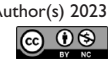
Making a ‘sex-difference fact’

Article

S|S|S

Social Studies of Science
2023, Vol. 53(4) 475–494



DOI: 10.1177/03063127231168371
journals.sagepub.com/home/sss

Making a 'sex-difference fact': Ambien dosing at the interface of policy, regulation, women's health, and biology

Helen Zhao[1], Marina DiMarco[2], Kelsey Ichikawa[3], Marion Boulicault[4], Meg Perret[3], Kai Jillson[3], Alexandra Fair[3], Kai DeJesus[3] and Sarah S. Richardson[3]

Abstract

The U.S. Food and Drug Administration's (FDA) 2013 decision to lower recommended Ambien dosing for women has been widely cited as a hallmark example of the importance of sex differences in biomedicine. Using regulatory documents, scientific publications, and media coverage, this article analyzes the making of this highly influential and mobile 'sex-difference fact'. As we show, the FDA's decision was a contingent outcome of the drug approval process. Attending to how a contested sex-difference fact came to anchor elite women's health advocacy, this article excavates the role of regulatory processes, advocacy groups, and the media in producing perceptions of scientific agreement while foreclosing ongoing debate, ultimately enabling the stabilization of a binary, biological sex-difference fact and the distancing of this fact from its conditions of construction.

Keywords

sex differences, SABV, women's health, drug regulation, scientific facts, zolpidem

[1]Columbia University, New York, NY, USA
[2]University of Pittsburgh, Pittsburgh, PA, USA
[3]Harvard University, Cambridge, MA, USA
[4]Massachusetts Institute of Technology, Cambridge, MA, USA

Corresponding author:
Helen Zhao, Department of Philosophy, Columbia University, Philosophy Hall, 1150 Amsterdam Avenue, New York, NY 10027, USA.
Email: hz2491@columbia.edu

In 2013, a striking example of sex disparities in health came to Americans' attention. According to the Food and Drug Administration (FDA), the household prescription sleep drug zolpidem (trade name Ambien) was especially dangerous for women (FDA, 2013). The FDA felt so strongly about this that it announced that it was halving the recommended dosage for women. Well-known and trusted women's health advocates, such as the non-profit advocacy group Society for Women's Health Research (SWHR) and Janine Clayton of the National Institutes of Health (NIH) Office for Women's Health Research (OWHR), appeared in the media touting the FDA's decision as a victory against sex discrimination in medical research and connecting the case of zolpidem to the need for reform at the highest levels of science policy and drug regulation (Rabin, 2013). In 2014, Clayton and NIH Director Francis Collins used the FDA's recent decision to introduce sex-based dosing for Ambien to lay the groundwork for a sweeping new NIH policy requiring the study of 'Sex as a Biological Variable' (SABV) in preclinical research in mouse models and cell cultures (Clayton & Collins, 2014). Zolpidem quickly became a prize example of advocates of SABV policy, featuring in perspective pieces, teaching materials, and advocacy literature around women's health and the importance of biological sex differences.

This SABV advocacy narrative presents the previous lack of sex-based dosing for zolpidem as the consequence of a long history of inattention to biological sex differences. For advocates, the case of zolpidem presents a compelling call to ameliorate gender inequality in medical research, continuous with the mission of the 1993 Revitalization Act, which directed the NIH to establish guidelines for including women and minorities in clinical research, by investing in the field that the SWHR has dubbed 'sex-based biology' (IOM, 2001; Marts, 2002). They predict that many more drugs and medical interventions will, like zolpidem, require sex-based dosing once sex difference research is conducted (Zucker & Prendergast, 2020). As we show, versions of this narrative have been repeated over the past decade, cycling among biomedical journals, media reporting on sex disparities in adverse drug events, and women's health reports, educational materials, and other gray literature. Together, these materials established zolpidem as an exceptionally mobile and legible sex-difference fact. For advocates, the case of zolpidem came to represent a set of arguments, interests, concerns, and stories at the core of U.S. women's health advocacy.

Through examination of the FDA's 2013 decision to institute sex-based dosing for zolpidem and the decision's afterlife, this paper presents a grounded empirical study of the role of regulatory and policy actors in the concretization of a *sex-difference fact*. As we reconstruct below, the FDA decision was not a response to rigorous evidence of sex-based biology linked to sex-specific adverse outcomes, but rather a pragmatic, contingent judgment to use subgrouping by sex to address safety concerns about zolpidem during a contentious drug approval process. Based on close analysis of the regulatory process, media coverage, gray literature, and research publications, we illustrate how regulatory decisions at the FDA, women's health advocacy, and research policies at the NIH transformed zolpidem into the 'perfect example' (Rosen, n.d.) of biomedical sex differences, despite dissensus in the pharmacological literature.

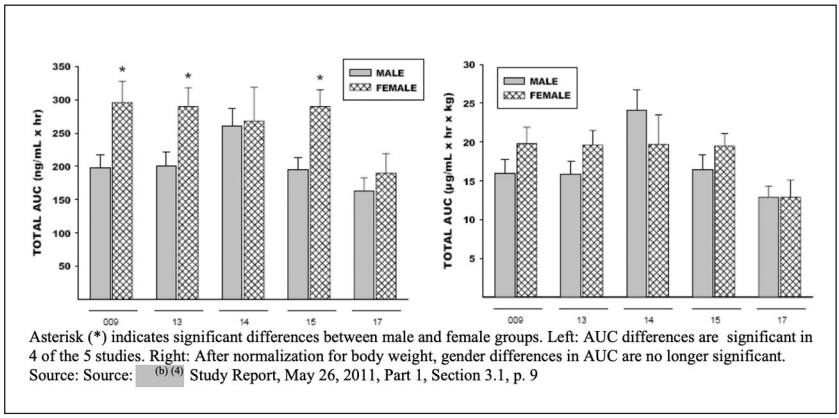
The FDA recommendation

The FDA first approved zolpidem in 1992. Marketed as Ambien, zolpidem became one of the most commonly prescribed drugs in the United States. In 2008, the drug company Transcept Pharmaceuticals sought approval for a new zolpidem formulation, Intermezzo. Unlike Ambien and its cousins Ambien CR (an extended release version, approved in 2005) and Zolpimist (a spray formulation, approved in 2008), Intermezzo was intended to treat a specific form of insomnia: not trouble falling asleep or staying asleep, but 'middle of the night wakening' (BioSpace, 2011). In the first submission in 2008, safety and efficacy data showed that two doses, 1.75 mg and 3.5 mg, were effective. Transcept reported no clinically relevant sex differences in pharmacodynamics (meaning drug effect) as assessed using the digit symbol substitution test (DSST), a common test of cognitive function.

FDA rejected this submission, expressing safety concerns about next-day driving specific to the dosing regimen of Intermezzo (Katz, 2009). Because patients were meant to take Intermezzo in the middle of the night, they would have less time between their dose of zolpidem and next-day driving. Transcept agreed to assess this using a driving study in which participants performed a highway driving test 3- and 4-hours after taking a 3.5 mg dose of Intermezzo in the middle of the night (CDER, 2011b). This study of 20 male and 20 female participants showed no clinically significant impairment in driving performance at 4-hours post-dose, although one female participant, noted in regulators' correspondence as the participant with the lowest weight in the study, fell asleep while driving (CDER, 2011b, p. 33).

In 2011, Transcept resubmitted Intermezzo with this new evidence related to next-day driving impairment, again with two dose options for all patients. Transcept argued that the driving study showed no impairment at 4-hours post dose, which would mean Intermezzo was safe if used as directed. They also reported no sex differences in driving impairment. FDA's own review of this study noted that 'men and women were equally likely to be represented among the high responders' in both the driving study and other pharmacodynamic analyses (CDER, 2011b, p. 123). But FDA, still concerned about driving safety, rejected this submission as well.

