

What your doctor should know about women

We respond to many drugs and treatments differently than men do—with potentially dangerous consequences. Here, the sex differences that matter most **BY LINDA MARSA**

FIVE MINUTES into a cesarean section, Angela DeLessio-Morrison woke up to searing pain. “There was this intense burning, like my abdomen was on fire, and I could feel myself being cut and worked on,” recalls the Huntington, New York, resident. But because she had been sedated with paralytic drugs to prevent her from squirming, she was unable to scream and alert the doctors that the anesthesia had worn off. “I heard talking in the room; I heard the instruments. It was like being strapped down and tortured,” she says. For decades after her 1987 trauma, DeLessio-Morrison was “consumed

with terror” that she’d wake up during another operation. “I was continually reliving in my mind this horrible experience that no one else could understand,” she recounts.

What happened to DeLessio-Morrison stems in part from her doctors’ not realizing that women often respond differently to anesthesia than men do. Studies say women wake up from anesthesia faster and are three times as likely to complain of being awake during surgery. “In recent years, we’ve become more aware of these variations, but we still need to do more to identify gender-related risk factors,” says Daniel J. Cole,

MD, an anesthesiologist at Ronald Reagan UCLA Medical Center and president-elect of the American Society of Anesthesiologists.

Anesthesia is just one of many examples in which gender differences affect the outcome of medical care. Your sex influences the course of potentially life-threatening ailments such as heart disease and sleep apnea. Biological variation can also lead to dangerous reactions to drugs. While there have been moves in the right directions in research, gender differences are understudied, and even when they’re known, information does not necessarily make it to the average doctor’s office. “The scary

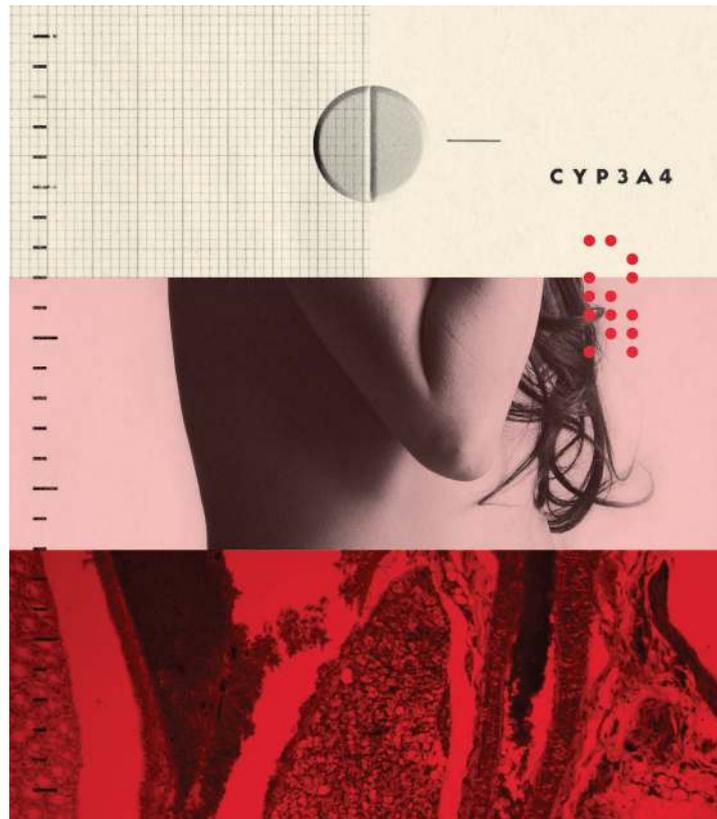
truth is there is no way for us to know how many women are going undiagnosed or not treated appropriately because of our lack of knowledge,” says Janine Austin Clayton, MD, associate director for research on women’s health at the NIH.

THE MISSING DATA ON WOMEN

SINCE 1993 the National Institutes of Health Revitalization Act has required that women be included in NIH-funded clinical research; as a result, today about half of participants in these studies are female. The FDA has also investigated differences in how medical devices function in the two sexes. But the effects of gender often have not been tested in the earliest stages of research, when the work is done with animals and human cells. Scientists have avoided using female animals because they worried—unnecessarily, it turns out—that hormonal fluctuations and reproductive cycles would skew results. With human cells, the problem is that researchers were not aware that their sex matters; they have been studying cells largely without knowing whether they came from a male or female source.

“The overreliance on male animals and unidentified cells in preclinical research obscures key sex differences that could guide clinical studies,” says Clayton. For instance, research using female rodents has suggested that estrogen could play a role in protecting women against multiple sclerosis.

