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Analyzing Pain Modulation Through Analgesics and Devices in the United States: How Studies Historically Exacerbated the Gender Pain Gap

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ABSTRACT

Pain medicine has a long history, with the Egyptians and Babylonians using bleeding and trepanning to modulate pain (Doleys). With the birth of pain medicine came the birth of inequities. In fact, in the United States, drugs may not be as effective for half of the population. This paper compiles studies conducted over 2 decades by pain medicine specialists on women's pain treatment, studying factors involved in women being treated differently for chronic/episodic pain. These studies tested different drug dosages and medical devices to highlight the lack of female data in analgesic studies, showing the impact of historic bias on female health. Findings indicate women have not been prioritized in pain studies, affecting their healthcare quality and drug efficacy in these populations. The importance of women-centric studies, clinical trials with more female data, and women in analgesic R&D is emphasized.

1. Literature Review

Understanding the historical exclusion of women in pain studies necessitates a deeper look into pain perception's biological underpinnings.

Processing and "feeling" pain is a complex neurobiological phenomenon that depends on the nuanced central and peripheral nervous systems. It is rooted in the idea that we have receptors that try to warn us away from bodily harm and damage, and therefore send distasteful neural signals that produce painful sensations.

The first detectors of stimuli attributed to feelings of pain would be nociceptors, specialized peripheral sensory neurons, and they are found in the skin, muscle, joints, bone, and viscera (internal organs in the main body cavities) (Dubin and Patapoutian, 2010, Dafny, 2020). Nociceptors are typically triggered by temperature/thermal, mechanical (strain), and chemical (pH change due to local inflammation) stimuli, so a "noxious stimulus" can be put into any of these three categories (“Nociception”, n.d.).

Furthermore, nociceptors comprise two main fibers. Firstly, the myelinated Aδ or A-δ fibers are responsible for primary pain responses. Next, there are unmyelinated C fibers which are responsible for secondary acute pain responses (“Nociceptor”, n.d.). The difference in pain

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response type is attributed to the difference in speed of neural transmission, as it has been proven that myelin increases the speed of electrical impulses in neurons as it insulates an axon ("Myelin: A Specialized Membrane", 2014).

Meanwhile, the central nervous system, which consists of the brain and the spinal cord, plays an essential role in the processing and perception of pain though it does not contain nociceptors. In the spinal cord, many neural connections amplify pain signals before they are transmitted to higher brain regions and pain signals travel through many pathways to ultimately reach brain regions involved in processing pain and pain perception. However, according to the Gate Control Theory of Pain, some of these pain signals can be attenuated at the spinal cord, meaning they can be restricted from being sent up to the brain to be processed ("Gate Control Theory of Pain", n.d.).

For example, the thalamus, which is known as a "relay" system for the brain, directs nociceptive intel to other areas for pain perception, mainly to the cerebral cortex. However, the pathways terminate in two subdivisions of thalamic nuclei (specialized areas of the thalamus that are each responsible for processing different impulses- motor or sensory- then sending them through nerve fibers to the part of the cerebral cortex responsible for interpretation) ("Thalamus", 2024). These subdivisions are the ventral posterior lateral nucleus and ventromedial nucleus. From here, information is sent to other cortical/subcortical regions like the amygdala, hypothalamus, periaqueductal grey (which is responsible for the propagation and modulation of pain), basal ganglia, etc. (Mokhtar, 2023). Additionally, the insula and anterior cingulate cortex are activated consistently when nociceptors are activated, and the activation of these two brain regions has been proven to be associated with the "experience" of pain (Garland, 2012).

Neurotransmitters also play an important role in mediating pain such as glutamate (the central nervous system's primary excitatory neurotransmitter) and substance P (involved in the transmission of pain signals). Endogenous opioid peptides like endorphins are known to provide "analgesic effects"; they relieve pain. Neuromodulators (substances that act together with neurotransmitters rather than directly activating ion-channel receptors) such as serotonin, norepinephrine, and dopamine modulate pain perception and contribute to the neurochemical processes underlying pain sensation (Lentz, 1998). Analgesics, either by inhibiting the travel of pain signals to the brain or altering the brain's interpretation of pain signals, seek to reduce pain or inflammation.