FDA responded to Transcept expressing concern about patients whose zolpidem levels remained higher than 40 ng/mL at 4-hours post-dose, a level that FDA asserted was associated with driving impairment at the 3-hours post-dose timepoint (CDER, 2011b). In making this judgment, the FDA review team rejected pharmacodynamic measures, including the DSST test and subjective patient self-assessment of somnolence, as metrics of next-day driving safety. Instead, regulators focused solely on predictions of likely driving impairment based on pharmacokinetic (meaning rate of clearance of the drug from the body) differences among patients. The July 2011 Letter from FDA to Transcept was also the first safety correspondence in which the FDA explicitly referred to demographic categories as possible targets for analysis regarding Intermezzo. FDA wrote that, 'women have, on average, greater zolpidem plasma levels at a given dose than men; estimates range from about 40-70% greater' (Michaloski & Katz, 2011, p. 3). They flagged that '[a]nalysis of impairment by gender may have shown a trend for increased impairment' and speculated that this 'would be consistent with the higher blood levels



Asterisk (*) indicates significant differences between male and female groups. Left: AUC differences are significant in 4 of the 5 studies. Right: After normalization for body weight, gender differences in AUC are no longer significant.
Source: Source: (b) (4) Study Report, May 26, 2011, Part 1, Section 3.1, p. 9

Figure 1. Pharmacokinetic sex differences across 5 studies, before (left) and after (right) normalization for body weight (CDER, 2011b, p. 107).

observed in women' (CDER, 2011b, pp. 35–36). As FDA reviewer Ronald Farkas explained, regulators 'therefore asked the drug company to conduct additional pharmacokinetic and pharmacodynamic analysis to determine if specific baseline patient characteristics, such as gender and body weight, could predict high blood levels' (CDER, 2011b, p. 27).

In response to this suggestion, Transcept submitted data demonstrating that any apparent sex differences in pharmacokinetics were likely due to differences in body weight (CDER, 2011b, p. 99). As Transcept argued, 'gender differences in weight-normalized variables were smaller and generally not significant' (CDER, 2011b, p. 38). Transcept further noted that, in any case, there was no correlation between pharmacokinetic levels and higher likelihood of impairment or adverse drug events in their studies (CDER, 2011b, pp. 38–39). In response, FDA maintained that despite these findings, other non-sex-related analyses conducted by the FDA showed that weight alone did not predict an individual's zolpidem clearance rate (CDER, 2011b, p. 28). The FDA was still concerned that, on average, female subjects had slower clearance rates than men, irrespective of the attenuating effect of weight adjustment (CDER, 2011a, p. 31, 2011b, p. 39).

This dispute over whether a non-statistically significant difference should motivate safety assessments rehearses longstanding debates about whether valid but statistically insignificant subgroup analyses are ever sufficient for attending to biomedically meaningful differences in clinical populations (Epstein, 2007). The heart of the dispute can be seen in Figure 1, from the 2011 Center for Drug Evaluation and Research report. On the left, we see a statistically significant sex difference in zolpidem clearance rates in three out of five studies, indicated by asterisks. On the right, the numbers are adjusted for body weight. After adjustment, no studies show a statistically significant sex difference and sex differences are greatly attenuated, including one study in which the sex disparity is reversed.

But with FDA threatening not to approve Intermezzo after an extended review process, in November 2011 Transcept proposed sex-specific dosing for Intermezzo: females should take 1.75 mg, and males should take the full 3.5 mg dose. Based on data from previous safety and efficacy studies, this dosing scheme would decrease the probability that any patients would have blood zolpidem levels above 40 ng/mL at 3, 4, or 5 hours post-dose. Transcept did not perform any new studies in order to make this argument. Instead, they reanalysed two previous studies, ZI-05-009 (a pharmacokinetic analysis) and ZI-06-010 (a sleep study in which males and females had been given either a 3.5 mg dose, a 1.75 mg dose, or a placebo). ZI-06-010 was retroactively interpreted to show that a 1.75 mg dose in females was comparably effective to a 3.5 mg dose in males in treating middle-of-the-night wakening (CDER, 2011b). Reanalysing the data from study ZI-05-009 to disaggregate by sex and by dose, Transcept showed that reducing the dose for females would reduce the likelihood that any patients, male or female, would have blood zolpidem levels above 40 ng/mL in the morning. To strengthen these findings, Transcept pooled data from this study with a number of other studies in which females had received a 3.5 mg dose. In order to use these studies to make inferences about the 1.75 mg dose in females, blood zolpidem levels for females who took the 3.5 mg dose were divided in half (see Tables 2 and 3, CDER, 2011b, p. 9). Transcept found that the lower 1.75 mg dose was effective in males as well as females, but used this result to argue that a 1.75 mg dose would be effective in females, not as a reason to lower the dose to 1.75 mg for all patients.

On the basis of Transcept's proposed dosing change, FDA approved Intermezzo in November 2011 (CDER, 2011b; Katz, 2011) with sex-specific dosing: 1.75 mg for women, and 3.5 mg for men (CDER, 2011b). The recommended dosing scheme that secured Intermezzo's approval was not based on a dosing strategy tailored to mechanistic hypotheses about biological differences between demographic groups, nor on postmarketing analysis of adverse event reporting. Rather, it was a pragmatic concession that enabled the drug manufacturer to show comparable safety and efficacy for males and females without performing any additional studies.

While Intermezzo has since been discontinued due to market failure (Weinstein, 2013), its legacy lives on in dosing recommendations for other zolpidem formulations. Directly motivated by the Intermezzo review process (Farkas et al., 2013), in January 2013, FDA changed its recommended dosing for all formulations of zolpidem, recommending that Ambien dosage for women be cut in half, issuing the following public guidance:

> FDA has informed the manufacturers that the recommended dose of zolpidem for women should be lowered from 10 mg to 5 mg for immediate-release products (Ambien, Edluar, and Zolpimist) and from 12.5 mg to 6.25 mg for extended-release products (Ambien CR). FDA also informed the manufacturers that, for men, the labeling should recommend that health care professionals consider prescribing the lower doses—5 mg for immediate-release products and 6.25 mg for extended-release products. (FDA, 2013)

Zolpidem thus became the first drug class with a recommendation for sex-specific dosage on the drug label for every formulation, a decision that received extensive media

coverage and was hailed by women's health advocates and sex-difference-biology researchers and advocates as a breakthrough.

A 'hallmark example' for sex difference science

The 2013 FDA decision was widely covered in the media, including in mainstream outlets such as the *New York Times*, *Forbes*, and *ABC News*. Headlines broadcast that 'Drug Agency Recommends Lower Doses of Sleep Aids for Women' (Tavernise, 2013), 'FDA: Cut Ambien Dosage for Women' (Clark & Stark, 2013), and 'FDA Takes Action on Ambien; Concedes Women At Greater Risk' (Falkenberg, 2013). Bioscientists and women's health advocates applauded the FDA's decision as a turning point for addressing sex disparities in adverse drug events. In May 2013, women's health researcher and advocate Sabra Klein, a microbiologist at Johns Hopkins, and Gregory Poland, an immunologist at the Mayo Clinic, invoked FDA's decision on zolpidem in the opening words of an editorial in *Vaccine* about the importance of sex differences for developing personalized vaccines (Klein & Poland, 2013), suggesting that sex-based dosing may soon extend to this domain. In a 2017 *National Public Radio* interview, Paula Johnson, formerly head of the Connors Center for Women's Health and Gender Biology and chief of the Division of Women's Health at Brigham and Women's Hospital, invoked Ambien as an example of 'drugs that are metabolized quite differently in women leading to different effects' (TED Radio Hour, 2017). Johnson argued that prescription practices for drugs relevant to cardiac care ought to be modeled on FDA's recommended sex-specific dosing of Ambien. Likewise, in an interview with the *New York Times*, the OWHR's Clayton dramatized the lessons from Ambien for women's health: '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' (Rabin, 2013).

