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Sex and Gender Issues in Pain

I. Understand the differences in the terms “sex” and “gender” (Pardue et al. 2001).

   A. Be aware of the biological (e.g. physical, anatomical, developmental) and chromosomal differences between males and females (human and nonhuman), which are typically referred to as “sex.”

   B. Be aware that “gender” refers to one’s self-identity as being female or male, based on social and environmental as well as biological factors.

II. Understand the nature of sex differences in the epidemiology of pain in relation to age and reproductive history.

   A. Know that in population-based surveys, women typically report more frequent and/or severe pain than men (Unruh 1996).

   B. Know that women are at greater risk for several chronic painful disorders, including temporomandibular disorders, fibromyalgia, migraine headache, interstitial cystitis, joint pain, irritable bowel syndrome, complex regional pain syndrome, and trigeminal neuralgia (Unruh 1996; Jones and Nyberg 1997; LeResche 1999; Buckwalter and Lappin 2000; Dao and LeResche 2000). Be aware that these differences vary with age and are associated with endogenous or exogenous sex hormone changes, for example, in the case of migraine headaches (Silberstein 2001). Women are at greater risk for autoimmune disorders that have a pain component, such as rheumatoid arthritis, lupus, and scleroderma (Buckwalter and Lappin 2000).

   C. Know that men are at greater risk for some pain disorders, including cluster headache and pancreatitis (Dodick et al. 2000; Lin et al. 2000).

   D. Recognize that several pain conditions are unique to reproductive organs—either to women, including dysmenorrhea, vulvodynia, and labor pain, or to men, such as testicular pain and pain associated with prostatitis (Wesselmann and Reich 1996).

   E. Know that some studies suggest greater procedural and postoperative pain among females than males (Froehlich et al. 1997; Averbuch and Katzper 2000; Taenzer et al. 2000), while other studies have reported no sex differences (Lander et al. 1990; Gear et al. 1996).

III. Understand sex differences in nociceptive responses and pain perception in both animal (acute and chronic) and human (acute) experimental pain models.

   A. Know that nonhuman animal models reveal sex differences in nociceptive responses, but the results vary across pain assays. For example, females are more sensitive to electrical stimuli and to chemical provocations such as formalin (Aloisi et al. 1994, 1995; Mogil et al. 2000). Be aware that findings from studies of heat stimuli are less consistent, with more studies than not reporting no sex differences (Mogil et al. 2000).

   B. Know that hormonal responses to nociceptive stimuli differ according to sex (Aloisi 1997).

   C. Know that among humans, women report lower pain thresholds and tolerances than men, and that ratings of suprathreshold stimuli are often higher among women than men across a wide range of painful stimuli (Fillingim and Maixner 1995; Riley et al. 1998).

IV. Understand differences in analgesic responses both within the same sex (e.g., during childbearing) and between sexes.

A. Know that endogenous analgesic responses can differ both quantitatively and qualitatively by sex (Bodnar et al. 1988; Mogil et al. 1993) and that there are female-specific endogenous analgesic systems, including pregnancy-induced analgesia (Gintzler and Liu 2000) and analgesia produced by vaginocervical stimulation (Komisaruk and Whipple 2000).

B. Be aware that nonhuman animal research, primarily in rodents, suggests greater opioid analgesia in males than females (Fillingim and Ness 2000; Kest et al. 2000). Limited research on non-opioid analgesics suggests that sex differences may also be present for these agents (Walker and Carmody 1998; Chiari et al. 1999).

C. Know that among humans, research suggests that sex differences can be measured between mu- and kappa-opioid agonists. For example, following oral surgery, females experienced either more robust or more prolonged analgesia than males using kappa- (or weak mu-) opioid analgesics (Miaskowski et al. 2000). Be aware that limited experimental research suggests that women show greater analgesic responses to potent mu-opioid agonists (Sarton et al. 2000; Zacny 2002).

D. Know that for nonsteroidal anti-inflammatory drugs, the variability in response may be gender-related such that females demonstrate less effect than males (Walker and Carmody 1998), although findings of no sex difference have also emerged (Averbuch and Katzper 2000).

V. Understand biological and psychosocial contributions to sex differences in pain responses (Fillingim 2000).

A. Know that developmental factors influence the structural and functional sex differences in nervous system development (McEwen 2001). Be aware that brain function and activation during pain can differ between males and females (Paulson et al. 1998).

B. Know that sex hormone receptors can influence nociceptive activity through genomic and nongenomic or membrane effects (Aloisi 2000).

