

Gender/Sex Differences in Pain And Analgesia

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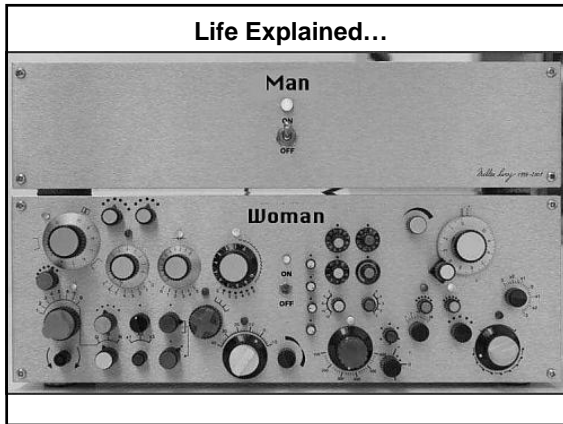
Objectives

- Define differences between "gender" and "sex" when describing research findings related to pain.
- Describe pathophysiologic differences in the pain experience.
- Discuss studies related to sex/gender differences in pain perception and expression.

Definitions



- "Sex" defines *biological* differences
- "Gender" defines *psychosocial* differences



PATHOPHYSIOLOGIC FINDINGS

- Animal Studies
- Human Studies

A collage of black and white photographs showing children interacting with various dogs. The top photo shows a child hugging a large black dog. Below it, there are three smaller photos: a pug, a child with a beagle, and a child with a small dog.

Animal Studies

- Literature review of biological studies from 1980-2004 (Mogil & Chanda, 2005; Wiesenfeld-Hallin, 2005):
 - Female rodents more sensitive to noxious stimuli than males
 - Female rodents produced less endogenous analgesia than males
- Male rats showed more paw flinching following pain induction with Endothelin-1; normally released after stress, cold induction, or injury (McKelvy, Mark & Sweltzer, 2007)
- No sex differences in response to incisional pain on paws of rats (Banik et al., 2006; Kroin et al., 2003)
- Morphine more effective in males with experimentally induced pain; females required more morphine postoperatively (Ji et al., 2006)*

*Analgesic response in rodents may be skewed due to male rodents having significantly more body fat than females; the opposite is true in humans (Greenspan et al., 2007)

Human Studies

- **Twins**
 - No genetic differences however environmental influences played a role (Kato et.al., 2006)
 - No genetic influence on neck pain but women reported a higher prevalence (Fejer, Harvigsen & Kyvik, 2006)
- **Thermal application**
 - No significant differences in nociceptive transmission or neuronal sensitization (Jensen & Peterson, 2006)

Human Studies

- **Pain Modulation**

Literature review 1887-2005: (Rhudy & Williams, 2005)

 - Males have reduced pain in combination with sexual/erotic stimuli
 - Females have increased pain with fear/threat or high emotional arousal
 - No differences between males and females in the presence of anxiety

Exposure to deep tissue pain produced more endogenous analgesia in males than females

 - Traced by PET scan in anterior thalamus, ventral basal ganglia, and amygdala (Zubieta et.al., 2002)

Testosterone correlated positively with increased macrophage migration inhibitory factor which is a neuroendocrine mediator; whereas estradiol correlated negatively (Aloisi et.al., 2005)

Human Studies – Vital signs

- **Systolic B/P and stroke volume revealed a negative correlation in women versus men when pain was induced by hand cold pressor test** (al'Agisi, Petersen & Wittmers, 2002)
- **Heart rate elevated in men that perceived pain with hot water immersion, but not in women** (Tousignant-Lafamme et.al., 2005)