More broadly, zolpidem was cited by SABV policy and sex-difference science advocates as demonstrating the harms to women and to society of ignoring sex differences. The case for SABV policies, advanced across North America and Europe in a variety of media, hinged centrally on the promise of sex difference research for preventing adverse drug events in women. Advocates argued that women experience more adverse drug reactions than do men and that this is a result of biological sex differences, which are large in magnitude and extend to every biological system. They contended that these sex differences are systematically underdocumented in clinical and preclinical research, and that analysis of sex differences in preclinical research will lead to more personalized treatments by tailoring dosage to sex.

Two months after the FDA decision, in July 2013, Kathryn Sandberg, Director of the Center for the Study of Sex Differences in Health, Aging & Disease at Georgetown University, and Joseph Verbalis, Division Chief of Endocrinology at Georgetown, published a commentary in the journal *Biology of Sex Differences* that used the distinctive risks to women of zolpidem to motivate a call for more sex difference science. Asking, 'Why were these sex differences discovered only after the drug was marketed?', they called for addressing the problem at the level of basic, preclinical biology by ensuring the use of both male and female animal models (Sandberg & Verbalis, 2013). Zolpidem,

they argued, exemplifies the consequences of 'sex discrimination' in biomedical research.

In scientific and popular articles alike, prominent sex difference researchers and SABV policy advocates used zolpidem to underscore the urgency of policy changes to require analysis of sex differences in biomedical research, even at the level of basic bench science. So canonical did the example become that in some cases sex-based dosing for zolpidem was incorrectly presented *as a result* of the NIH's SABV policies. For example, Maron (2020) claimed that SABV initiatives 'have not only resulted in a better understanding of sex-specific drug response but also led to the first drug in FDA history to be prescribed based on sex: zolpidem.'

The FDA decision on zolpidem traveled beyond the U.S. as well. It was cited in the international Sex and Gender Equity in Research (SAGER) guidelines (Heidari et al., 2016), which were developed by the European Association of Science Editors to 'encourage a more systematic approach to the reporting of sex and gender in research across disciplines.' In their 2016 announcement of the SAGER guidelines, Heidari et al. pointed to zolpidem as an example of the risks of inattention to sex/gender, contending that [s]ex and gender-based analysis…would have provided sufficient information to guide dosing and applicability of drugs in men and women prior to approval' (Heidari et al., 2016).

Media uptake energized SABV policy advocates. A 2014 *60 Minutes* segment on Ambien sex differences (CBS News, 2014) interviewed Larry Cahill, a neuroscientist at the University of California, Irvine, and key architect of the NIH SABV policy. Cahill argued that '[Ambien] is a textbook example of what is wrong. How did it happen that for 20 some years, women, millions of them, were essentially overdosing on Ambien?' Reporter Lesley Stahl underscored the take-away: 'Ambien is typical of a much larger problem and that further study of sex differences is needed.' The *60 Minutes* segment has since been cited in academic publications, sometimes as the sole citation, when discussing the implications of the FDA decision (Cahill, 2014; Mazure & Jones, 2015; D. Y. Yoon et al., 2014).

Through circulation across these many media, zolpidem became a stock example in sex-difference literature, which positioned zolpidem as a 'hallmark example of displaying significant sex differences in drug response' (Madla et al., 2021); 'a perfect example' that women differ from men in symptoms, treatment responses, and adverse drug reactions (Rosen, n.d); 'a prominent example of the effect of the imbalance during preclinical research' (Karp & Reavey, 2019); 'a prominent example relating to the neglect of females in preclinical and clinical research' (Zakiniaeiz et al., 2016); 'a classically cited example' (Stephenson et al., 2018); an 'illustrative example' (Zucker & Prendergast, 2020); 'a famous example' (Pearse & Young-Pearse, 2019); and 'perhaps the most widely known example' of sex differences in drug metabolism (Stephenson et al., 2019). In short, women's health and sex difference scientists prolifically used the case of Ambien to suggest that biological sex differences in drug metabolism have been overlooked and to direct more resources and research attention to sex difference science. Researcher-advocates and medical journalists alike found the household drug of Ambien a particularly poignant touchstone for conveying the importance of sex difference science.

Selective citation and dissensus in the biomedical literature

The pharmacology research literature on zolpidem, however, is quite distinct from women's health and sex-difference scientists' use of zolpidem as a foundational example. Over several decades, pharmacologists have explored the interaction of sex-related variables with outcomes in this drug class using a variety of study designs and methodologies, including both human and animal studies. Studies of zolpidem pharmacology include investigations of group (age, race/ethnicity, sex) differences in drug clearance rates, post-dose effects of zolpidem intake, and the causal relationship between clearance rates and drug effects.

Early research on zolpidem looked for, but did not find, evidence of clinically relevant sex differences. For instance, a 1995 analysis of sex differences in zolpidem pharmacokinetics and pharmacodynamics did not find any sex differences (Salvà & Costa, 1995). Later research showed some evidence of lower mean clearance rates of zolpidem among women compared to men, but more often than not those differences were no longer statistically significant after adjusting for body weight (Greenblatt et al., 2000, 2014, 2019; Guo et al., 2014; S. Yoon et al., 2021). A 2000 study of sex-dependent effects in comparative kinetics and responses found a statistically insignificant sex difference for zolpidem clearance ($p<0.06$), but no sex-dependent pharmacodynamic effects that would point to a role for this clearance rate differential in adverse events (Greenblatt et al., 2000).

There are wide interindividual differences among men and among women in zolpidem clearance rates. Age may be a more important mediating factor than gender or weight: in a study of zolpidem and aging, Olubodun et al. (2003) analysed within-sex differences in pharmacokinetics stratified by age and observed the lowest clearance rates in elderly men. While pharmacological research does not rule out sex differences in zolpidem pharmacokinetics that are relevant to pharmacodynamic effects, there is no consensus view of the biological or clinical significance of these mixed findings on sex differences, including how body weight interacts with sex and age. What is plain is that when clearance rates are adjusted for body weight, any effect of sex is greatly attenuated (S. Yoon et al., 2021).

Even if true sex differences in clearance rates exist, the pharmacological literature does not find higher rates of adverse drug events in women compared to men following zolpidem use (Greenblatt & Roth, 2012; Greenblatt et al., 2000, 2014; Roehrs & Roth, 2016; Vermeeren et al., 2014). Six studies (Booth et al., 2016; Gustavsen et al., 2008, 2009; Partinen et al., 2003; Vermeeren et al., 2014; Verster et al., 2002) have investigated post-dose effects of zolpidem on psychomotor and driving performance. Four of these include analyses of sex differences. Gustavsen et al. (2008) reported higher standardized incidence ratios of driving accidents among men zolpidem users compared to women, while Vermeeren et al. (2014) reported no sex differences 4-hours after administration of Intermezzo. Gustavsen et al. (2009) found no association between zolpidem blood concentration levels and driving impairment. Booth et al. (2016) observed an association between zolpidem use and higher driving accident rates among elderly women drivers compared to men, but this observational study could not distinguish whether accident

rates were higher due to the specific interaction of zolpidem with sex-related variables or simply due to the greater prevalence of sleep disorders among women.