2. Introduction

This paper makes the following contributions: 1) Explains the correlation between various factors in pain medicine administration/development (such as clinical trial datasets, regulatory structures, and physician treatments) and the varying responses to pain analgesics in men and women and the flaws of various medical devices, 2) Determines whether or not the factors listed can be used to explain why women react negatively to pain medications compared to their male counterparts and why women are given flawed medical devices to treat their pain, and 3) Puts forth ways to ensure analgesics and medical devices/technological equipment are just as effective in female bodies in the future and serve women.

3. Methods and Materials

In this section, I will be going over the processes and systems that have either contained flaws or have loopholes that encourage healthcare violations and can have extreme impacts on patients.

Specifically, I will be addressing the clinical trial process by explaining each step, going over physician care and how many physician-patient interactions tend to go when the subject is chronic or episodic pain, and lastly addressing the medical device approval process and deep-diving into the 510(k) clearance method.

3.1. Description of the Clinical Trial Process

Drugs that modulate pain and provide analgesic effects are developed using an understanding of pain mechanisms, identifying ideal molecular targets, screening a variety of chemical compounds to scope out chemicals that can be made into drugs with pain-relieving properties, performing preclinical testing and transitioning into clinical trials, seeking regulatory approval, and finally ensuring that the drug is successful, economically viable, and safe once implemented.

Analyzing the regulatory approval process itself will help make Section 3.1 very clear. When pain relief drugs are approved by the FDA, they go through an extensive process that includes the following: preclinical research, IND (Investigational New Drug) applications, 3 phases of clinical trials along with placebo-controlled trials in phases 2 and 3, sometimes double-blind trials (participants nor researchers know who receives the drug or placebo to minimize bias), submission of data, and an FDA review along with an acceptance or rejection (Office of the Commissioner, 2018).

So, in order for a particular demographic to be adequately included, they have to be included in each phase of the clinical trial process. Though this seems like an easy task to accomplish, I will elaborate on the reasons why we are not seeing that today.

But what can be taken from this is that the approval process has flaws and this has real-world consequences that I will go into detail on later. After all, we are seeing women being excluded from datasets in the past still having a huge impact on the quality of analgesics and medical devices in today's day and age.

Medical devices go through a similar process in order to be approved, and I will go into detail on this process later on. But these trials have failed to consider women, for a multitude of reasons.

3.2. The Variation in Physician Treatment of Women's Pain and The Gender Differences in the Impacts of OTCs and Prescription Drugs

A study from 2001 conducted by primary contributor Carol S. Weisse, PhD, finds that female and male physicians make different decisions about pain management in female patients (Weisse, et. al, 2001). For instance, female physicians tend to prescribe higher doses of analgesics (hydrocodone, a semisynthetic opioid, in this case) to women while male physicians tend to prescribe higher doses to men. The study at hand was on treating hypothetical kidney stone pain to discover possible differences in treatment approaches. This data was collected to suggest that female and male physicians may react differently to gender and racial cues. This can be harmful because a lack of objectivity when it comes to pain medication prescriptions can fuel gender biases that perpetuate the gender pain gap.

21 years later (in May 2022), another study was conducted, this time by primary contributor Hermine Nguefack regarding gender differences in the adverse effects of medication taken by people living with chronic pain (Nguefack, et. al, 2022). Women reported more adverse effects than men. This particular study, however, warned that the reporting of these effects and the

experience of these effects cannot directly be attributed to differences in gender identity and gender roles, but the paper makes it clear that they should certainly be explored.

The study also mentions that the use of prescribed and OTC pain medications is significantly higher in women than men. They also say that due to biological differences, women tend to experience more adverse effects. It points to a 2008 study performed by Gail D Anderson which finds that women have a higher incidence of drug-induced liver toxicity, adverse gastrointestinal events as a result of NSAIDs like aspirin and ibuprofen, and even allergic reactions manifesting in the form of skin rashes (Anderson, 2008). Anderson finds that there are large gaps in our knowledge of sex differences in clinical pharmacology.

The impact of this is that studies have been done for the past 2 decades on how we have historically fallen short. Women have been excluded time and time again from pivotal studies that dictated the primary OTCs and prescription drugs on the market.

3.3. Description of the 510(k) Clearance Process and Introducing Its Risk Factors and Potential Harms

Not only have drugs been a part of the conversation on pain modulation and the gender pain gap, but medical devices that work to relieve pain have also been scrutinized for their failure to include women. As studies are being done to include more women in data pools, existing structures are in place that are allowing for at-times-antiquated research to be carried forward and implemented in real-world markets. In the United States, the FDA (a regulatory organization with an incredibly broad scope) itself has a process that could potentially be flawed or lead to outdated studies being used to this day.

