



## Sex differences in pain

*They're real — but stem from a complex interplay of factors*

BY GARY B. ROLLMAN, PHD

As an experimental psychologist whose research emphasizes individual differences in pain reactivity, I'm often asked about whether men and women respond differently to pain. Many people assume that women are the more stoic sex, saying things like, "If men had children, there would only be one-child families."

In fact, however, both clinical and laboratory studies find that women are more sensitive to pain than men, on average. But there's no simple explanation for this difference.

### Sex matters

Our reactions to pain are determined by a plethora of variables, explained by the *biopsychosocial* model as the interaction of biologic, psychologic and social influences on behaviour. Studying sex differences in pain is part of a renewed appreciation that sex matters in many medical conditions. Clinicians and scientists now recognize that both biologic and social factors influence the manifestation, presentation and management of disease. New societies, journals and medical curricula are trying to improve the quality of medical treatment for both women and men.

Extensive reviews have concluded that women are more likely than men to experience a variety of pain-

ful conditions, including fibromyalgia, temporomandibular pain, rheumatoid arthritis, low back pain, migraine and chronic tension headache, abdominal pain, reflex sympathetic dystrophy (complex regional pain syndrome), irritable bowel syndrome, and numerous other disorders. On the other hand, men have a higher prevalence of cluster headache, duodenal ulcer, and post-herpetic neuralgia, among others.

Clearly, biologic factors can account for some of these differences. Women have a more complex genitourinary system than men, much greater hormonal variation (both short- and long-term), smaller body size, and lower bone mass and muscle strength. Recent research indicates that central nervous system (CNS) differences are likely important to sex differences in pain responses. Sex steroids affect CNS development and function, and stress activates the hypothalamic-pituitary-adrenal (HPA) axis differently in males and females. Also, estrogen plasma levels are associated with recurrent pain, whereas andro-

gens, perhaps by interacting with the immune system, are analgesic.

### Opioid responses

Numerous studies have shown that mu opioids have superior pain-relieving properties in male animals (with some debate still about humans) and that testosterone can augment opioid potency. In contrast, predominantly kappa opioid agonists, such as pentazocine, nalbuphine, and butorphanol, produce significantly greater analgesia in women and female lower animals. Ongoing work should clarify sex-specific differences in opioid pharmacology and how they affect genetic influences. It may also lead to new, separate classes of analgesics for men and women.

Imaging studies suggest that the CNS processes noxious signals differently in men and women. Laser stimulation of the back of the hand caused a larger response in the sensory intensity and attentional cortical regions in males. Females showed more activation of the area that integrates emotion, memory

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and response selection to noxious stimulation. Functional magnetic resonance imaging (fMRI) has revealed that, even when stimuli are matched for subjective pain level, men have higher activity in areas involved in pain intensity and suffering, although it's not clear whether this reflects higher distress or greater activation of regions that prepare someone to cope with discomfort.

Using positron emission tomography (PET), a study of women and men with irritable bowel syndrome (IBS) given painful rectal stimulation uncovered numerous differences in brain response. The brains of men with IBS showed higher activity in regions for nociceptive and cognitive processing, motor planning and sympathetic responses, while women's preferentially triggered the emotion-based limbic centres and suppressed cognitive processes.

#### Culture counts

The distinction between CNS responses in areas for sensation and emotion highlights possible psychosocial differences in male and female pain reactions, shifting the emphasis from *sex* to *gender*. Gender studies, rather than focusing on biologic differences between the sexes, examine the characteristics a culture or society defines as masculine or feminine. Traditional

stereotypes suggest that socialization of young children influences pain responses. Boys are often rewarded for withstanding pain, while girls are told to accept it as a normal part of life.

In pain research, women generally report greater bodily distress and more numerous, intense and

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frequent somatic symptoms than men. These differences hold regardless of age, time period, treatment setting, study format, and whether it's prospective or retrospective.

While biologic factors play a role, it's been suggested that there's a gender gap in symptom appraisal and assessment — women may pay more attention to bodily signs and ambiguous or mild sensations, perhaps influenced by experiences of menstruation, pregnancy and menopause. Similarly, the distinct social roles of males and females probably influences expressiveness about discomfort, stoicism, and readiness to consult a physician and assume the patient role. The higher prevalence in women of depressive and anxiety disorders — which often have prominent somatic features — could also contribute to sex differences in symptom reporting.

Another consideration is gender bias in both clinical research and medical practice. There's evidence that women may show greater willingness than men to admit to discomfort, particularly to a female interviewer; studies finding positive sex differences are more likely to be published than those detecting none; and female patients expressing distress over their pain face a higher risk of being viewed as emotionally disturbed, histrionic or somatizing.

Consequently, clinicians might be quicker to attribute women's symptoms to psychosocial causes.

#### Banishing gender bias

The upshot is that clinicians have an obligation, irrespective of the patient's sex, to accept that a pain report is valid and deserves a full diagnostic workup and the best available management. Stereotypes are useless as a basis for medical practice. Even careful studies reporting sex differences present data based on large samples of males and females, so they can only tell us about group differences, not individuals. The patient sitting across from you is a unique human being who's different — biologically, psychologically and socially — from a research-based composite. She or he deserves treatment on a gender-free basis. **PE**