



bodywise



On top of suffering more migraines, fibromyalgia, and a host of other ache-inducing ailments, women feel pain more acutely than men. **CATHLEEN MEDWICK** reports on a cutting-edge science that could improve your chances of getting relief.

Women, Men, and **Ouch!** the Painful Truth

I WONDER, NOW, WHY I NEVER asked the question: Does it hurt? My mother was dying of breast cancer, but she didn't talk about her pain. At least not to me. Shortly after her funeral, though, one of her supposed friends remarked (with a good deal of scorn) that Mom had driven her crazy with nonstop complaining.

Oh, really? Can't complain, even when you feel like the pain is killing you?

It took me years (okay, decades) to stop fuming over that spectacularly insensitive remark. I asked myself, *What if my mother had* [CONTINUED ON PAGE 168]



[CONTINUED FROM PAGE 166] *been a man?* Would her friend have sympathized? Men have long been thought (and expected) to be more stoic. But are they really better at handling pain? Or are men and women wired to feel it differently?

The scientific consensus on that last question is yes, thanks in large part to Jeffrey Mogil, PhD, director of the pain genetics laboratory at McGill University in Montreal. His work on pain is leading to new treatments targeted to a patient's genetic makeup, the holy grail of a hot new field called pharmacogenetics.

■ MOGIL FIRST TURNED HEADS in the scientific community in 2003 when he identified a gene that influences receptivity to painkillers—but only in women. His team of researchers found that redheaded, fair-skinned women, in particular, who have a variant of that gene (melanocortin-1, which happens also to be a determinant of hair color) got much more relief from a class of painkillers that includes Talwin and Stadol than other women, while the drugs had only a modest effect on all the men. “I think ultimately we’re going to find that there are

simply different neural circuits for men and women,” Mogil says. “The implications of that are pretty amazing, right? Because it suggests that if you develop a drug based on a protein in the male pathway, that drug will only kill pain in men and not women. And if you develop a drug that’s based on the protein in the female pathway, that drug would only kill pain in women and not men.

So you would have pink and blue pills for pain. Imagine the marketing campaign!”

Mogil lights up as he tells me this. We are walking through his comfortably low-tech laboratory at McGill—not much in the way of fancy scopes or imaging equipment—manned by a smattering of lab technicians and earnest graduate students. Mogil is a disarmingly cheerful man, something of a surprise considering that he spends his days thinking about pain. He proudly points to a crayon portrait of him at work by his son, then 6, and to the coffeemaker he scored for the lab’s “conference-slash-lunchroom.” Then he opens another door, puts a finger to his lips, and shows me his

research subjects, cages full of contented-looking mice. I am reassured to learn that most of the testing brings them only to the threshold where they begin to sense pain, not beyond. He takes my palm and prods it gently with a thin wire on a tool called a von Frey filament, then with another, sharper wire, until I pull my hand away. Once the mouse flinches and begins

to lick its paw (more urgent licking equals more pain), the testing is over. The lab technician notes the response on a computer grid and returns the mouse to its cage.

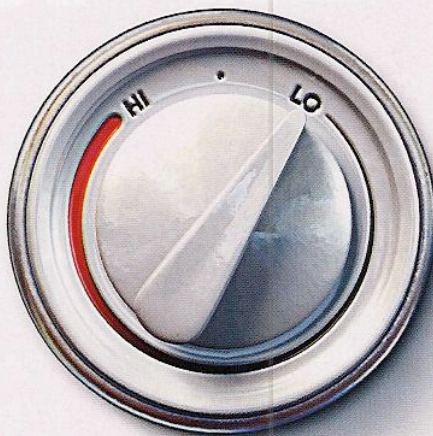
This is, I learn, an equal-opportunity laboratory for male and female rodents: a

testament to Mogil’s conviction that pain must be studied in women as well as men. By working with both sexes in his laboratory, he has bucked a tradition in medical research based on a false assumption that females show too much variability in their responses due to hormonal cycling. The focus on males seems ridiculous to him, because the vast majority of clinical pain patients are women. “Women are more sensitive [CONTINUED ON PAGE 170]

Men and women may have different neural circuits for pain.

WHILE RESEARCHERS POKE around genes and molecular pathways to find the next great painkiller, what you may want to know right now is which drug to take for a pounding headache—or for cramps, a back spasm, sore joints. There can be vast differences in how individuals respond to a medication, says Scott Fishman, MD, chief of the division of pain medicine at the University of California, Davis, so relief may require trial and error. Still, a few guidelines will help you feel better faster:

1 | HEADACHE
Occasional: For a garden-variety tension headache, first try acetaminophen (Tylenol), says Russell Portenoy, MD, chair of the department of pain medicine and palliative care at Beth Israel Medical Center in New York City. “It’s the safest of all the over-the-counter pain relievers at recommended dosages,” he



Pain Relief: Best Treatments for 4 Common Miseries

says. If your headache doesn't disappear, choose a nonsteroidal anti-inflammatory drug (NSAID) like ibuprofen (Advil) or naproxen sodium (Aleve), Fishman suggests. Aspirin also works, but because it has a slightly higher risk for gastrointestinal bleeding, most doctors don't recommend it for more than a few days in a row, says Portenoy (see “Everyday Drugs, Worrisome Side Effects,” page 148). Aspirin for heart disease prevention is taken at a lower dose.