Last year, to remedy this research “blind spot,” as Clayton calls it, the NIH began developing rules requiring grant applicants to take animals’ sex into account in their applications. To put more muscle behind the rules, the NIH has requested that medical journals not publish the results of studies that don’t have this mix. The agency dispensed \$10.1 million to more than 80 scientists to underwrite exploring the effects of gender in studies with laboratory animals, cells and human subjects. “This scientific



effort by the NIH is a long-term investment that may pay off in new discoveries,” says Susan Wood, PhD, director of the Jacobs Institute of Women’s Health at George Washington University.

That could change the future of research. But right now there are many drugs and treatments on the market that have never been tested on women. “That’s why we need research and specialized training for doctors: to help them know what to do—and what to look for—when a woman is sitting in the exam room,” Clayton says.

WHY DRUGS AFFECT YOU MORE

UNTIL 1993, women of childbearing age were routinely excluded from trials of new drugs because researchers feared the chemicals might harm fetuses. With so many drugs tested almost exclusively on men, their effects on women didn’t become evident until after they were approved. But women experience a disproportionate share of adverse side effects, and many of these reactions are severe.

Eight of the 10 drugs pulled from the market from 1997 to 2000 were more dangerous for women, according to a Government Accountability Office study. These included the once-popular diet-drug combo fen-phen, which was taken primarily by females, as well as pills used equally by the genders, like Posicor, a hypertension treatment that slowed down or stopped the heart in some women, and the diabetes drug Rezulin, which caused liver damage in some women.

In 2013, for the first time, the FDA issued a sex-specific guideline for a drug. For women, the agency halved the recommended dose of the sleep aid Ambien, which was approved before gender equality in testing went into effect, and of other drugs that contain the active ingredient zolpidem. The reason: Women metabolize the drug more slowly, which means it lingers in their systems longer, putting them at

risk for overdoses and next-day drowsiness (a concern for drivers). According to a recent government report, from 2009 to 2011 women accounted for 68 percent of emergency room visits due to overdoses of Ambien and other drugs that contain zolpidem.

It’s not just zolpidem. Women process a big group of meds, including anesthetics, differently, and sometimes those discrepancies lead to dangerous consequences. With anesthetics, the disparities occur not only because women are smaller, which often means they need to be given lower doses to produce the right results, but also because women’s body chemistry is distinct from men’s. Numerous studies indicate that the liver enzyme CYP3A4, which is responsible for metabolizing more than half of all prescription drugs, is more active in women. Muscle-to-fat ratio is a factor as well: Some meds, such as tranquilizers known as benzodiazepines (for instance, Valium and Xanax), are attracted to fatty tissue, which is typically more abundant in a woman than a man, so these types of drugs stay in women’s bodies longer. Reproductive hormones also affect the metabolic processes that break down drugs.

Those physiological differences can create surprising—and at times significant—variations in the way men and women react to drugs. For instance, one small study suggests that the newer and widely used SSRI antidepressants may be more effective in women, while men tend to do better with an older class of depression medication known as tricyclics. Scientists suspect these different effects are caused by gender-related variations in some liver enzymes.

Some drugs place women at significantly higher risk of developing an uncommon condition called torsade de pointes—a potentially

part of the reason is that their symptoms are often different from men's.

The problem is that heart disease plays out differently for men and women, notes Rita Redberg, MD, director of Women's Cardiovascular Services at the University of California, San Francisco. About 90 percent of heart attacks in men are triggered by fatty plaque buildup, which obstructs blood vessels. Seventy percent of women also suffer from plugged-up arteries, but in the remaining 30 percent, their plaque is spread more evenly on blood vessel walls, which prevents the smaller arteries from dilating appropri-



The hormonal profiles of women with high blood pressure **are not the same as those of men.** This implies that some drugs may work better for men than for women.



fatal irregular heartbeat. For this reason, two possible troublemakers, the antihistamine Seldane and a heartburn pill called Propulsid, were removed from the market. Many medications that increase the odds of developing torsade are still being sold, including the heart drugs Cardioquin, Corvert and Norpace; some antidepressants (for instance, Zoloft and Prozac); some antipsychotic drugs (such as Haldol, Thorazine and lithium); and common antibiotics like erythromycin, when administered intravenously.