Human Studies – Women's Menstrual Cycle

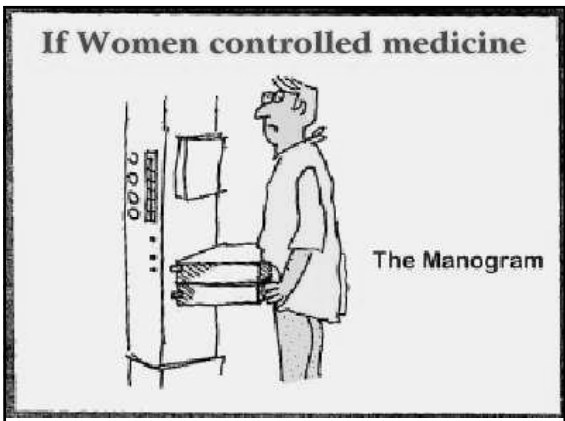
- Biological studies literature review 1980-2004 (Becker et al., 2005; Weisenfeld-Hallin, 2005):
 - Pain tolerance, sensitivity and pain threshold varies with stage of menstrual cycle
- Meta-analysis of 16 studies, pain related to pressure, cold, thermal, and ischemic muscle pain revealed higher pain thresholds during the follicular phase versus the luteal phase (Mlaskowski & Levine, 2004)
- Sensitivity to visceral pain varied at different phases of the menstrual cycle (Arendt-Nielsen et al., 2004)
- Sensitization of the trigeminal nerve with capsacin showed increased area of allodynia during menstrual phase vs luteal phase; overall wider area of allodynia in women versus men despite phase of menstrual cycle (Gazerani et al., 2005)
- Estrogen increased excitability of sensory neurons and trigeminal afferent fibers causing noxious stimulation (Cairns, 2007)

Human Studies – Response to pain treatments

- Comprehensive literature review found opioids to be more effective in women than men; men needed 24-40% more. Kappa receptor agonists more effective in women than men (Mlaskowski & Levine, 2004)
- Gender variance for morphine requirements disappeared in patients >75 years old (Aubrun et al., 2005)
- Vibratory stimulation experimentally applied to mitigate pain increased pain thresholds for women but not men (Dahlin et al., 2006)

Biological Differences

- Overall, there is more evidence that pain perception and response is more likely mediated by psycho-social variables than by biological differences (Main & Spanswick, 2000)



Sex Differences in Pain Prevalence

- Women have higher prevalence of:
 - Fibromyalgia
 - Myofascial pain syndromes
 - Migraine headaches
 - Irritable bowel syndrome
 - Osteoarthritis
 - Rheumatoid arthritis
 - Hip, neck, and facial pain
 - Chronic back pain -females aged 70-77
 - Generalized pain

(Feyer, Kyvik & Hartvigsen, 2006; Jacobs et.al., 2006; McClish et.al., 2006; Frissora & Koch, 2005; Miaszkowski & Levine, 2004; Main & Spanswick, 2000)



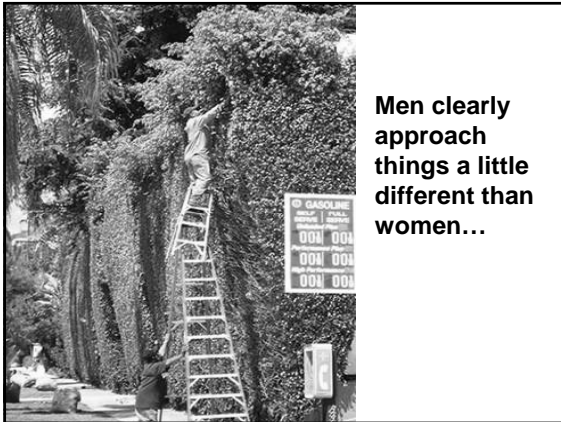


Pain Prevalence

- Women of reproductive age are more likely to seek help for orofacial pain conditions (Shinal & Fillingim, 2007)
- Men have higher prevalence of:
 - Cluster headaches 5 x more prevalent in men than women (Cairns, 2007)
- No gender differences in prevalence of:
 - Sickle cell pain episodes, pain ratings, or opioid usage (McClish et al., 2006)
 - Sick days related to back pain ages 16-44 years, non-pregnant females vs males (Sydsjo et al., 2003)
 - Pain related to lung cancer (Hoffman et al., 2007)

Pain Prevalence Related to Surgery

- Laparoscopic cholecystectomy – women had higher VAS, increased analgesic use and higher body temperatures post-op (Uchiyama et al., 2006)
- Arthroscopic knee surgery – on a VAS of 0-100, women reported an average post-op pain score of 84, verses 57 for men (Rosseland & Stubhaug, 2004)
- Hip arthroplasty – Women enrolled in Medicare reported more pain walking and are more disabled post THA (Holtzman, Saleh & Kane, 2002)



Gender Differences Related to Pain Treatment

- **General**
 - In patients (n=5690) with degenerative lumbosacral pathology, women were more likely to have medical imaging ordered versus men who were more likely to have surgery recommended. (Taylor et.al., 2005)
 - Women with cancer and AIDS related pain, were less likely to have adequate pain management than men (Miaskowski & Levine, 2004)
- **Chest pain – disturbing differences between how women are treated versus men...**