C. Know that sex differences in immune responses can contribute to sex differences in pain sensitivity (Da Silva 1999; Gregory et al. 2000).

D. Be aware of the normal biological differences between the sexes, e.g., weight and body mass composition, as they apply to pharmacokinetic differences as well as cyclical hormonal variations with age (Berkley and Holdcroft 1999).

E. Know that hormonal fluctuations associated with the estrous or menstrual cycle have been associated with pain and analgesia (Riley et al. 1999; Fillingim and Ness 2000). Exogenous hormones have also been related to clinical pain (LeResche et al. 1997; Wise et al. 2000; Musgrave et al. 2001) and to experimental pain sensitivity (Fillingim and Edwards 2001).

F. Know that genetic factors appear to determine some sex differences in pain and analgesia (Mogil 2000).

G. Know that multiple psychosocial variables may contribute to sex differences in clinical and experimental pain responses, including (but not limited to) anxiety (Edwards et al. 2000), abuse history (Spertus et al. 1999), coping (Affleck et al. 1999; Keefe et al. 2000), gender roles (Robinson et al. 2001), and family history (Fillingim et al. 2000).

VI. Understand that the patient's sex may influence treatment seeking, delivery of treatment, and treatment effectiveness.

A. Know that women seek more pain-related health care than men (Unruh 1996; Barsky et al. 2001), and that women in the general population are more likely than men to use prescription narcotics (Eggen 1993; Simoni-Wastila 2000).

B. Know that women are more likely than men to suffer an adverse effect after analgesia (Ciccone and Holdcroft 1999).

C. Know that women and men presenting with pain complaints (e.g., ischemic cardiac pain or back pain) may be offered different diagnostic tests and/or treatments (Safran et al. 1997; Roger et al. 2000; Weisse et al. 2001).

D. Be aware that some research suggests that rehabilitation and multidisciplinary pain treatment produces more robust clinical improvement in women than men (Jensen et al. 2001), while other findings indicate similar treatment gains for women and men (Mannion et al. 2001).

E. Be aware that the determinants of treatment effectiveness may differ for women and men (Burns et al. 1998).

VII. Understand the factors that may influence the outcome of pain experiments or therapies for men and women.

A. Know that health care delivery occurs in a sociocultural context and that the characteristics of providers and patients and the setting in which health care is provided may influence women and men in different ways.

B. Know that the attitude of the person matters and that within-sex variation in pain is greater than between-sex variation in pain.

C. Know that time (e.g., daily circadian rhythms) and environmental factors (e.g., music, lighting) may influence women and men differently.

REFERENCES

Affleck G, Tennen H, Keefe FJ, et al. Everyday life with osteoarthritis or rheumatoid arthritis: independent effects of disease and gender on daily pain, mood, and coping. *Pain* 1999; 83:601–609.

Aloisi AM. Sex differences in pain-induced effects on the septo-hippocampal system. *Brain Res Brain Res Rev* 1997; 25:397–406.

Aloisi AM. Sensory effects of gonadal hormones. In: Fillingim RB (Ed). *Sex, Gender, and Pain*, Progress in Pain Research and Management, Vol. 17. IASP Press, Seattle, 2000, pp 7–24.

Aloisi AM, Albonetti ME, Carli G. Sex differences in the behavioural response to persistent pain in rats. *Neurosci Lett* 1994; 179:09–82.

Aloisi AM, Sacerdote P, Albonetti ME, Carli G. Sex-related effects on behaviour and beta-endorphin of different intensities of formalin pain in rats. *Brain Res* 1995; 699:242–249.

Averbuch M, Katzper M. A search for sex differences in response to analgesia. *Arch Intern Med* 2000; 160:3424–3428.

Barsky AJ, Peekna HM, Borus JF. Somatic symptom reporting in women and men. *J Gen Intern Med* 2001; 16:266–275.

Berkley KJ, Holdcroft A. Sex and gender differences in pain. In: Wall PD, Melzack R (Eds). *Textbook of Pain*. Edinburgh: Churchill-Livingstone, 1999, pp 951–965.

Bodnar RJ, Romero MT, Kramer E. Organismic variables and pain inhibition: roles of gender and aging. *Brain Res Bull* 1988; 21:947–953.

Buckwalter JA, Lappin DR. The disproportionate impact of chronic arthralgia and arthritis among women. *Clin Orthop* 2000; 87:159–168.

Burns JW, Johnson BJ, Devine J, Mahoney N, Pawl R. Anger management style and the prediction of treatment outcome among male and female chronic pain patients. *Behav Res Ther* 1998; 36:1051–1062.

