

## Sex, Gender, and Pain: “Men Are from Mars, Women Are from Venus . . .”

May L. Chin, MD\*

Richard Rosenquist, MD†

**W**ith tongue in cheek, the above quotation is borrowed from a best selling book by author John Gray, who wrote to offer advice on better communication between men and women. Perhaps, intuitively, we have known all along that there are more than just chromosomal differences between males and females. Granted then, we are not surprised that issues related to pain are no exception.

Epidemiological studies and pain research have shown that women and men experience and cope with pain differently.<sup>1,2</sup> As duly noted from the outset of a review,<sup>3</sup> sex and gender are not the same and each term is defined separately in accordance with the Institute of Medicine. Sex and gender differences in pain are multifaceted and include the prevalence of pain in disease states, the actual report of pain, social and cultural influences, as well as responses to analgesics.<sup>1,4,5</sup> In addition, there appear to be more painful conditions where female prevalence is greater than male prevalence.<sup>1</sup>

Numerous animal and human studies demonstrate sex differences in opioid-mediated analgesia.<sup>4,6,7</sup> In a large study of over 4300 patients in which morphine was prescribed to treat postoperative pain, female patients reported higher pain scores and had higher morphine requirements. However, among elderly patients (older than 75 yr), there was no difference observed between the sexes.<sup>6</sup> In fact, age is a confounding factor when evaluating sex differences in pain. Aging is associated with myriad changes, which can affect the incidence and perception of pain. These include biological, social, psychological changes, and changes in the prevalence of disease and or clinical pain states.<sup>1</sup>

In a brief review, Hurley and Adams<sup>3</sup> highlight our current understanding of sex and gender differences in pain including those observed in basic research using animal models. Unlike research in human subjects in which variables such as gender roles and psychological factors may significantly influence the report of pain and analgesia, animal studies, on the other hand, are unlikely to be affected by such variables. But the authors point out that, in animal models, there are other variables that can affect pain tolerance and pain threshold, such as age and strain of the animal, and that differences between male and female rodents may vary depending on the type of injury and the estrous cycle of the female. Until these and other variables are accounted for, one should exercise caution in the extrapolation of studies from animals to humans.

The search for a mechanistic understanding of observed sex and gender differences in pain is still in its infancy. There are clear indications that multiple factors individually and collectively play a role, yet our recognition and understanding of the individual factors and their complex interaction is minimal at present. These factors include, but are not limited to, genetic, hormonal, social roles, exercise, and information processing in the brain.

In animal models examining the antinociceptive effects of opioids, more than 90% of studies that demonstrated a male predominance used a  $\mu$  receptor agonist. However, a  $\kappa$  agonist used in four of five studies demonstrated greater female antinociception to opioid agonists.<sup>8,9</sup> There is clear evidence that there is neither a uniform class effect for opioids nor can it be assumed that  $\mu$  opioids primarily work on males and  $\kappa$  opioids

---

From the \*Department of Anesthesiology and Critical Care Medicine, George Washington University Medical Center, Washington, DC; and †Department of Anesthesiology, University of Iowa, Iowa City, Iowa.

Accepted for publication March 31, 2008.

Address correspondence and reprint requests to May L. Chin, MD, Department of Anesthesiology and Critical Care Medicine, George Washington University Hospital, 900 23rd Street, NW, Washington, DC 20037. Address e-mail to chinm@gwu.edu.

Copyright © 2008 International Anesthesia Research Society

DOI: 10.1213/ane.0b013e3181788ca3

primarily work on females. In addition, further studies have demonstrated a genetic basis for this difference in response.

Recognition of sex and gender differences led to a mandate by the National Institutes of Health that all human clinical trials supported with National Institutes of Health funds have a representative sample of females. In human studies, there is an enhanced ability to gain a direct verbal report of pain as well as assess other components such as suffering, memory, expectation, and fear. Although some aspects of pain appear to have a greater degree of transparency, reliability, and simplicity, other aspects are infinitely more complex and defy assignment to one sex or another. Sex-related threshold differences diminish with advancing age and disappear after 40 yr of age.<sup>10</sup> Hormonal variation, puberty, reproductive status, and menstrual cycle have all been shown to affect pain threshold and perception. In general, females have lower pain thresholds and less tolerance to noxious stimuli.<sup>11</sup> "Macho" males have a further increase in pain tolerance when compared with males without a similarly strong male role belief. In males without a clear male role, pain thresholds were no different than females.<sup>12</sup> Stereotypical gender roles and expectations affect pain perception. Males report less pain and have higher thresholds in the presence of a female examiner, an effect that is increased in the presence of an attractive female.<sup>13</sup> The exact opposite was present in females who reported more pain and had lower thresholds with attractive male examiners.<sup>14</sup> Thus, the individual performing the test may produce dramatically different test results without any overt attempt to introduce bias. Differences between men and women have also been attributed to maladaptive coping strategies, such as catastrophizing.