Due to the FDA predicate rule also known as the 510(k) process, devices that were made, marketed, and tested in previous years, possibly decades, can serve as predicate devices. This means that newer technologies that are modeled off of these pre-existing predicates do not require as much clinical and laboratory testing and data submission.

One of the key things to note is that the 510(k) does not require a predicate device to meet any of the standards that typical PMA (Premarket Approval) devices must meet to be marketed in the United States. This is no small issue. In fact, 98% of devices can be approved for sale without any studies in humans. The 510(k) process plays a significant role in this, as these devices do not need new or revised evaluations. They can merely claim that they are the new and improved versions of older devices and get away with design flaws and more. This has devastating impacts as I will go on to explain later on in this paper.

4. Results and Discussion

In this section, I will be addressing the results of the implementation of the processes and systems I explained the nuances of in Section 2 (Methods and Materials).

I will be going over how the clinical trial process has had inherent biases by historically excluding women and the reasons that were provided.

I will also address the various biases that are frequently involved in physician-patient interactions, when the patient is a woman to be precise. I will talk about how female and male doctors tend to have different pain treatment methods and even different methods of practice.

Lastly, I am going to be describing the use of media in understanding the medical device approval process. Specifically, I will use "The Bleeding Edge", a film released in 2018 that had a pervasive impact on audiences in the United States. It brought alarming levels of attention

to the healthcare community and gave reasons for patients to care about the regulatory bodies that evaluate the devices they use.

4.1. Clinical Trial Development

Historically speaking, clinical trials have excluded women due to the erroneous belief that men and women only had reproductive differences, but this has been disproved countless times, especially knowing now that women have a greater nerve density and are therefore more susceptible to chronic pain and experiencing more intense pain than men ("Do Women Feel More Pain More Intensely than Men?", 2021).

Furthermore, regulatory agencies typically bar women of reproductive age from clinical trials to protect vulnerable populations, prevent harm to unborn fetuses, and preserve female fertility (this was done since the 1970s due to the miserable failure of thalidomide, a drug initially intended as a tranquilizer) (Tzure, 2023). Concern for hormonal variability (due to menstrual cycles, menopause, the use of contraceptives, etc.) has deemed women as riskier, more expensive, and more challenging test subjects for clinical trials (Liu and Mager, 2016).

While some may argue that including women in clinical trials introduces hormonal variability that convolutes datasets and complicates data interpretation, we find that advancements in research techniques can compensate for these differences, ensuring scientists are provided both robust and inclusive data.

This has frequently masked female responses to drugs as a result. In fact, Dr. Meera Kirpekar, a clinical assistant professor of anesthesiology, perioperative care, and pain medicine at NYU Langone, found that until 2016, over 80% of pain studies had only involved male participants, whether humans or rats (Lennon, 2022).

This has had consequences in real time. It is incredibly important to test the cardiovascular effects of drugs in clinical trials, and women have been excluded from a majority of these studies. Only ⅓ of cardiovascular clinical trial subjects are women, and this has led to poorer outcomes for women with heart-related conditions and women who take medications that have unexpected impacts (Westervelt, 2015). The consequences of this, as can be imagined, are drastic and long-lasting.

It is evident that the exclusion of women historically in clinical trials has led to women being treated differently and has shaped their experiences with analgesics. Many of them find pain medications to be less effective than men would find them or they experience countless side effects that were not accounted for in the initial studies conducted on said medication. Studies in the future need to account for this and more women need to be included in pain medicine datasets.

4.2. The Interaction Between Pain Medicine Specialists and Patients

There are a few ways in which physicians and pain medicine specialists can interact with patients differently in order to promote high healthcare standards.

Primarily, physicians need to develop an understanding of invisible illnesses that are oftentimes the drivers of chronic pain in women. Understanding how to treat these illnesses or reduce the pain and symptoms associated with them is essential in improving patient trust and satisfaction.

Furthermore, physicians also need to be aware of their internal biases and the reasons why these prejudices could impact the way they treat their patients. These biases actually are found to have a tangible impact on patient health outcomes.

In fact, researchers at the David Geffen School of Medicine at the University of California Los Angeles found that the mortality rate for female patients when they were treated by a female doctor was 8.15% compared with 8.38% when a male physician was responsible for their treatment. The researchers regard this as a "clinically significant difference" (Pratt, 2024).