Some of the pharmacological literature directly addresses regulation and the question of sex-based dosing. Two paired publications analyzed sex disparities in zolpidem clearance and the relationship between these disparities and adverse events, using the same data submitted by Intermezzo to the FDA (Greenblatt et al., 2013, 2014). The studies found that while there are clear sex disparities in clearance rates, they are rendered non-statistically significant after adjustment for body weight and do not predict disparities in adverse cognitive or other effects. Greenblatt et al. (2019) commented explicitly on the FDA's sex-based dosing decision, arguing that even at a high 12.5 mg dose of zolpidem, pharmacokinetic differences explained only 8% of variation in cognitive outcomes. Yoon et al. (2021, p. 9) similarly concluded that the pharmacokinetic increase of 30% in zolpidem blood levels for females is 'much less than two-fold that in males' and that the FDA's dose reduction recommendation lacked 'concrete evidence.'

Women's health and sex-based biology advocacy publications in the biomedical research literature show little awareness of this dissensus on sex differences and zolpidem in pharmacology, nor of the chain of reasoning that led to the FDA's unique sex-based dosing guidance for zolpidem products. When zolpidem appears in relation to SABV or is positioned within a women's health agenda in the published biomedical literature, it is frequently in commentaries and perspectives supporting the NIH's SABV policy and urging compliance. In many cases, an article will straightforwardly report the fact that the FDA issued sex-specific dosing recommendations and provide the FDA's justification for this, that slower clearance in women puts them at greater risk for next-day impairment. Other times, zolpidem is named without citation as a parenthetical example of the potential for harm when sex as a biological variable is disregarded (e.g., Bond et al., 2021).

Within this advocacy literature in biomedical research publications such as *PNAS, Neuron*, *Nature*, and *Biology of Sex Differences*, citational practices are selective or incomplete. When referencing the zolpidem case, many papers solely cite the FDA's 2013 Drug Safety Communication. Those papers are then cited by later papers, further distancing them from the original source of data. For example, Zakiniaeiz et al. (2016) assert that 'the FDA changed the dosage guidelines for females because similar doses as those prescribed for men posed greater health risks in women, due to sex-related differences in clearance rates.' In this passage, Zakiniaez et al. cite Greenblatt et al. (2000), in spite of the fact that this study did not find sex differences in pharmacodynamic effects ('There was no evidence of a substantial or consistent sex difference in pharmacodynamic effects or in the kinetic-dynamic relationship'). Several subsequent papers then cite Zakiniaez et al. (Karp & Reavey, 2019; Kim et al., 2021) as the sole reference for zolpidem's sex-specific effects and risks. Much of the time, there are no scientific citations at all, implying that sex-based dosing for zolpidem is settled science. For example, in support of the claim that 'female sex is a risk factor for a wide range of adverse drug reactions,' the authors of a 2017 article in *Neuropsychopharmacology* assert that the FDA reduced zolpidem dosage for women because their slower metabolism led to higher next-day drowsiness, but offer no citation for this claim (Bale & Epperson, 2017).

Factual inaccuracies or omissions about the FDA sex-based dosing decision, including the evidence that informed it as well as the actual content of the FDA guidance, are common in the published advocacy literature. Duffy and Epperson (2022) mistakenly claim that the FDA halved the dose for females 'after adverse reports consistently indicated higher next-morning sedation in females taking 10 mg.' Several papers inaccurately claim that observations of emergency room visits and car accidents led to sex-based dosing for zolpidem (e.g., McGregor, 2017). An *Advanced Drug Delivery Reviews* paper about sex differences in drug therapy erroneously claims that the FDA's sex-based dosing guidance occurred when, 'After decades of post-marketing drug surveillance, women were found to be more susceptible to next-day effects due to a slower rate of drug elimination, with emergency department visits from exclusively females with cognitive defects' (Madla et al., 2021). This assertion about emergency department visits references a paper (Bush, 2014) that does not provide any evidence of cognitive defects to support this claim. Similarly, many papers reference car accidents in the same sentence as the FDA dosing decision, sometimes implying that car crashes were the only impetus for the change. For example, Stephenson et al. (2019) write that, zolpidem 'was removed from the market after multiple women were involved in fatal motor vehicle accidents in the morning postadministration.' This statement also incorrectly implies that zolpidem was taken off the market, when in reality only the label recommendations were changed.

In this SABV advocacy literature published in scientific journals, three specific points are obscured: First, that body weight significantly obviates the sex disparity in zolpidem clearance rates. Second, that clearance rates of zolpidem do not predict sex disparities in adverse outcomes. Third, that the FDA's original recommendation was that men as well as women start zolpidem at the lower dosage. These three points have, subsequently, made zolpidem a flashpoint in debates over the rigor of sex-based biology, the need for policies such as SABV, and the priorities of women's health advocacy.

Contesting zolpidem, critiquing sex difference science

Today, zolpidem remains the sole drug with sex-based dosing on its label in the U.S., and with the exception of Canada, this dosing strategy has not been affirmed by other national drug agencies. For example, the European Medicines Agency did not revise zolpidem dosing for women, considering the data insufficient to show an interaction between sex and outcomes (Pharmacovigilance Risk Assessment Committee, 2014). Critics of SABV policies have used zolpidem to challenge predictions that studying sex differences in preclinical and clinical biomedical research will alleviate health disparities between men and women (Ciccia, 2021; Richardson et al., 2015; Shattuck-Heidorn & Richardson, 2019). In a 2015 perspective in *Proceedings of the National Academy of Sciences*, Richardson et al. (2015) invoked zolpidem to highlight how 'policies mandating the study of sex-related variables…are an impoverished approach' to addressing higher rates of adverse drug events among women, emphasizing that 'body weight eliminates the statistical significance of sex as a variable in clearance of zolpidem,' and arguing that any higher rates of adverse events among women must be analysed against the backdrop of higher rates of zolpidem use and greater polypharmacy among women compared to men. In a 2017 op-ed in the *Guardian*, Cordelia Fine and Rebecca Jordan-Young similarly

cited Ambien as a prime example of inaccurately attributing a disparity between men and women to biological sex rather than considering variables that correlate with sex, such as body weight (Fine & Jordan-Young, 2017). The feminist science writer Angela Saini concluded in her 2017 book *Inferior: How Science Got Women Wrong* that, 'If anything, zolpidem highlight[s] the pitfalls of including sex as a variable in medical research' (Saini, 2017).

In the biomedical literature, Greenblatt et al.'s (2019) paper 'Zolpidem and Gender: Are Women Really At Risk?' contested zolpidem as a hallmark example of the need for SABV policies, arguing that, 'Because body weight, not sex, is the independent biological variable, sex-based preclinical research protocols would likely not have predicted sex differences in rates of adverse events with zolpidem.' They further argue that underdosing women for sleep conditions brings greater public health risks, including the risk of driving while sleep-deprived (Greenblatt, 2014; Greenblatt et al., 2019; Shattuck-Heidorn & Richardson, 2019). Greil et al. (2022) in the *Journal of Human Psychopharmacology* describe the FDA recommendation as 'controversial' and observe that 'it is not clear whether sex should be considered when dosing zolpidem,' noting that physicians in Germany, Switzerland, and Australia generally do not follow the FDA's sex-based dosing guidelines. Similarly, when arguing for the limitations of binary sex categorization in biomedical research, Greaves and Ritz (2022, p. 8) highlight sex-based dosing for zolpidem as an example of 'mistreatment of individuals who do not conform to the group mean.'