Chiari A, Tobin JR, Pan HL, Hood DD, Eisenach JC. Sex differences in cholinergic analgesia I: a supplemental nicotinic mechanism in normal females. *Anesthesiology* 1999; 91:1447–1454.

Ciccone GK, Holdcroft A. Drugs and sex differences: a review of drugs relating to anaesthesia. *Br J Anaesth* 1999; 82:255–265.

Da Silva JA. Sex hormones and glucocorticoids: interactions with the immune system. *Ann Acad Sci NY* 1999; 876:102–117; discussion 117–118, 102–117.

Dao TT, LeResche L. Gender differences in pain. *J Orofac Pain* 2000; 14:169–184.

Dodick DW, Rozen TD, Goadsby PJ, Silberstein SD. Cluster headache. *Cephalalgia* 2000; 20:787–803.

Edwards RR, Augustson E, Fillingim RB. Sex-specific effects of pain-related anxiety on adjustment to chronic pain. *Clin J Pain* 2000; 16:46–53.

Eggen AE. The Tromso Study: frequency and predicting factors of analgesic drug use in a free-living population (12–56 years). *J Clin Epidemiol* 1993; 46:1297–1304.

Fillingim RB. *Sex, Gender, and Pain,* Progress in Pain and Research Management, Vol. 17. Seattle: IASP Press, 2000.

Fillingim RB, Edwards RR. The association of hormone replacement therapy with experimental pain responses in postmenopausal women. *Pain* 2001; 92:229–234.

Fillingim RB, Maixner W. Gender differences in the responses to noxious stimuli. *Pain Forum* 1995; 4:209–221.

Fillingim RB, Ness TJ. Sex-related hormonal influences on pain and analgesic responses. *Neurosci Biobehav Rev* 2000; 24:485–501.

Fillingim RB, Edwards RR, Powell T. Sex-dependent effects of reported familial pain history on clinical and experimental pain responses. *Pain* 2000; 86:87–94.

Froehlich F, Thorens J, Schwizer W, et al. Sedation and analgesia for colonoscopy: patient tolerance, pain, and cardiorespiratory parameters. *Gastrointest Endosc* 1997; 45:1–9.

Gear RW, Gordon NC, Heller PH, et al. Gender difference in analgesic response to the kappa-opioid pentazocine. *Neurosci Lett* 1996; 205:207–209.

Gintzler AR, Liu NJ. Ovarian sex steroids activate antinociceptive systems and reveal gender-specific mechanisms. In: Fillingim RB (Ed). *Sex, Gender, and Pain,* Progress in Pain Research and Management, Vol. 17. Seattle: IASP Press, 2000, pp 89–108.

Gregory MS, Duffner LA, Faunce DE, Kovacs EJ. Estrogen mediates the sex difference in post-burn immunosuppression. *J Endocrinol* 2000; 164:129–138.

Jensen IB, Bergstrom G, Ljungquist T, Bodin L, Nygren AL. A randomized controlled component analysis of a behavioral medicine rehabilitation program for chronic spinal pain: are the effects dependent on gender? *Pain* 2001; 91:65–78.

Jones CA, Nyberg L. Epidemiology of interstitial cystitis. *Urology* 1997; 49(Suppl):2–9.

Keefe FJ, Lefebvre JC, Egert JR, et al. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. *Pain* 2000; 87:325–334.

Kest B, Sarton E, Dahan A. Gender differences in opioid-mediated analgesia: animal and human studies. *Anesthesiology* 2000; 93:539–547.

Komisaruk BR, Whipple B. How does vaginal stimulation produce pleasure, pain, and analgesia? In: Fillingim RB (Ed). *Sex, Gender, and Pain,* Progress in Pain Research and Management, Vol. 17. Seattle: IASP Press, 2000, pp 109–134.

Lander J, Fowler Kerry S, Hill A. Comparison of pain perceptions among males and females. *Can J Nurs Res* 1990; 22:39–49.

LeResche L. Gender considerations in the epidemiology of chronic pain. In: Crombie IK, Croft PR, Linton SJ, LeResche L, Von Korff M (Eds). *Epidemiology of Pain*. Seattle: IASP Press, 1999, pp 43–52.

LeResche L, Saunders K, Von Korff MR, Barlow W, Dworkin SF. Use of exogenous hormones and risk of temporomandibular disorder pain. *Pain* 1997; 69:153–160.