This clearly indicates that a certain objectivity is needed in this field, especially when prescribing strong pain medications to male and female patients or just treating their pain in general.

Acknowledging and addressing these gender biases can help health professionals promote equitable care and reduce health disparities. Together, our essential healthcare workers can come together to foster a culture of accountability, equity, and accuracy.

4.3. Analysis of the Medical Device Approval Process in the U.S. through Research Prompted by Media

The public is gradually becoming more and more aware of the negative impacts of the predicate rule. "The Bleeding Edge", a 2018 documentary, played a key role in educating the public on this clearance process that allows new medical devices to be approved based on similarity rather than through comprehensive research studies. This has had a significant impact on the population, particularly for women.

For example, the documentary goes into detail about 5 devices, 3 of which are exclusively for women. Take transvaginal mesh, for example. This was a medical device included in the documentary that is meant to treat SUI (stress urinary incontinence, a condition in which movement or activity can cause urine to leak since pressure is being placed on the bladder) and POP (pelvic organ prolapse, a condition where 1 or more of the organs in the pelvis slip down from their normal position and bulge into the vagina) (NHS, n.d., Lombardo, 2018, Mayo Clinic, 2024, "Transvaginal Mesh", 2017).

Though this was meant to be an implant that would treat countless women, it was incredibly controversial. It ended up causing chronic pain, infections, and organ perforation in many women.

One brand in particular, Coloplast, has been quite injurious to women. In fact, on April 12, 2022, one woman was awarded $2.5 million in a lawsuit against Coloplast (Miller, 2024). The jury concluded that the mesh was designed in a defective fashion and failed to warn surgeons about the risks of the injuries sustained by pelvic mesh implants.

But this is just 1 device. Essure, a permanent birth control device with metal coils inserted into the fallopian tubes, is a device approved through the 510(k) process and used by many to prevent pregnancy. "The Bleeding Edge" highlights the various adverse effects that many women have experienced as a result of the insertion of this device, such as extreme pain, allergic reactions, autoimmune disorders, and organ perforation.

The only risks highlighted by the FDA during the period when implantation was allowed and Bayer (the company responsible for the device) was still placing this product on the market were light to moderate pain and other symptoms like dizziness and nausea (Center for Devices and Radiological Health, n.d.). However, the allergic reactions, disorders, organ damage, and severe pain resulting from the implantation were not mentioned and many people, both physicians and patients, were not warned about the impacts.

However, the FDA did take action, and as of December 31, 2018, Bayer stopped selling and distributing the Essure device in the United States and by December 31, 2019, all unused but sold Essure units were required to be returned to Bayer and the product was no longer available

for implantation (Center for Devices and Radiological Health, n.d.). This was definitely a step in the right direction since as of December 31, 2017, the FDA had received 26,773 medical device reports related to Essure (CBS News, n.d.).

However, the coverage of this particular device and others was met with backlash. The Advanced Medical Technology Association released the following statement: "Kirby's film does a disservice to the hundreds of millions of patients worldwide who have benefited from medical technology."

Meanwhile, this is what Bayer had to say in response to the making of this film, "As a leader in women's healthcare, Bayer believes strongly that women and their physicians should make reproductive health decisions based on sound science. In contrast, the portrayal of Essure in The Bleeding Edge lacks scientific support, despite the fact that Bayer provided the producers with extensive scientific information on Essure before the completion of the film."

Furthermore, power morcellators were another device approved through the 510(k) process and were used in minimally invasive surgeries with the purpose of removing uterine fibroids (growths in the uterus) (Mayo Clinic, 2023). These are medical devices used during laparoscopic/minimally invasive surgeries to ensure that tissue can be removed through a small incision site. Once again, this device was meant to be beneficial.

However, it ended up leading to the spread of undetected cancerous tissues in many patients, and the spread of cancer in these women was devastating. Many of them thought they had just undergone a routine procedure, not something that would cause their lives to be altered completely. The controversy initially began in 2013 when Dr. Amy Reed, an anesthesiologist, underwent a hysterectomy with the removal of uterine tissue via the use of a power morcellator (Martin, L., Shelton, J., & Goldberg, J., n.d.).

Sadly, her pathology report showed signs of leiomyosarcoma (a type of rare cancer that grows in the smooth muscles, like the uterus) ("Leiomyosarcoma", n.d.). It was believed that during the morcellation process, small fragments of malignant tissue were "seeded throughout her peritoneal cavity". Following this, concern was raised about the approval of this device. After all, the FDA first approved power morcellators for gynecologic surgery in 1995 and since then, approval has been hinged on the 510(k) process.