Nevertheless, under the stadium lights of advocates at the NIH, in women's health, and in sex-based biology, zolpidem continues to be portrayed as a settled sex-difference fact, bolstered by a muddled narrative about the relationship between metabolic clearance, actual adverse events, and statistical significance after adjustment for weight. Zolpidem remains widely featured as a hallmark example of the importance of biological sex differences in the clinic and in biomedical research. In the 2020 popular science book *The Better Half: On the Genetic Superiority of Women*, Sharon Moalem narrates that while he had been trained not to discriminate between the sexes in dosing of Ambien, a 'safety review of Ambien' finally led the FDA in 2013 to recognize that 'women metabolize drugs like Ambien more slowly than men' (Moalem, 2020). Writing in 2020 about 'how male-centric medicine impacts women's health every day,' Alyson McGregor, director for the division of sex and gender in emergency medicine at Brown University, celebrated the FDA's 2013 decision as a breakthrough moment for sex-specific dosing: 'Nearly twenty years after [zolpidem's] release, and after thousands of reports from patients who experienced adverse effects, the Food and Drug Administration issued its first sex-specific prescribing guidelines' (McGregor, 2020). Most recently, a McKinsey market report highlighted the case of zolpidem as an example of sex-specific treatment in hailing women's health as the next frontier in health investment, replete with 'enormous opportunities for value creation' (Kemble et al., 2022).

The making of a hallmark sex-difference fact

Zolpidem bears comparison to the drug BiDil, a combination of heart medications approved in 2005 for use in African Americans. BiDil, the first race-specific drug

approved by the FDA, was touted as a sign of progress in pharmacogenomics and a stepping stone toward precision medicine. As Jonathan Kahn has made clear, however, the approval of BiDil for a specific racialized population was the result of an opportunistic strategy to secure approval and market monopoly using data that had already been rejected by the FDA as inadequate (Kahn, 2008, 2012). Though this process was initiated by the drug company rather than regulators and concerned efficacy rather than safety, in both cases, the strategy for FDA approval entailed carving up existing study data by demographic categories to salvage a drug approval from the wreckage of an earlier failure. Zolpidem, like BiDil, came to serve as a rhetorical lodestone that was supposed to point toward the future of health equity and precision medicine. BiDil's approval naturalized what we might call a 'race-difference fact,' contributing to the reification of race as a legible and clinically meaningful form of biological difference (Kahn, 2008).

As the first class of drugs with sex-specific dosing guidelines on the label itself, the case of zolpidem represents a critical moment within an ongoing set of social and scientific conversations about health justice, sex differences, and the inclusion of men, women, and gender-diverse people in biomedical research (Epstein, 2007; Pape, 2021). In the SABV discourse specifically, a vision of a future of distinct drugs and therapeutic regimes for men and women is presently being developed using the language of personalized and precision medicine (e.g., Jenkins & Miller, 2016). These conversations, while speculative, link sex-based dosing to a powerful vision of medical practice and marketing that tailors drugs and other products to groups and individuals with particular biomarkers (Denny & Collins, 2021). While the race-essentialist implications of this vision have been carefully probed in the case of BiDil, the case of how a contingent, contested, and constructed 'fact' about zolpidem metabolism became a hallmark example of sex differences in biomedicine at the highest-levels of research, policy, and regulation can help scholars and diverse stakeholders examine the promise and perils of a sex-based approach to health equity and precision medicine.

As historical, sociological, and philosophical analysis of sex-difference science has demonstrated, there are reasons to be concerned about sex difference claims that have come to be seen as settled science (e.g., Fausto-Sterling, 2012; Jordan-Young, 2010; Longino, 1990; Richardson, 2013; Sanz, 2017). Biological sex difference claims have historically been vital to the maintenance of essentialist conceptions of sex and gender roles in folk belief and in law and public policy. Gender and science scholars have grappled with the stickiness and persistence of sex-difference claims even in the face of vigorous empirical criticism and better-supported alternative frameworks. Jordan-Young and Karkazis (2019: 54) innovated the term 'zombie fact'—an unsubstantiated yet indestructible idea 'that seemingly can't be killed with new research or even new models that would make old research irrelevant or subject to new interpretations'—to describe a set of deeply-lodged ideas about the relationship between testosterone and male-stereotypical assumptions. Longino (1990) used unquestioned presuppositions in sex-difference science to illuminate the role that background assumptions play when scientists judge data as evidence for or against a hypothesis. Analysis of how zolpidem became a hallmark sex-difference fact contributes to this cross-disciplinary feminist STS literature on the formation, stabilization, and resistance to critique of sex difference claims in particular, as well as to the broader STS scholarship on facticity.

STS scholarship provides a number of frames for understanding how scientific claims become facts (Jasanoff, 1990; Knorr-Cetina, 1981; Shapin & Schaffer, 1985). Latour and Woolgar (1986, pp. 176, 86–87) classically defined scientific facts as statements that resist reference to 'the condition of their construction' and are stabilized through contentious processes of alignment and weathering. Within the ecology of laboratory science, fully established facts then become black-boxed, alienated and distanced from the conditions of their creation and embedded in reified form in the apparatus of ongoing knowledge production. Some aspects of this account, in particular the distancing of the 'fact' from its conditions of construction, fit the zolpidem sex-difference fact well.

Transcept submitted Intermezzo with a sex-specific dosing recommendation to bring closure to a contested and expensive drug approval process. The Intermezzo analysis, in turn, sparked the FDA's reanalysis of pharmacokinetic data for other formulations of zolpidem, which led to a blanket recommendation to halve the dose for women. Though lauded as a hallmark example of the need for consideration of biological sex differences at every level of biomedical research, the FDA's approach to sex-based dosing for this drug was not predicated on sex-difference biology. Instead, regulators relied on contextual judgments that drug clearance rates are relevant to next-day driving impairment, despite lack of direct evidence of a correlation between zolpidem blood levels and driving impairment, and that non-statistically-significant sex differences in drug clearance after adjustment for body weight can still be understood as potentially clinically significant sex differences. These assumptions were contested and even contradicted by evidence submitted as part of the drug approval process, and continue to be controversial in the biomedical literature on zolpidem pharmacology. Jasanoff (1990, p. 229) has argued that because regulatory science involves oversight and pressures from Congress, the courts, and the public, the line between good and bad science is constantly being redrawn as a means of negotiating the politics of risk assessment. She writes, 'Advisory committees, we know from experience, rarely restrict their deliberations to purely technical issues. In fact, the experts [of advisory committees] themselves seem at times painfully aware that what they are doing is not "science" in any ordinary sense, but a hybrid activity that combines elements of scientific evidence and reasoning with large doses of social and political judgment.' Likewise, the FDA's drug safety assessment did not result from the settling of factual disputes about the existence of a sex difference. Rather, it resulted from contingent and pragmatic considerations that led to a judgment about the right recommended dose for women.

Social, historical, scientific, policy, and media analysis of this singular example of sex-based drug dosing and its life within SABV advocacy discourse reveals the role of women's health advocates and sex difference scientists in elevating particular sex-difference claims within a twenty-first-century program that champions a particular notion of gender/sex health equity: one that relies on distinct, binary biological categories to render visible differences in health outcomes (Epstein, 2007; Pape, 2021). For many, the FDA's legally-binding determination foreclosed ongoing scientific debates about sex differences in zolpidem pharmacology and about the extent of sex differences in biomedicine more generally. But it was the subsequent framing of the zolpidem dosing guidance within women's health and SABV advocacy that transformed the FDA's sex-based dosing guidance into a hallmark sex-difference fact. Advocates used the media to amplify

this frame, and media hype in turn influenced advocates' framing of zolpidem sex-based dosing as a sex-difference fact. This process introduced distortions, distancing the claim that there are biological sex differences in response to the drug zolpidem from its original context and justification and shedding key qualifications that accompanied the FDA's determination, including the recommendation that most men should also start at a lower dose. The zolpidem sex-difference fact became not only settled science—to the point that it often no longer required citation in the scientific literature—but a hallmark fact on which larger research and advocacy agendas could rest (Chandak & Tatonetti, 2020; Cirillo et al., 2020; Khramtsova et al., 2019).

