01/03/nih-biomedical-research-funding/

Steffen, A., & DeCarlo, A. (2022, December 16). *Weaving Women's Health into the Yale Medical School Curriculum*. Yale School of Medicine. Retrieved March 19, 2023, from https://medicine.yale.edu/news-article/weaving-womens-health-into-the-yale-medical-school-curriculum/

Tseng, J. (2008, July). *Sex, Gender, and Why the Differences Matter | Journal of Ethics | American Medical Association*. AMA Journal of Ethics. Retrieved March 22, 2023, from https://journalofethics.ama-assn.org/article/sex-gender-and-why-differences-matter/2008-07

Unapproved Drugs. (2021, June 2). FDA. Retrieved March 19, 2023, from https://www.fda.gov/drugs/enforcement-activities-fda/unapproved-drugs

Wu, K. J. (2016, August 2). *"I'm XY and I Know It": Sex Determination Systems 101 - Science in the News*. Science in the News. Retrieved March 18, 2023, from https://sitn.hms.harvard.edu/flash/2016/im-xy-know-sex-determination-systems-101/

Zucker, I., & Prendergast, B. J. (2020, June 5). Sex differences in pharmacokinetics predicts adverse drug reactions in women. *Biology of Sex Differences*, *11*(32), 1-14. https://doi.org/10.1186/s13293-020-00308-5