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# Sex differences, adverse effects and adherence

OPINIONS

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## Drug therapy is impacted by a patient's biological sex and gender identity. Both have a bearing on adverse effects and adherence.

Absorption, distribution, metabolism and elimination of medications vary depending on sex. Physiological differences in body composition, organ function and hormones are well documented. However, less is known about the variations in target proteins to which medications bind. The effect and adverse effects of a medication can differ depending on a patient's sex. It is also easy to overlook the significance of gender identity in experiences with medication in clinical practice and research. Gender roles shape our gender identity through social and cultural expectations. Biological sex and gender identity also involve changes throughout life. Women have traditionally been underrepresented in studies that lead to clinical guidelines. Knowledge about differences in biological sex is relevant for those prescribing medication as well as researchers in light of the focus on women's health.

> ***«Dosage recommendations in product information stem from clinical trials with men, which can result in women receiving incorrect doses»***

## Doses are tailored for men

Dosage recommendations in product information stem from clinical trials with men, which can result in women receiving incorrect doses. Women generally weigh less than men, and weight-adjusted dosing has been suggested. However, animal studies suggest that women are not simply scaled-down men (1). Expectations for medication dosing and effect in women cannot be based on weight alone. Women have more body fat than men, which can affect the distribution and effect of fat-soluble medications. Women's heart rhythms differ from men's, which can influence the effect of cardio-selective medications. Female hormones can affect how medications are metabolised in the liver (2). Hormonal status in women changes with menarche, contraception, pregnancy and menopause. All of these examples suggest a need for sex-based prescribing of specific medications in addition to weight-adjusted dosing (1).

> ***«Women generally use more of all types of medications than men throughout most of their adult life»***

## Women have more adverse effects

Women generally use more of all types of medications than men throughout most of their adult life. This is also true when hormonal contraception is excluded (3). They experience more adverse effects, and these are closely associated with higher drug concentrations and prolonged elimination. These adverse effects cannot be explained by weight differences, but are understood to be sex-specific (4). The World Health Organization's (WHO) adverse event database reports more adverse effects in women, while men were reported to experience more serious adverse effects. The greatest difference occurs during a woman's reproductive years (18 - 44 years), regardless of the category of healthcare professional doing the reporting (5). A study from the US Food and Drug Administration (FDA) database found that differences between women and men disappeared after adjusting for prescription rates (6).

## Adherence is poorer in women

It has been suggested that being female is an independent predictor of low medication adherence, and women have been shown to have poorer medication adherence in the context of metabolic and cardiovascular diseases (7). Differences have been found not only in observational data but also in prospective studies. Women discontinued trial medications more frequently than men in randomised placebo-controlled cardiovascular outcome trials, and this finding is not explained by the greater number of adverse effects

experienced by women (8). An analysis of almost 1000 medication adherence studies found that less than 1 % described sex and gender as distinct variables (9). Nausea during pregnancy or concerns about the effects from the medication when breastfeeding are examples of how different life stages and the associated altered physiology and perception can impact on adherence.

***«Choice of medication and dosage are key factors in relation to adverse effects and adherence in women, but biological sex does not explain all experiences from clinical practice and studies»***

## Perspective

Choice of medication and dosage are key factors in relation to adverse effects and adherence in women, but biological sex does not explain all experiences from clinical practice and studies. Communication and behaviour in connection with adverse effects and adherence are influenced by factors relating to gender identity. Motivation and psychological, social and cultural factors also have a bearing. Many studies do not control for these factors, highlighting the need to develop better methods for studying drug therapy in light of differences in sex.

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