Sitting at the convergence of a landmark drug regulatory decision, widespread popular media coverage, national science policy, and pharmacological science, zolpidem is a richly informative site at which to understand the heterogenous structures upholding a successful sex-difference fact in elite twenty-first century biomedicine. This hallmark sex-difference fact was constructed, validated, and maintained by regulatory authority, dominant research paradigms, powerful folk conceptions of sex differences, and actors across biomedical science, public-facing media, and policy institutes. Zolpidem's approval, revised recommended dosing, and circulation in popular media coverage and SABV discourse illustrates how diverse processes beyond the laboratory can produce certainty and consensus about contingent and contested sex-difference claims.

Acknowledgements

We thank David J. Greenblatt, Jonathan Kahn, and Madeleine Pape for comments on an early version of this paper, and members of the Harvard GenderSci Lab for rich discussions that contributed to the development of this paper.

Funding

Support for this article was provided in part by the Robert Wood Johnson Foundation. The views expressed here do not necessarily reflect the views of the Foundation.

References

Bale, T. L., & Epperson, C. N. (2017). Sex as a biological variable: Who, what, when, why, and how. *Neuropsychopharmacology*, 42(2), 386–396. https://doi.org/10.1038/npp.2016.215

BioSpace. (2011, July 15). FDA issues Transcept Pharmaceuticals, Inc. with second CRL for sleep-aid drug Intermezzo. *BioSpace*. https://www.biospace.com/article/releases/fda-issues-transcept-pharmaceuticals-inc-with-second-crl-for-sleep-aid-drug-intermezzo-/

Bond, K. M., McCarthy, M. M., Rubin, J. B., & Swanson, K. R. (2021). Molecular omics resources should require sex annotation: A call for action. *Nature Methods*, 18(6), 585–588. https://doi.org/10.1038/s41592-021-01168-6

Booth, J. N., Behring, M., Cantor, R. S., Colantonio, L. D., Davidson, S., Donnelly, J. P., Johnson, E., Jordan, K., Singleton, C., Xie, F., & McGwin, G. (2016). Zolpidem use and motor vehicle collisions in older drivers. *Sleep Medicine*, 20, 98–102. https://doi.org/10.1016/j.sleep.2015.12.004

Bush, D. M. (2014). *The DAWN Report: Emergency department visits attributed to overmedication that involved the insomnia medication zolpidem* [The CBHSQ Report]. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration.

https://www.samhsa.gov/data/sites/default/files/DAWN-SR150-Zolpidem-2014/DAWN-SR150-Zolpidem-2014.pdf

Cahill, L. (2014). Equal ≠ the same: Sex differences in the Human Brain. *Cerebrum: the Dana Forum on Brain Science*, 2014, 5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4087190/

CBS News. (2014, 7 February). 60 Minutes: Drugs can affect men and women differently. https://www.cbsnews.com/news/drugs-can-affect-men-and-women-differently/

CDER. (2011a). *Clinical pharmacology and biopharmaceutics review(s)* (Application No. 22328). US Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022328Orig1s000ClinPharmR.pdf

CDER. (2011b). *Medical reviews* (Application No. 022328). US Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022328Orig1s000MedR.pdf

Chandak, P., & Tatonetti, N. P. (2020). Using machine learning to identify adverse drug effects posing increased risk to women. *Patterns*, 1(7), 100108. https://doi.org/10.1016/j.patter.2020.100108

Ciccia, L. (2021). Sexual dimorphism: Innate or acquired? A reinterpretation of biological differences. *Revista Bioética*, 29, 66–75. https://doi.org/10.1590/1983-80422021291447

Cirillo, D., Catuara-Solarz, S., Morey, C., Guney, E., Subirats, L., Mellino, S., Gigante, A., Valencia, A., Rementeria, M. J., Chadha, A. S., & Mavridis, N. (2020). Sex and gender differences and biases in artificial intelligence for biomedicine and healthcare. *npj Digital Medicine*, 3(1), 11. https://doi.org/10.1038/s41746-020-0288-5

Clark, D., & Stark, L. (2013, January 10). FDA: Cut ambien dosage for women. *ABC News*. https://abcnews.go.com/Health/fda-recommends-slashing-sleeping-pill-dosage-half-women/story?id=18182165

Clayton, J. A., & Collins, F. S. (2014). Policy: NIH to balance sex in cell and animal studies. *Nature*, 509(7500), 282–283. https://doi.org/10.1038/509282a

Denny, J. C., & Collins, F. S. (2021). Precision medicine in 2030—Seven ways to transform healthcare. *Cell*, 184(6), 1415–1419. https://doi.org/10.1016/j.cell.2021.01.015

Duffy, K. A., & Epperson, C. N. (2022). Evaluating the evidence for sex differences: A scoping review of human neuroimaging in psychopharmacology research. *Neuropsychopharmacology*, 47(2), 430–443. https://doi.org/10.1038/s41386-021-01162-8

Epstein, S. (2007). *Inclusion: The politics of difference in medical research*. University of Chicago Press.

Falkenberg, K. (2013, January 10). FDA takes action on Ambien; Concedes women at greater risk. *Forbes*. https://www.forbes.com/sites/kaifalkenberg/2013/01/10/fda-takes-action-on-ambien-concedes-women-at-greater-risk/?sh=26be0c9683e1

Farkas, R. H., Unger, E. F., & Temple, R. (2013). Zolpidem and Driving Impairment—Identifying Persons at Risk. *New England Journal of Medicine*, 369(8), 689–691. https://doi.org/10.1056/NEJMp1307972

Fausto-Sterling, A. (2012). *Sex/gender: Biology in a social world*. Routledge.

FDA. (2013). *Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist)* [Drug Safety Communications]. US Food and Drug Administration. https://www.fda.gov/files/drugs/published/Drug-Safety-Communication–Risk-of-next-morning-impairment-after-use-of-insomnia-drugs–FDA-requires-lower-recommended-doses-for-certain-drugs-containing-zolpidem-%28Ambien–Ambien-CR–Edluar–and-Zolpimist%29.pdf

Fine, C., & Jordan-Young, R. (2017, April 6). We've been labelled 'anti-sex difference' for demanding greater scientific rigour. *The Guardian*. https://www.theguardian.com/commentisfree/2017/apr/06/anti-sex-difference-scientific-rigour-gender-research-feminism

Greaves, L., & Ritz, S. A. (2022). Sex, gender and health: Mapping the landscape of research and Policy. *International Journal of Environmental Research and Public Health*, 19(5), 2563. https://doi.org/10.3390/ijerph19052563

Greenblatt, D. J. (2014). Sleep-promoting medications: Weighing the hazards of use versus non-use. *Clinical Pharmacology in Drug Development*, 3(3), 167–169. https://doi.org/10.1002/cpdd.127

Greenblatt, D. J., Harmatz, J. S., Moltke, L. L. V., Wright, C. E., Durol, A. L. B., Harrel-Joseph, L. M., & Shader, R. I. (2000). Comparative kinetics and response to the benzodiazepine agonists triazolam and zolpidem: Evaluation of sex-dependent differences. *Journal of Pharmacology and Experimental Therapeutics*, 293(2), 435–443.