Treatment of Chest Pain

- Women were twice as likely as men to have a non-fatal MI or death within one year of having chest pain (Clements et.al., 2006)...yet:
 - Waited longer for initial ECG when presenting to ED with chest pain (Takakuwa, Shofer & Hollander, 2007)
 - Were less likely to receive an exercise ECG, undergo coronary angiography, angioplasty, or CABG, or be prescribed antiplatelet and statin therapies, even with confirmed coronary artery disease (Clements et. al., 2006)
 - Were less likely to be re-vascularized (Clements et.al., 2006)
 - Were less likely to receive statins, antilipidemic medications or to have cholesterol measurements than men with high risk angina (Hendrix, Mayhan & Egan, 2005)

Treatment of Chest Pain

- Younger women have significantly higher mortality rates than men following MI and CABG (Wenger, Shaw & Vaccarino, 2008)...yet:
 - African-American females that presented to the ER with chest pain received cardiac monitoring 37.5% of the time as compared to 54.5% of non-African-American males (Pezzin, Keyl & Green, 2007)
 - Women with acute coronary syndrome and chronic kidney disease were less likely to receive ACE inhibitors, ASA, and coronary angiography than men (Sonson et al., 2004)
 - Women with chest pain suffered an increased rate of refractory ischemia and re-hospitalization as compared to men (Anand et al., 2005)

Treatment of Chest Pain

- Men with angina pectoris were more likely to undergo ECG, angiography, & surgical revascularization, receive daily ASA, and be prescribed triple anti-anginal medications than women. Post MI, men were more likely to be referred to a cardiologist, and were more likely to be prescribed a beta blocker (Sekhri et al., 2008; Crilly & Bundred, 2005).



SOOOO...LIKE I SAID!

Gender Differences in Pain Description/Expression/Behaviors



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"I'm going to order a broiled skinless chicken breast, but I want you to bring me lasagna and garlic bread by mistake."

Pain Description

- On body maps, women drew larger anatomical areas of pain, had more hypochondriasis, and less ability to cope with and ignore pain (George et al., 2007)
- Women with osteoarthritis and knee pain showed increased pain as the day progressed whereas men showed increased coping as the day progressed (Keefe et al., 2004)
- Women overall, report higher pain scores compared to men, with like pain problems (Bingefors & Isacson, 2004)
- Spinal cord injured women had more nociceptive pain and higher analgesic use than men; however pain localization, descriptors, and intensity ratings were comparable (Norrbrink et al., 2003)
- Women with acute coronary syndromes were more likely than men to report chest "discomfort" versus "pain", identify areas other than the chest as painful, and report anxiety (Chen et al., 2005)

Pain Expression/Behaviors

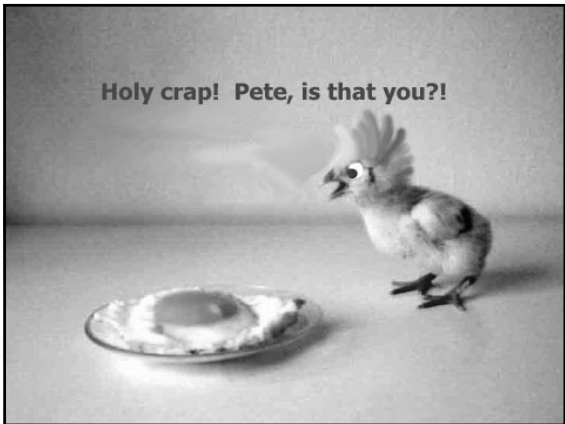
- Women exhibited facial grimacing more than men with toxic heat stimulation (Kunz, Gruber & Lautenbacher, 2006)
- Women had a lower reflex threshold and pain threshold to cutaneous electrical stimulation (Komiyama et al., 2005)
- In age 70-77, women had more chronic back pain correlated with economic difficulties, loneliness and obesity (Jacobs et al., 2006)
- Women aged 55-74 with osteoarthritic knee pain reported higher pain scores, decreased ADL, and more related complications than males in this age group. Men had similar results at an older age, 75-84 (Paradowski et al., 2006)
- In multiple studies, women displayed a lower threshold and tolerance overall for pressure and pain (Garcia et al., 2007; Soetanto, Chung & Wong, 2006; Chesterson et al., 2003)

Pain Expression/Behaviors

- A Norwegian study revealed that women reported more chronic pain and higher pain intensity than men; however, men with chronic pain reported more interference with quality of life (Rustoen et al., 2004).
- Marcus (2003) had different findings with men reporting greater mean severity scores, higher levels of disability, and reduced physical and psychological quality of life, as compared to women.
- In patients with chronic pain from fibromyalgia, arthritis, back problems and migraine headaches, depression was twice as prevalent in women as depression in men (Munce & Stewart, 2007).