YOUR HEART IS DIFFERENT FROM HIS

THE American Heart Association's decade-long Go Red for Women campaign has greatly increased awareness of gender differences in heart disease. "The latest statistics show that female mortality is finally starting to decline," says Noel Bairey Merz, MD, director of the Barbra Streisand Women's Heart Center at Cedars-Sinai Medical Center in Los Angeles. But women still have lower rates of recovery and survival, and studies suggest

ately. That deprives heart muscle of oxygen, causing tightness, pressure or a burning sensation in the chest. Yet most medical therapies, such as statins and clot-busting drugs, are directed against the obstructive coronary disease that's typical in men.

In addition, more women than men receive misleading test results for heart disease. An angiogram is considered the gold standard for detecting blockages in coronary arteries. But that test may miss important problems in the small arteries in women, who are more likely to have dysfunction that does not show up clearly on an angiogram. Even standardized treadmill stress tests may not be as accurate in women because of their lower rates of larger artery blockages and higher rates of smaller blood vessel problems.

YOUR SNORING MAY BE MORE DANGEROUS

SLEEP APNEA is a serious disorder that occurs when a person's breathing is interrupted repeatedly during sleep, sometimes hundreds of times a night, and

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SHOULD YOU TAKE STATINS?

IN LATE 2013, the American Heart Association presented new heart-disease-prevention guidelines based largely on calculations of risk rather than cholesterol count, a change that should greatly increase statin use among healthy people. If the guidelines were fully implemented, the drugs would be taken by an estimated 22 percent of symptomless women between the ages of 40 and 75.

Statins are not risk-free: The drugs' known side effects include muscle pain, memory problems and increased risk of diabetes. While no one questions the use of statins in people who show signs of heart disease or who have extremely high cholesterol, many experts wonder if healthy women really need to be medicated. Doubters say that since comparatively few women were involved in clinical tests of statins, data on benefits for them are sketchy at best.

What's more, statins work mainly by ratcheting down levels of LDL (the "bad" cholesterol), which is not as big a heart risk for women as for men. High levels of triglycerides (a kind of blood fat) and low levels of HDL (the "good" cholesterol) present much more potent dangers for females, says Barbara Roberts, MD, a cardiologist at the Alpert Medical School of Brown University. Low HDL can be controlled by increasing your intake of monounsaturated fats such as olive oil. "If a woman does not have established heart disease or familial high cholesterol—which is inherited—then there is no evidence taking a statin will lower her risk of having a heart attack or dying of heart disease," says Roberts. "None."

SECOND SEX...

CONTINUED FROM PAGE 65 self-pity well into college. But, you know, eventually . . .”

She trails off. *Eventually*. In writing my latest novel, I got to explore where anger goes sometimes and where it should go. In men I see the horrific results when it explodes out into the world, but more often I see the anger tamed, over time, into ambition and competition, two forces that usually get them ahead. In women it's more complicated. We look at women who've channeled that energy similarly, who seem overly competitive or ambitious, and decide that somewhere there must be something wrong. Are they bad mothers? Bad wives? So girls' anger too often goes elsewhere. In the case of my heroine, it leads to violent rebellion, but most women don't end up pillaging boats. Where does the anger go? I ask my sister.

“As it turns out,” she says wryly, “sitting in a place of anger, or resentment, or self-pity, just isn't effective. It can feel really good for a while, like trying on an old sweater. Cozy and familiar, but then all of a sudden you're like, Eww, this sweater smells bad—*get it off me!*”

We laugh together, as always. The bartender is used to us. We tip big because we've been loud and because, you know, we're nice. The answer to “Why should I be nice?” is that the world could stand more kindness and less anger. I'm glad my sister raises money and a family, as opposed to, say, terrorizing the high seas. Still, as I watch her leave to pick up her kids—the sitter is picking up mine—I wonder if asking women to be nicer is just another obstacle, something we should break before it breaks us.

A few days later, she emails me: “Three women I know are applying for this job I told them about. All three are asking lots of read-as-insecure questions (‘But do you think I'd be good at this?’). Meanwhile, this one guy I know who is applying just said, ‘Hell yeah, thanks so much, sending in my application right now.’ Very frustrating gender observation.”

“Does it make you angry?” I write back, reminding her of our conversation at the bar.

“Shut up,” she replies, and that might be the solution right there. ☺

DANIEL HANDLER's latest novel, *We Are Pirates*, is being released this month.

WHAT YOUR DOCTOR SHOULD KNOW

CONTINUED FROM PAGE 127 is usually accompanied by loud snoring. The disruption of breathing reduces the flow of oxygen to the body and brain, causing a cumulative deficit that can contribute to heart disease and brain damage—an effect that is possibly more severe in women than in men.