Greenblatt, D. J., Harmatz, J. S., & Roth, T. (2019). Zolpidem and gender: Are women really at risk? *Journal of Clinical Psychopharmacology*, 39(3), 189–199. https://doi.org/10.1097/jcp.0000000000001026

Greenblatt, D. J., Harmatz, J. S., Roth, T., Singh, N. N., Moline, M. L., Harris, S. C., & Kapil, R. P. (2013). Comparison of pharmacokinetic profiles of zolpidem buffered sublingual tablet and zolpidem oral immediate-release tablet: Results from a single-center, single-dose, randomized, open-label crossover study in healthy adults. *Clinical Therapeutics*, 35(5), 604–611. https://doi.org/10.1016/j.clinthera.2013.03.007

Greenblatt, D. J., Harmatz, J. S., Singh, N. N., Steinberg, F., Roth, T., Moline, M. L., Harris, S. C., & Kapil, R. P. (2014). Gender differences in pharmacokinetics and pharmacodynamics of zolpidem following sublingual administration. *Journal of Clinical Pharmacology*, 54(3), 282–290. https://doi.org/10.1002/jcph.220

Greenblatt, D. J., & Roth, T. (2012). Zolpidem for insomnia. *Expert Opinion on Pharmacotherapy*, 13(6), 879–893. https://doi.org/10.1517/14656566.2012.667074

Greil, W., de Bardeci, M., Seifert, J., Bernegger, X., Cattapan, K., Stassen, H., Wagner, A. L., Sieberer, M., Grohmann, R., & Toto, S. (2022). Treatment of depression: Are psychotropic drugs appropriately dosed in women and in the elderly? Dosages of psychotropic drugs by sex and age in routine clinical practice. *Human Psychopharmacology*, 37(1), e2809. https://doi.org/10.1002/hup.2809

Guo, T., Mao, G., Zhao, L., Xia, D., & Yang, L. (2014). Comparative pharmacokinetics of zolpidem tartrate in five ethnic populations of China. *Acta Pharmaceutica Sinica. B*, 4(2), 146–150. https://doi.org/10.1016/j.apsb.2014.02.001

Gustavsen, I., Al-Sammurraie, M., Mørland, J., & Bramness, J. G. (2009). Impairment related to blood drug concentrations of zopiclone and zolpidem compared to alcohol in apprehended drivers. *Accident Analysis and Prevention*, 41(3), 462–466. https://doi.org/10.1016/j.aap.2009.01.011

Gustavsen, I., Bramness, J. G., Skurtveit, S., Engeland, A., Neutel, I., & Mørland, J. (2008). Road traffic accident risk related to prescriptions of the hypnotics zopiclone, zolpidem, flunitrazepam and nitrazepam. *Sleep Medicine*, 9, 818–822. https://doi.org/10.1016/j.sleep.2007.11.011

Heidari, S., Babor, T. F., De Castro, P., Tort, S., & Curno, M. (2016). Sex and gender equity in research: Rationale for the SAGER guidelines and recommended use. *Research Integrity and Peer Review*, 1, 2. https://doi.org/10.1186/s41073-016-0007-6

IOM. (2001). *Exploring the biological contributions to human health: Does sex matter?* T. M. Wizemann & M. L. Pardue (Eds.), National Academies Press. http://www.ncbi.nlm.nih.gov/books/NBK222288/

Jasanoff, S. (1990). *The fifth branch: Science advisers as policymakers*. Harvard University Press.

Jenkins, M. R., & Miller, V. M. (2016). 21st Century women's health: Refining with precision. *Mayo Clinic Proceedings*, 91(6), 695–700. https://doi.org/10.1016/j.mayocp.2016.03.017

Jordan-Young, R. (2010). *Brain storm: The flaws in the science of sex differences*. Harvard University Press.

Jordan-Young, R., & Karkazis, K. (2019). *Testosterone: An unauthorized biography*. Harvard University Press.

Kahn, J. (2008). Exploiting race in drug development: BiDil's interim model of pharmacogenomics. *Social Studies of Science*, 38(5), 737–758. https://doi.org/10.1177/0306312708091928

Kahn, J. (2012). *Race in a bottle: The story of BiDil and racialized medicine in a post-genomic age*. Columbia University Press.

Karp, N. A., & Reavey, N. (2019). Sex bias in preclinical research and an exploration of how to change the status quo. *British Journal of Pharmacology*, 176(21), 4107–4118. https://doi.org/10.1111/bph.14539

Katz, R. (2009, October 28). *Complete Response Letter, NDA #22328* [Letter to Transcept Pharmaceuticals, Inc.]. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022328Orig1s000OtherActionLtrs.pdf

Katz, R. (2011, November 23). *NDA Approval, NDA #22328* [Letter to Transcept Pharmaceuticals, Inc.]. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/022328s000ltr.pdf

Kemble, E., Pérez, L., Sartori, V., Tolub, G., & Zheng, A. (2022). *Unlocking opportunities in women's healthcare*. McKinsey & Company. https://www.mckinsey.com/industries/healthcare-systems-and-services/our-insights/unlocking-opportunities-in-womens-healthcare

Khramtsova, E. A., Davis, L. K., & Stranger, B. E. (2019). The role of sex in the genomics of human complex traits. *Nature Reviews Genetics*, 20(3), 173–190. https://doi.org/10.1038/s41576-018-0083-1

Kim, J. Y., Min, K., Paik, H. Y., & Lee, S. K. (2021). Sex omission and male bias are still widespread in cell experiments. *American Journal of Physiology-Cell Physiology*, 320(5), C742–C749. https://doi.org/10.1152/ajpcell.00358.2020

Klein, S. L., & Poland, G. A. (2013). Personalized vaccinology: One size and dose might not fit both sexes. *Vaccine*, 31(23), 2599–2600. https://doi.org/10.1016/j.vaccine.2013.02.070

Knorr-Cetina, K. D. (1981). *The manufacture of knowledge*. Pergamon Press.

Latour, B., & Woolgar, S. (1986). *Laboratory life: The construction of scientific facts*. Princeton University Press.

Longino, H. E. (1990). *Science as social knowledge: Values and objectivity in scientific inquiry*. Princeton University Press.

Madla, C. M., Gavins, F. K. H., Merchant, H. A., Orlu, M., Murdan, S., & Basit, A. W. (2021). Let's talk about sex: Differences in drug therapy in males and females. *Advanced Drug Delivery Reviews*, 175, 113804. https://doi.org/10.1016/j.addr.2021.05.014

Maron, J. L. (2020). Evaluating Therapeutics and interventions throughout the female life course. *Clinical Therapeutics*, 42(3), 379–380. https://doi.org/10.1016/j.clinthera.2020.02.008

Marts, S. A. (2002). Interdisciplinary research is key to understanding sex differences: Report from the Society for Women's Health Research Meeting on understanding the biology of sex differences. *Journal of Women's Health & Gender-Based Medicine*, 11(6), 501–509. https://doi.org/10.1089/152460902760277859

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

McGregor, A. J. (2017). The effects of sex and gender on pharmacologic toxicity: Implications for clinical therapy. *Clinical Therapeutics*, 39(1), 8–9. https://doi.org/10.1016/j.clinthera.2016.12.007

McGregor, A. J. (2020). *Sex matters: How male-centric medicine endangers women's health and what we can do about it*. Hachette Books.

Michaloski, C. B., & Katz, R. (2011, July 14). *Complete Response Letter, NDA #22328* [Letter to Transcept Pharmaceuticals, Inc]. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022328Orig1s000OtherActionLtrs.pdf

Moalem, S. (2020). *The better half: On the genetic superiority of women*. Farrar, Straus and Giroux.

