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SCIENCE FACT OR SCIENCE FICTION:

ARE MEDICATIONS AND MEDICAL DEVICES MORE DANGEROUS FOR WOMEN?

While medications and medical devices can improve health, they also hold potential risks for men and women. The level and frequency of these risks can differ depending on the sex and gender of patients. Physiological, molecular and cellular differences mean that male and female bodies react differently to medications and medical devices due to biological sex[1].

HOW WOMEN PROCESS DRUGS DIFFERENTLY THAN MEN

Body fat: Women usually have more body fat than men, which means fat-soluble drugs might linger.

Liver: Female hormones can affect how drugs are metabolized by the liver.

Kidneys: Women's kidneys are smaller, which affects how drugs are eliminated from the body.

Heart: Women's heart rhythms are slightly different from men's, so drugs affecting the heart might have different risks or results.

Weight: Women tend to be smaller than men, so the same dosage might have a bigger effect[2].

Beyond just biology, the psychosocial construct of gender can also play a role in the risks and effectiveness of drugs and medical devices. Gender refers to socially constructed roles, behaviours, expressions and identities. Gender bias may cause doctors to display bias when treating patients, which can result in misdiagnosis or the dismissal of patients' symptoms[3,4]. Sex and gender considerations have often been ignored in the development and prescription of medications and medical devices[5,6]. The unfortunate result is that drugs and devices intended to improve health tend to be more dangerous for women.

SAFETY STARTS WITH RESEARCH

Explaining why medications and medical devices are more dangerous for women begins with preclinical research, where there is a tendency to exclude female animals from experiments[7]. Excluding females means researchers do not have the opportunity to identify and study sex differences in diseases and creates assumptions that similar medical treatments will work for both sexes. Women have also been historically underrepresented in clinical trials[5], meaning that medical solutions are often not tested properly for safety in women before they enter the market. For example, in clinical trials for statins, used to lower cholesterol, women represented only 18.6% of participants in the 1990s and 31.5% of participants in the 2000s[8]. In recent years, the trend has begun to improve. From 2015 to 2016, women made up 43% of participants in clinical trials globally and 45.2% in Canada[9]. While this represents a positive sign towards improved safety for women, in Canada, women are still underrepresented in early-phase trials and in research on certain therapeutic areas.

Pregnant and breastfeeding women may be excluded completely from trials[5] because there have been cases where drugs went to market that were later found to cause birth defects in the offspring of women who took them. Examples include diethylstilbestrol (DES), a drug used to support women who had a history of miscarriage, and thalidomide, an anti-nausea drug, both of which were prescribed to pregnant women between the 1950s and 1970s. Since then, there has been a resistance to include pregnant women in clinical trials because the potential risk of harm for both women and their offspring. So, while excluding pregnant women from clinical trials can seem well-intentioned, it also results in a lack of available data on sick women who become pregnant and pregnant women who become sick[10].

Even when both males and females are included in preclinical and clinical research, the results from studies must also be disaggregated by sex, in order to account for significant differences related to effectiveness and safety. For example, men and women were included for clinical trials for desmopressin, a medication used to treat nocturia, or increased urge to urinate at night. However,

researchers needed to disaggregate the data from the trial results to discover that the safe and effective dose of desmopressin for women was significantly lower than the safe and effective dose for men[11].

SAFETY IN MEDICATIONS

Males and females absorb, metabolize and excrete medications differently due to biological factors, yet these differences are often overlooked[12]. Between 1997 and 2000, the FDA in the US removed ten drugs from the market due to adverse events; astoundingly, eight of these ten posed greater risks to women[13]. Terfenadine, an antihistamine, and Cisapride, a gastric reflux medication, were withdrawn because they caused fatal arrhythmias, or abnormal heart rate, in women only. Fatal arrhythmias occurred because females have naturally longer intervals between heartbeats and male sex hormones decrease the heart's sensitivity to arrhythmia-promoting drugs[13]. Safe prescription dosage levels can also differ by sex. For example, Health Canada released a warning in 2014 to halve the recommended dose of the sleeping pill Zolpidem for women. Morning blood levels of Zolpidem were 40% higher in women, which increased women's risk of impaired driving after taking the same dose as men[14].

SAFETY IN MEDICAL DEVICES

High-risk medical devices that require surgery need to be tested in small groups and over shorter time periods[6]. Medical devices go through less surveillance and many devices go to market without having gone through clinical trials, making them risky for both men and women[15]. However, there have been numerous recent examples of medical devices that have posed greater risks for women. One example is artificial hearts. The majority of artificial hearts are made in a standard size, which is too large for many women. Manufacturers justify making the larger size more available because 80% of patients who choose to get an artificial heart are men. However, this may be due to gender biases in doctors' proposed treatments and referrals for artificial hearts, as the same number of men and women actually suffer from heart disease[16].

Certain conditions that require medical devices only affect women. Birth control patches, for example, can increase patients' risk of stroke[17]. Textured breast implants, which are made to stop implants from slipping and scarring, have also been linked to lymphoma, a cancer affecting lymphocytes, or essential cells of the immune system[18].

Tension-free vaginal tape (TVT) slings, or vaginal mesh implants, which are used to treat incontinence and pelvic organ prolapse in women, are often made from polypropylene material, which can break apart and cause severe pain. Health Canada and the U.S. FDA issued multiple warnings from 2008-2011 after thousands of women reported painful side effects from the implants[6,19]. A study from Oxford University's Centre for Evidence-Based Medicine found that pelvic meshes had not gone through any clinical trials in women before they were approved[20].

CONCLUSION

While medications and medical devices pose risks for both men and women, the risk of harm depends on the sex and gender of patients and there are numerous recent examples of potential danger for women. Increased risk for women stems from a lack of females in preclinical and clinical trials, the failure to disaggregate data by sex (even if females are included in trials), and gender bias on the part of clinicians. People, no matter their sex or gender, deserve medications and medical devices that are safe. Ensuring safety starts with the appropriate integration of sex and gender in health research.

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