But sleep apnea is often missed in women, partly because the stereotypical patient is an overweight, middle-aged man. (The truth is that after menopause, females are as likely to suffer from this condition as males.) Another confounding factor is that women often have different symptoms than men. Instead of complaining about excessive daytime sleepiness, women more often report that they feel tired and down.

Too often physicians attribute women's sleeplessness to depression and prescribe pills to banish the blues rather than try to get at the root cause of their wakefulness, says Monica Mallampalli, PhD, director of scientific programs at the Society for Women's Health Research.

Yet even when women do sleep apnea tests at home, the diagnostic tools can fail to detect the real problems because often they aren't calibrated for females. “Women tend to have less of a drop in oxygen levels than men. That's because women are more likely to have episodes in which the airways narrow rather than collapse completely, as happens with men,” says Nancy Collop, MD, director of the Emory Sleep Center in Atlanta.

HYPERTENSION HARMS YOU MORE

MANY doctors are not aware that the latest research suggests that hypertension appears to do more damage to women than to men. For instance, in a recent study of men and women over age 53 with untreated high blood pressure, the women's blood vessels were 30 to 40 percent more diseased than those of men with a comparable level of hypertension. The women's arteries were stiffer and more inflamed, conditions that boost the risks of heart disease and stroke. Researchers led by Carlos Ferrario, MD, a cardiologist at Wake Forest Baptist Medical Center, also found “significant differences” in the biological mechanisms that cause hypertension in the sexes: The hormonal

profiles of women with high blood pressure are not the same as those of men. This implies that some drugs may work better for men than for women.

Despite these findings, “the general belief among clinicians is that therapeutic approaches for high blood pressure should be gender blind,” says Ferrario. However, he argues, “the drugs we use and the dosages shouldn’t be equivalent in men and women.” Treatment guidelines, Ferrario says, should be modified: Women may need to be treated earlier and more aggressively than men.

SPECIAL CONCERNS FOR DIABETICS

IT IS NOT common practice for doctors to emphasize heart disease prevention when they treat women with diabetes, but it should be. For instance, a 2013 study found that among women under 60, having type 2 diabetes raises the odds they will develop coronary artery disease fourfold, a figure much higher than previously believed, reports lead author Rita R. Kalyani, MD, an endocrinologist at Johns Hopkins University School of Medicine. For men in that age group, however, the study finds that the presence of type 2 diabetes has little or no effect on heart disease risk, probably because men already have high odds of developing that disease. (Type 1 diabetes also increases the danger of heart trouble in women.)

“When women get diabetes, the heart-protective effects of estrogen go away. That means younger women with diabetes have the same heart disease risks as men or postmenopausal women,” says Betul Hatipoglu, MD, an endocrinologist at the Cleveland Clinic. And among people with diabetes, the prognosis for heart disease is significantly worse for women than for men; women are more disabled by it, and they have lower survival rates when they’re hit by a heart attack.

“Our research suggests doctors need to work harder to prevent heart disease in women under 60 with diabetes,” says Kalyani. “Doctors need to understand the crucial importance of heart disease prevention for women of any age if they have diabetes.” ©

LINDA MARSA’s most recent book is *Fevered: Why a Hotter Planet Will Hurt Our Health and How We Can Save Ourselves*. @lindamarsa

WHAT YOU CAN DO TO PROTECT YOURSELF

— The next time you receive a prescription, “find out what the drug’s effects are supposed to be so you can be on the lookout for effects that are not intended,” says the NIH’s Janine Austin Clayton, MD.

— “If you’re being treated for heart disease but continue to have symptoms, find a physician at a women’s heart center to work with,” suggests L.A. heart specialist Noel Bairey Merz, MD. “If there isn’t one available in your area, then get a second opinion, preferably at a medical-school-affiliated facility.”

— If you consistently wake up feeling tired, consider getting tested for sleep apnea. To boost the odds that the most advanced equipment will be used, go to a sleep lab that’s accredited by the American Academy of Sleep Medicine, suggests Nancy Collop, MD, director of the Emory Sleep Center in Atlanta.

— The conventional wisdom is that people under 60 should strive for blood pressure levels below 140/90. If your numbers are above this mark, take the situation seriously—even if your doctor doesn’t—and try to improve your blood pressure by making lifestyle changes, suggests Carlos Ferrario, MD, a cardiologist at Wake Forest Baptist Medical Center.

— If you have diabetes, talk with your physician about extra steps you should take—such as exercising more—to control your heart disease risk factors. “That’s a conversation that needs to occur now,” says Rita R. Kalyani, MD, an endocrinologist at Johns Hopkins.