Olubodun, J. O., Ochs, H. R., Von Moltke, L. L., Roubenoff, R., Hesse, L. M., Harmatz, J. S., Shader, R. I., & Greenblatt, D. J. (2003). Pharmacokinetic properties of zolpidem in elderly and young adults: Possible modulation by testosterone in men. *British Journal of Clinical Pharmacology*, 56(3), 297–304. https://doi.org/10.1046/j.0306-5251.2003.01852.x

Pape, M. (2021). Co-production, multiplied: Enactments of sex as a biological variable in US biomedicine. *Social Studies of Science*, 51(3), 339–363. https://doi.org/10.1177/0306312720985939

Partinen, M., Hirvonen, K., Hublin, C., Halavaara, M., & Hiltunen, H. (2003). Effects of after-midnight intake of zolpidem and temazepam on driving ability in women with non-organic insomnia. *Sleep Medicine*, 4(6), 553–561. https://doi.org/10.1016/j.sleep.2003.06.005

Pearse, R. V., & Young-Pearse, T. L. (2019). Lost in translational biology: Understanding sex differences to inform studies of diseases of the nervous system. *Brain Research*, 1722, 146352. https://doi.org/10.1016/j.brainres.2019.146352

Pharmacovigilance Risk Assessment Committee. (2014). *Assessment report: For Zolpidem-containing medicinal products*. European Medicines Agency. https://www.ema.europa.eu/en/documents/referral/zolpidem-article-31-referral-prac-assessment-report_en.pdf

Rabin, R. C. (2013). The drug-dose gender gap. *The New York Times*. https://well.blogs.nytimes.com/2013/01/28/the-drug-dose-gender-gap/

Richardson, S. S. (2013). *Sex itself: The search for male and female in the human genome*. The University of Chicago Press.

Richardson, S. S., Reiches, M., Shattuck-Heidorn, H., LaBonte, M. L., & Consoli, T. (2015). Opinion: Focus on preclinical sex differences will not address women's and men's health disparities. *Proceedings of the National Academy of Sciences of the United States of America*, 112(44), 13419–13420. https://doi.org/10.1073/pnas.1516958112

Roehrs, T. A., & Roth, T. (2016). Gender differences in the efficacy and safety of chronic nightly zolpidem. *Journal of Clinical Sleep Medicine*, 12(3), 319–325. https://doi.org/10.5664/jcsm.5574

Rosen, S. E. (n.d.). When the standard of care is treating women like little men [Katz Institute for Women's Health]. *Expert Insights*. https://www.northwell.edu/katz-institute-for-womens-health/articles/standard-of-care-treating-women-like-little-men

Saini, A. (2017). *Inferior: How science got women wrong-and the new research that's rewriting the story*. Beacon Press.

Salvà, P., & Costa, J. (1995). Clinical Pharmacokinetics and Pharmacodynamics of Zolpidem: Therapeutic Implications. *Clinical Pharmacokinetics*, 29(3), 142–153. https://doi.org/10.2165/00003088-199529030-00002

Sandberg, K., & Verbalis, J. G. (2013). Sex and the basic scientist: Is it time to embrace Title IX? *Biology of Sex Differences*, 4(1), 13. https://doi.org/10.1186/2042-6410-4-13

Sanz, V. (2017). No Way out of the binary: A Critical History of the scientific production of Sex. *Signs: Journal of Women in Culture and Society*, 43(1), 1–27. https://doi.org/10.1086/692517

Shapin, S., & Schaffer, S. (1985). *Leviathan and the air-pump: Hobbes, Boyle, and the experimental life*. Princeton University Press.

Shattuck-Heidorn, H., & Richardson, S. S. (2019, May 30). Focusing on differences between the sexes is leading medical researchers astray. *Washington Post*. https://www.washingtonpost.com/outlook/2019/05/30/focusing-differences-between-sexes-is-leading-medical-researchers-astray/

Stephenson, E. D., Farzal, Z., Kilpatrick, L. A., Senior, B. A., & Zanation, A. M. (2019). Sex bias in basic science and translational otolaryngology research. *The Laryngoscope*, 129(3), 613–618. https://doi.org/10.1002/lary.27498

Stephenson, E. D., Farzal, Z., Zanation, A. M., & Senior, B. A. (2018). Sex bias in rhinology research. *International Forum of Allergy & Rhinology*, 8(12), 1469–1475. https://doi.org/10.1002/alr.22179

Tavernise, S. (2013, January 10). Drug agency recommends lower doses of sleep aids for women. *The New York Times*. https://www.nytimes.com/2013/01/11/health/fda-requires-cuts-to-dosages-of-ambien-and-other-sleep-drugs.html

TED Radio Hour. (2017, February 10). *Paula Johnson: When does medicine leave women behind?* https://www.npr.org/2017/02/10/514153036/when-does-medicine-leave-women-behind

Vermeeren, A., Vuurman, E. F., Leufkens, T. R., Van Leeuwen, C. J., Van Oers, A. C., Laska, E., Rico, S., Steinberg, F., & Roth, T. (2014). Residual effects of low-dose sublingual zolpidem on highway driving performance the morning after middle-of-the-night use. *Sleep*, 37(3), 489–496. https://doi.org/10.5665/sleep.3482

Verster, J. C., Volkerts, E. R., Schreuder, A. H., Eijken, E. J., van Heuckelum, J. H., Veldhuijzen, D. S., Verbaten, M. N., Paty, I., Darwish, M., Danjou, P., & Patat, A. (2002). Residual effects of middle-of-the-night administration of zaleplon and zolpidem on driving ability, memory functions, and psychomotor performance. *Journal of Clinical Psychopharmacology*, 22(6), 576–583.

Weinstein. (2013, May 15). *Purdue puts Intermezzo DTC to bed*. MM+M - Medical Marketing and Media. https://www.mmm-online.com/home/channel/purdue-puts-intermezzo-dtc-to-bed/

Yoon, D. Y., Mansukhani, N. A., Stubbs, V. C., Helenowski, I. B., Woodruff, T. K., & Kibbe, M. R. (2014). Sex bias exists in basic science and translational surgical research. *Surgery*, 156(3), 508–516. https://doi.org/10.1016/j.surg.2014.07.001

Yoon, S., Jeong, S., Jung, E., Kim, K. S., Jeon, I., Lee, Y., Cho, J.-Y., Oh, W.-Y., & Chung, J.-Y. (2021). Effect of CYP3A4 metabolism on sex differences in the pharmacokinetics and pharmacodynamics of zolpidem. *Scientific Reports*, 11(1), 19150. https://doi.org/10.1038/s41598-021-98689-z

Zakiniaeiz, Y., Cosgrove, K. P., Potenza, M. N., & Mazure, C. M. (2016). Balance of the sexes: Addressing sex differences in preclinical research. *The Yale Journal of Biology and Medicine*, 89(2), 255–259.

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

Author biographies

Helen Zhao is a philosopher of science who works on values in science and medicine.

Marina DiMarco is a philosopher of science who works on feminism, biology, and medicine.

Kelsey Ichikawa is an STS researcher and the lab manager of the Harvard GenderSci Lab.

Marion Boulicault is a philosopher of science who takes a feminist approach to questions in the ethics of technology, philosophy of science, and bioethics, with a focus on measurement and quantification practices.

Meg Perret is a feminist scholar of science, technology, and the environment.

Kai Jillson is a graduate of the University of Southern Maine, with a degree in Human Biology, and is currently a prospective medical student studying sex bioessentialism in medicine.

Alexandra Fair is an historian of science studying the linguistic strategies Anglo-American eugenic theorists use to reconstitute eugenic ideology in modern academic and political spaces.

Kai DeJesus is an undergraduate researcher at Harvard University studying gender, sociology, and ethnic studies, with a focus on experiences of transness and dysphoria.

Sarah S. Richardson directs the Harvard GenderSci Lab and is a historian and philosopher of science who specializes in the sciences of sex, gender, sexuality, and reproduction.