You need something stronger: If the pain persists, talk to your doctor about a prescription-strength NSAID (Voltaren, Anaprox, Celebrex). For severe headaches, you may be prescribed drugs that contain butalbital (a barbiturate), caffeine, and either aspirin (Fiorinal) or acetaminophen (Fioricet). Migraine sufferers are often helped by triptans (like

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[CONTINUED FROM PAGE 168] to pain than men," he says. "They have a higher ability to discriminate among different levels of pain." Some syndromes, including migraine and fibromyalgia, "have very, very skewed ratios, up to nine to one in favor of women." It's true, says Mogil, that women are more likely than men to seek medical attention for pain, to report it as worse, and to be less self-consciously stoic. But, he says, "you get the same differences in animals"—female mice seem to have a somewhat lower pain threshold than their male counterparts. Plus, he adds, research on human newborns shows that girls grimace more in response to a heel lance (a poke with a sharp tool) than male babies do. "I'm certainly not saying that there are no sociocultural explanations for these sex differences. All I'm saying is that males and females seem to be set up differently from the start, in their pure, core biology."

After some initial resistance, the scientific community has come around to Mogil's way of thinking. It has recently been shown that estrogen influences pain sensitivity; male experimental animals

injected with the hormone seem to have a lower pain threshold than before, whereas an injection of testosterone seems to raise the threshold in female animals. In fact, estrogen may act as a switch, turning on the ability to recognize pain.

■ GIVEN SUCH GROUNDBREAKING discoveries, you'd think doctors would happily prescribe the most powerful painkillers to women—but they don't. Women were twice as likely as men to be undertreated for pain, in a study of 550 AIDS patients at Memorial Sloan Kettering Cancer Center and other major facilities in New York City. In all fairness, doctors do worry about side effects and dependency, so they're reluctant to give women strong but potentially addictive drugs like opioids (morphine, OxyContin), especially because the government has been cracking down on physicians who overprescribe them. And even though scans can display the brain's response to pain—sometimes in living color—the sensory

experience remains subjective. At this point, having a patient rate her pain on a scale of one to ten is the most reliable tool a doctor has to knowing how she feels physically: "The only real way to get at how much pain a person is in," Mogil says, "is to ask them, and trust them." Still, in his opinion, "the danger of not believing people is much greater than the danger of overprescribing opioids. The big challenge we have is educating medical doctors. Politicians are even harder, but medical doctors are also thick as bricks."

An especially thorny problem for researchers like Mogil is the relief of chronic pain, which the medical profession long dismissed as the collateral damage of disease. "Chronic neuropathic pain [the kind that results from nerve damage from an injury, for example] can last five years, ten years, for the rest of your life," Mogil says. "It's really horrible for a lot of people." The good news is that chronic pain has finally come to be considered a disease in its [CONTINUED ON PAGE 173]

"I'm optimistic that the problem of pain is on its way to being solved."

Pain Relief: Best Treatments (continued)

Imitrex or Zomig). If the headache becomes chronic, your best bet is to work with a doctor or pain specialist to find the right drug cocktail (this is true with any kind of ongoing pain; go to painmed.org/patient to find a specialist). Drug options include short-acting opioids (Percocet, Vicodin), antidepressants such as Effexor or Cymbalta, which double as analgesics, and antiseizure medications like gabapentin (Neurontin) or pregabalin (Lyrica), recently approved as the first drug to treat fibromyalgia.

2 MENSTRUAL CRAMPS
Regular monthly discomfort: Take an over-the-counter NSAID. "Studies have shown that these are more effective than acetaminophen in reducing this kind of pain," says Portenoy.

You need something stronger: Your doctor may suggest a prescription-strength NSAID. Another option is suppressing your cycle with birth control pills, or—if the pain is bad enough—a short-acting opioid.

3 BACK PAIN
Flare-up: For the random spasm or ache, grab some Tylenol. "Most acute back pain is not inflammatory, so for many people, taking an analgesic like acetaminophen may be all they need," says Portenoy. When this doesn't work, then try an NSAID. **You need something stronger:** When you're in agony, or the discomfort doesn't relent in several days, ask your doctor about a combination drug such as Tylenol with codeine, a prescription NSAID, or a short-acting opioid. Drugs for chronic back pain include

antidepressants, antiepileptics, muscle relaxants such as cyclobenzaprine (Flexeril), and long-acting opioids like OxyContin.