Eventually, a media campaign was initiated to ban its use and several hospitals in the Philadelphia area, where the controversy began, also banned the use of power morcellation. Two Pennsylvania senators also got involved and pointed out to the FDA that there was a large gap in medical device approval and evaluation.

Overall, "The Bleeding Edge" illustrated the real-life implications of the 510(k) clearance process on medical device approval in the United States and how it has impacted countless individuals. This process can perpetuate the approval of flawed devices, and when brought to market, many physicians and patients can be hoaxed. This film, naturally, prompted public outcry and advocacy for reforms in regulatory practices.

However, despite the testimonials from patients and the arguments presented in the documentary, the efficacy of several of the devices mentioned is still heavily contested today. Nevertheless, it left a lasting impact on the medical community and signaled that the predicate rule may be efficient but it lacks the accuracy and comprehensiveness needed in the healthcare field today.

5. Conclusion

We can make tangible changes in further understanding the impacts of analgesics and medical devices/technological equipment on women by focusing on three key areas of improvement. By paving the way for these advancements, we can build the infrastructure needed to support women in research and just women in the healthcare field in general, whether they are health professionals or patients.

Firstly, we need to focus on more women's health issues, particularly when it comes to our understanding of reproductive health and the various afflictions women are facing.

Women's health issues like endometriosis, PCOS, etc. need to be better understood in order for us to properly take action. These actions include prescribing adequate medications and even designing newer chronic pain medications that work better and help women feel better.

After all, these conditions are certainly not rare. We find that over 11% of women in the United States alone experience endometriosis and 6-12% have PCOS (Sklar, 2022). These women are left with no solutions and are forced to live with it on a daily basis. This is difficult to go through, especially without adequate medications and analgesics. This paper finds that a historical lack of women in these research studies has resulted in the conditions that many women experience not being well-researched enough and contributes the idea that we need to direct pure focus towards these issues.

However, there are steps we can take to ensure that women are being treated with respect and are being given treatments that adequately treat or at least alleviate the pain they are going through. These include changing physician perception but also include how we conduct research studies and how many women we are involving in said projects.

I will talk about this further in the rest of my conclusion, but the point ultimately is that women should be a part of the initiatives that drive the effort to make it easier to be a woman with an invisible illness or a woman in pain. These studies are a wake-up call. Our lack of awareness of these issues is transparent and disappointing for patients.

Secondly, we must put research funding towards women's projects. Female voices can help create an environment suitable for women to be included in studies and research. Plus, studies have shown that women have reported that female researchers and physicians tend to prioritize them and listen to their symptoms and health needs more than their male counterparts tend to do (Dusenbery, 2022).

This ties into a recent study that found that women tend to be more accurate as doctors than men, the benchmark being a high quality of patient treatment (Szabo, 2024).

Finally, we must include women in more R&D studies and clinical trials, and even form women-centric studies to test the efficacy of today's analgesics. By including more women in these studies, we will gain a better understanding of the various issues that are affecting them.

The truth is, without the ability to understand the rare diseases that women are afflicted with and the effects of the tools that physicians and healthcare professionals use to cure these diseases, we will never actually know how to improve their efficacy and make changes to regulatory systems in order to create real change.

This goes for both drugs that are regulated and evaluated with clinical trials and also medical devices that go through a similar regulatory process. The FDA handles the evaluation of both of these tools and remedial solutions, but we find that it is not necessarily doing a perfect job. The predicate rule is just one example of a variety of issues that have been brought up when it

comes to how our regulatory bodies in the United States monitor and act upon the placement of various products on the market.

In conclusion, addressing the gender pain gap is imperative in order to achieve equitable healthcare. By prioritizing women's health issues, funding female-led research, and ensuring inclusive clinical trials, we can greatly improve pain management for women and mitigate antiquated stigmas and age-old disparities.

I sincerely believe that these solutions can create the future many of us envision. Women treated with respect, given the healthcare solutions they deserve, and being treated like equals in society.

But by working together to find ways to enhance and improve our existing system, we can morph it into the system that many of us wish to see one day. That means a lot to me, as it is essential that half of the population feels that the healthcare system of today is also serving them. As a part of this half, this is both personal and professional, and the urgency of this issue cannot be further expressed.

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