In addition to numerous social effects that are poorly understood, there appear to be fundamental differences in brain activation and data processing in response to painful stimuli. Although brain imaging studies have reported differences in activity patterns between the two sexes, with some studies reporting greater activation in men,<sup>15</sup> the variation in brain activity patterns may be influenced by factors such as the type and intensity of the noxious stimuli. As such, the differences observed in brain imaging patterns may not be attributed to sex or gender alone.<sup>16</sup>

Although both animal and human research report sex and gender differences in pain, the reasons for these differences remain elusive. Possible explanations include molecular and genetic mechanisms; other factors include social, psychological, cultural influences, and experimental bias. The implications of sex and gender

differences in pain are important for patient care. For instance, these differences may affect how we address the management of acute and chronic pain<sup>17,18</sup> and how we assess the therapeutic effectiveness of analgesics in men and women. However, more work is required on this complex subject to allow better understanding of the magnitude of these findings, how they impact patient care, and what changes may be required to improve care. The review article in this issue of the journal<sup>3</sup> brings needed attention to this field and highlights the importance of incorporating gender and sex into the evaluation of current data and as variables in future research studies on pain.

## REFERENCES

1. LeResche L. Sex, gender, and clinical pain. Proceedings of the 11th World Congress on Pain. In: Flor H, Kalso E, eds. IASP Press; 2006:543-54
2. Keogh E, Herdenfeldt M. Gender, coping and the perception of pain. *Pain* 2002;97:195-201
3. Hurley RW, Adams MCB. Sex, gender and pain: an overview of a complex field. *Anesth Analg* 2008;107:309-17
4. Kest B, Sarton E, Dahan A. Gender differences in opioid-mediated analgesia. Animal and human studies. *Anesthesiology* 2000;93:539-47
5. Robinson ME, Wise EA. Gender bias in the observation of experimental pain. *Pain* 2003;104:259-64
6. Aubrun F, Salvi N, Coriat P, Riou B. Sex- and age-related differences in morphine requirements for postoperative pain relief. *Anesthesiology* 2005;103:156-60
7. Cepeda MS, Carr D. Women experience more pain and require more morphine than men to achieve a similar degree of analgesia. *Anesth Analg* 2003;97:1464-8
8. Binder W, Carmody J, Walker J. Effect of gender on anti-inflammatory and analgesic actions of two kappa-opioids. *J Pharmacol Exp Ther* 2000;292:303-9
9. Holtman JR Jr, Wala EP. Characterization of the antinociceptive effect of oxycodone in male and female rats. *Pharmacol Biochem Behav* 2006;83:100-8
10. Pickering G, Jourdan D, Eschaliere A, Dubray C. Impact of age, gender and cognitive functioning on pain perception. *Gerontology* 2002;48:112-8
11. Riley JL III, Robinson ME, Wise EA, Myers CD, Fillingim RB. Sex differences in the perception of noxious experimental stimuli: a meta-analysis. *Pain* 1998;74:181-7
12. Pool GJ, Schwegler AF, Theodore BR, Fuchs PN. Role of gender norms and group identification on hypothetical and experimental pain tolerance. *Pain* 2007;129:122-9
13. Levine FM, De Simone LL. The effects of experimenter gender on pain report in male and female subjects. *Pain* 1991;44:69-72
14. Gijsbers K, Nicholson F. Experimental pain thresholds influenced by sex of experimenter. *Percept Mot Skills* 2005;101:803-7
15. Derbyshire SW, Nichols TE, Firestone L, Townsend DW, Jones AK. Gender differences in patterns of cerebral activation during equal experience of painful laser stimulation. *J Pain* 2002;3:401-11
16. Paulson PE, Minoshima S, Morrow TJ, Casey KL. Gender differences in pain perception and patterns of cerebral activation during noxious heat stimulation in humans. *Pain* 1998;76:223-9
17. Rosseland LA, Stubhaug A. Gender is a confounding factor in pain trials: women report more pain than men after arthroscopic surgery. *Pain* 2004;112:248-53
18. Keogh E, McCracken LM, Eccleston C. Do men and women differ in their response to interdisciplinary chronic pain management? *Pain* 2005;114:37-46