Psychosocial Pain Differences – General Inferences

- Response to pain and pain report is modeled by learned behaviors; masculine features exhibiting restraint of pain report and expression, versus feminine features exhibiting outward expression and higher pain report.
 - Males that see themselves as more feminine (low identifying males) have lower pain tolerance than males that see themselves as masculine (high identifying males) (Pool et al., 2007)
- Anxiety has more influence on increasing pain report in men whereas depression influences pain report more in women.
- Studies regarding “coping” are variable.



Psychosocial Studies

- In adolescents (n=240) masculinity correlated with lower heat pain ratings in boys, but not girls (Myers et al., 2006)
- In boys and girls aged 12-18 (n=102), girls reported higher anxiety scores and anticipated more pain pre-operatively, than males. In females, higher pre-op anxiety predicted higher post-op pain scores, but not for males (Logan & Rose, 2004). PCA usage post-op day or OR and POD #1, did not vary significantly.

Psychosocial Influences

- Large prevalence study (n=4506) from Sweden revealed comorbidity between pain conditions and psychiatric/somatic problems was higher among women than men (Bingefors & Isacson, 2004)
 - Quality of life was affected by psychological issues in women, and headache complaints in males.
 - Poorer socioeconomic conditions correlated positively with both males and females
 - Economic difficulties, part time work, and being married correlated to higher pain reports among women
 - Education and unemployment in men contributed to higher pain reports
- Meta-analysis reveals emotion influences pain. Gender differences in the experience of pain may arise from how emotion is processed, which may in turn alter pain processing (Rhudy & Williams, 2005)

Depression and Pain

- Female elders report higher pain scores and higher overall pain intensity than male elders; elder females also report more depression (Tsai, 2007)
- In women with high reports of depression, they had more disability from pain than men; however depressed men used more medications (Keogh, McCracken & Eccleston, 2006)
- Women displayed a stronger relationship between mood, pain, and strength of disability than men (Hirsch et al., 2006)

Anxiety and Pain

- Higher trait anxiety scores revealed higher pain scores in men. (Elkitt & Jones, 2006; Chung & Wong, 2006)
- Anxiety and depression were predictors of increased pain and disability in both genders (Keogh, McCracken & Eccleston, 2006)
- Increased use of pain medications for chronic back pain in males was associated with more affective distress than in females; however opioid use was not associated with pain severity in either gender (Fellrigim et al., 2003)

Coping with Pain

- Cold-pressor induced pain study; one group given controls such as distraction or positive thinking, other group to just accept the pain (Keogh et al., 2004)
 - Females had overall lower pain tolerance but did better with accepting pain than males
 - When given controls, there was no difference between genders
- In another cold-pressor induced pain study, subjects either had to cope alone, or were given an empathetic experimenter. Women had lower pain tolerance, reported more pain, and had less coping ability despite the empathetic experimenter (Jackson et al., 2005)
- Empathetic care vs standard care during interventional procedures, reduced drug use in both genders, although overall, men used more drugs. In women, it reduced pain and anxiety ratings but not in men (Stinshoff et al., 2004)
- Emotion-focused coping strategies were more effective in decreasing pain in men with whiplash as compared to women (Jones & Elkitt, 2007)

No one is in charge of your happiness except you.




Coping may be a learned behavior and may need to be taught

Interdisciplinary treatment

- Pain management interventions aimed at improving function were effective in some domains for both sexes during the treatment, however women did not show a reduction in distress or pain at 3 months following treatment, whereas men did (Keogh, McCracken & Eccleston, 2005)

Smoking

(Gridler et al., 2005)



- Smokers in general have a higher pain tolerance probably due to blunted stress response reducing cortisol levels.
- Female smokers have greater thresholds for ischemic pain than non-smokers, but still lower than males.
- Male smokers had greater tolerance to cold-pressor pain than male non-smokers.

Responses to Stimuli

- In a laboratory setting, women are more sensitive than men to threatening stimuli; physical, emotional & verbal, thereby enhancing pain response. Men are more sensitive to positive events such as sexual/erotic stimuli, thereby resulting in a reduced pain response (Rhudy & Williams, 2005)

This guy just might have some pain issues!