Lin Y, Tamakoshi A, Matsuno S, et al. Nationwide epidemiological survey of chronic pancreatitis in Japan. *J Gastroenterol* 2000; 35:136–141.

Mannion AF, Junge A, Taimela S, et al. Active therapy for chronic low back pain: part 3. Factors influencing self-rated disability and its change following therapy. *Spine* 2001; 26:920–929.

McEwen BS. Estrogen's effects on the brain: multiple sites and molecular mechanisms. *J Appl Physiol* 2001; 91:2785–2801.

Miaskowski C, Gear RW, Levine JD. Sex-related differences in analgesic responses. In: Fillingim RB (Ed). *Sex, Gender, and Pain*, Progress in Pain Research and Management, Vol. 17. Seattle: IASP Press, 2000, pp 209–230.

Mogil JS. Interactions between sex and genotype in the mediation and modulation of nociception in rodents. In: Fillingim RB (Ed). *Sex, Gender, and Pain,* Progress in Pain Research and Management, Vol. 17. Seattle: IASP Press, 2000, pp 25–40.

Mogil JS, Sternberg WF, Kest B, Marek P, Liebeskind JC. Sex differences in the antagonism of stress-induced analgesia: effects of gonadectomy and estrogen replacement. *Pain* 1993; 53:17–25.

Mogil JS, Chesler EJ, Wilson SG, Juraska JM, SternbergWF. Sex differences in thermal nociception and morphine antinociception in rodents depend on genotype. *Neurosci Biobehav Rev* 2000; 24:375–389.

Musgrave DS, Vogt MT, Nevitt MC, Cauley JA. Back problems among postmenopausal women taking estrogen replacement therapy. *Spine* 2001; 26:1606–1612.

Pardue ML, Wizemann TM,Wizemann TM, Pardue ML. *Exploring the Biological Contributions to Human Health: Does Sex Matter?* Washington, DC: National Academy Press, 2001.

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; 76:223–229.

Riley JL, Robinson ME, Wise EA, Myers CD, Fillingim RB. Sex differences in the perception of noxious experimental stimuli: a meta-analysis. *Pain* 1998; 74:181–187.

Riley JLI, Robinson ME, Wise EA, Price DD. A meta-analytic review of pain perception across the menstrual cycle. *Pain* 1999; 81:225–235.

Robinson ME, Riley JL III, Myers CD, et al. Gender role expectations of pain: relationship to sex differences in pain. *Pain* 2001; 2:251–257.

Roger VL, Farkouh ME, Weston SA, et al. Sex differences in evaluation and outcome of unstable angina. *JAMA* 2000; 283:646–652.

Safran DG, Rogers WH, Tarlov AR, McHorney CA, Ware JE Jr. Gender differences in medical treatment: the case of physician-prescribed activity restrictions. *Soc Sci Med* 1997; 45:711–722.

Sarton E, Olofsen E, Romberg R, et al. Sex differences in morphine analgesia: an experimental study in healthy volunteers. *Anesthesiology* 2000; 93:1245–1254.

Silberstein SD. Headache and female hormones: what you need to know. *Curr Opin Neurol* 2001; 14:323–333.

Simoni-Wastila L. The use of abusable prescription drugs: the role of gender. *J Womens Health Gend Based Med* 2000; 9:289–297.

Spertus IL, Burns J, Glenn B, Lofland K, McCracken L. Gender differences in associations between trauma history and adjustment among chronic pain patients. *Pain* 1999; 82:97–102.

Taenzer AH, Clark C, Curry CS. Gender affects report of pain and function after arthroscopic anterior cruciate ligament reconstruction. *Anesthesiology* 2000; 93:670–675.

Unruh AM. Gender variations in clinical pain experience. *Pain* 1996; 65:123–167.

Walker JS, Carmody JJ. Experimental pain in healthy human subjects: gender differences in nociception and in response to ibuprofen. *Anesth Analg* 1998; 86:1257–1262.

Weisse CS, Sorum PC, Sanders KN, Syat BL. Do gender and race affect decisions about pain management? *J Gen Intern Med* 2001; 16:211–217.

Wesselmann U, Reich SG. The dynias. *Semin Neurol* 1996; 16:63–74.

Wise EA, Riley JL III, Robinson ME. Clinical pain perception and hormone replacement therapy in post-menopausal females experiencing orofacial pain. *Clin J Pain* 2000; 16:121–126.

Zacny JP. Gender differences in opioid analgesia in human volunteers: cold pressor and mechanical pain (CPDD abstract). *NIDA Res Monogr* 2002; 182:22–23.