4 JOINT PAIN
Once in a while: For the occasional achy hip or shoulder, either acetaminophen or an NSAID (which may help more if there's inflammation) should do the trick, says Fishman. **You need something stronger:** Treatments include prescription-level NSAIDs, muscle relaxants, short-acting opioids, and corticosteroid shots. Chronic pain patients may also be prescribed the new fibromyalgia drug Lyrica, as well as certain antidepressants.

■ **BEYOND DRUGS**
In addition to medication, a number of complementary treatments—including acupuncture, guided

imagery, cognitive and physical therapy, massage, and hydrotherapy—can help ease pain. Mindfulness meditation in particular has proven to be incredibly effective, says Jon Kabat-Zinn, PhD, author of *Full Catastrophe Living: Using the Wisdom of Your Body and Mind to Face Stress, Pain, and Illness*. Begin by simply focusing on your breath. Pay attention to every inhalation and exhalation through your nostrils. Picture the breath circulating all around your body, then imagine breathing specifically through the area where the pain is located. If you have a headache, for example, visualize the breath going through a hole at the top of your head; for menstrual cramps, it would flow through your pelvis. Do this for five to 20 minutes, and you should begin to notice the pressure diminish. —Naomi Barr

[CONTINUED FROM PAGE 170] own right. "People used to think, *Get rid of the disease and you'll get rid of the pain*," Mogil says. But that approach was utterly wrong-headed. "Pain is there to enable us to learn our physical limitations — to keep us from walking on a broken leg, or to teach a toddler not to keep jumping off a bunk bed. What's the reason to have pain in your arm five years after that gunshot wound? There's no injury anymore, right? Chronic pain has no use, and things that have no use and yet cause difficulties are diseases."

FOR MOGIL, THE BEST HOPE LIES in genetic research. "We know of a lot more molecules, a lot more genes and proteins that are involved in pain than we did ten years ago," he says. That means there are more targets to aim new drugs at. "The analogy I like to use is, drug development is still a crapshoot. You're throwing balls against the wall and hoping they stick. But the more balls you have to throw, the higher the probability that a few of them are going to stick. I'm optimistic that the problem of pain is on its way to being solved."

Mogil never tires of throwing balls of his own, exploring social and environmental factors in pain. It's already clear that emotions can make a difference; fearing that something is going to hurt, for example, increases the pain, while positive expectations lessen it. And subjects tend to rate their pain lower when they're distracted than when they're focusing on how much it aches or stings.

In the summer of 2006, Mogil created a new sensation with his finding that empathy amps up pain sensitivity in mice, whose genetic makeup is similar to that of humans. "It's well known to experts who study pain in people that social factors, such as how the spouse reacts to the patient's complaints, are huge in explaining how well chronic pain patients do," says Mogil. "If the spouse is solicitous and says, 'Oh, Harry, let me go get you some water, you poor baby,' this makes Harry's chronic pain worse. And if the spouse says, 'Oh, come on, Harry, suck it up,' it makes Harry's pain better." What Mogil discovered by watching mice was

that seeing another creature in distress can actually be painful: A mouse in mild discomfort (the equivalent of a slight stomachache, which researchers induce in the laboratory) will feel worse if it sees another mouse suffering — though, interestingly, only if they have shared a cage (a stranger's distress has no such effect). Mogil is now trying to isolate genes and proteins that define the neural circuit responsible for empathy.

With minds like Mogil's at work on pain relief, breakthroughs are bound to happen — provided that researchers get the support they need. "We've got all this knowledge," he says, "but so far not much has translated over to the bedside." He hopes that increased awareness of the problem will attract more research dollars: an uphill battle, since in recent years federal funding has been on a downslide, according to the NIH, leaving private donors to pick up the slack. "Other diseases have people doing bike-a-thons and having bake sales," he says. "Pain has nothing like that."

He tells me about an elderly woman who hasn't left her house in three years because she can't bear to put on clothes. "She has what's known as mechanical allodynia, where the slightest touch is perceived as excruciating pain. So she walks around naked in her house and can't leave. This doesn't deserve a bike-a-thon?"

It could happen. A number of highly energized organizations are mobilizing patients to fight for recognition of pain as a national health priority, and advocating for those who, like my mother, are desperate for support. Meanwhile, Mogil keeps throwing balls against the wall, using his expertise and intuition to fathom the intricate mechanisms of the human brain, and how they work to process pain. "We have this disadvantage in trying to study the most complicated thing in the universe," he says. "It's like asking a carburetor to understand itself. We're trying to understand the brain, and the only tool we have is a brain." That, and the heart to stick with this urgently needed research, which might one day open the door to a pain-free life. **U**

Fearing that something's going to hurt increases the pain, while positive expectations lessen it.

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