Gender Differences in the Pain Experience

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Objectives

- Present an overview of the gender/sex effects on pain
- Focus on the differences at the neurological/receptor level
- Discuss evidence of gender influence on experimental and “real” pain
- Evaluate the gender effects on medication efficacy and therapies
Case Studies: Pain Description

- 48 yr old (DG) with mass in pelvis, metastatic lesions in L3-4 and right femoral head, describes pain as “right hip, low back and deep pain”

- 54 yr old (FL) with mass in pelvis and metastatic lesions to T10-11, L3-4, right femoral head, describes pain as “right hip, low back and pelvic pain”

Nomenclature: Sex vs. Gender

- **Sex** = *anatomical* categorization of “male” and “female” (NB: anatomical may ≠ genetic)

- **Gender** may coincident with anatomical categorization but may also denote *identity* as “masculine” or “feminine”

Sex may ≠ Gender

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Prevalence: ♂ > ♀

- **Osteoarthritis:**
  - OA of the knee, is 2x as common in ♀ as in ♂
  - OA of the hips affects ♂ & ♀ equally.

- **Heart disease**
  - < age 50 ♀ have more chest pain but less heart disease than ♂ do
  - > age 50 ♀ have more silent heart disease than ♂ do.

- **Migraine Headaches:** 1 in 5 ♀ & 1 in 17 ♂ have migraines.

- **Fibromyalgia:** 9 x more ♀ than ♂

- **Irritable bowel syndrome (IBS):** ♀ > ♂

- **Rheumatoid arthritis:** 2-3x ♀ > ♂

- **Chronic pelvic pain**

- **Temporomandibular joint disorder**
  - female to male ratio is 4:1
Prevalence of Painful Conditions: ♂ > ♀

- Cluster headache
- Coronary heart disease
- Gout
- Ankylosing spondylitis
- Duodenal ulcer
- Pancreatic disease

IASP Fact Sheet: Differences in Pain between Women and Men, Sept. 2007
Pain Presentation: CAD

Chest pain most common symptom (women 70%) and men (71%)

Men
- Central chest pain
- Radiating pain to neck, jaw, upper abdomen, shoulders, and arms

Women
- Midback pain
- Nausea/vomiting
- Indigestion
- Dyspnea
- Palpitations

Men (29%) and women (30%) equally likely to present without chest pain

Longitudinal Changes in Chronic Pain

- **Methodology**: A 24-year study of pain patterns among 321 Swedish patients (aged 53-63 at the beginning of the study) assessed self-reported pain in the chest, abdomen and musculoskeletal system (back or hips, shoulders, elbows, legs or knees).

- **Results**:
  - Women report more pain than men
  - Statistically significantly women reported more musculoskeletal pain than men.

Longitudinal Changes in Chronic Pain

- Most notable gender difference involved pain in the extremities: less than one percent of the men, but 12.2% of the women reported persistent musculoskeletal pain in those areas.

- Chronic pain in elderly women is/will be a major health issue.

Gender Differences

- Women seem to show:
  - Lower pain thresholds
  - A greater ability to discriminate painful sensations
  - Higher pain ratings
  - A lower tolerance for pain

Gender-related responses to pain are not completely consistent

Dental Pain Model:

Pain Post Tooth Implantation

• Methodology: Followed 27 women and 21 men for 10 days after surgery to implant a replacement tooth

• Results:
  – The women described the surgery as significantly more painful than the men did
  – Both sexes rated the pain on a pain scale as similarly intense
  – In both sexes, pain fell by 50% within two days. In the 10 days following the surgery
  – Women tolerated low levels of pain much better than did the men.
  – Over time men were more disturbed than the women by persisting discomfort

Fein J, School of Dentistry, McGill University, Montreal, Quebec, Canada
http://painconsortium.nih.gov/genderandpain/models.htm
Effect of Blood Pressure on Pain Sensitivity

- ♀ have lower blood pressures (BP) than age-matched ♂

- Animal studies have shown an association between hypertension and diminished sensitivity to noxious stimuli\textsuperscript{1,2}

- ↓ pain sensitivity has been found in hypertensive humans\textsuperscript{3,4}

\textsuperscript{1}Dworkin BR, Filewich RJ, Miller NE, Craigmyle N. Baroreceptor activation reduces reactivity to noxious stimulation: implications for hypertension. Science 1979; 205: 1299–301.


Hypotension: Increased Pain Sensitivity

• **Methodology**
  – Sensitivity to heat pain was assessed in 40 subjects with chronic hypotension (mean blood pressure 96.5/57.7mmHg) and 40 normotensive control persons (mean blood pressure 121.8/77.2mmHg).
  – A contact thermode, tonic heat stimuli (45.5–47.5°C) were applied to the forearm.

• **Results:**
  – Hypotensive individuals exhibited markedly reduced pain threshold and pain tolerance, as well as increased sensory and affective pain experience
  – Suggests an inverse relationship between blood pressure and pain sensitivity across the whole blood pressure

Blood Pressure & Pain Perception

Confounding Factors: ? Race

- **African Americans rated the thermal stimuli as more unpleasant and more intense than whites**

- Resting systolic BP was related to pain ratings
- There was a trend for women to rate the thermal stimuli as more unpleasant and more intense than men
- These sex differences were explained, at least in part, by differences in resting systolic blood pressure

Gender Differences in Pain Perception across Cultures: Hong Kong Chinese

- Women had
  - Lower threshold ($p < .001$)
  - Lower tolerance ($p < .001$) for pressure pain
  - Reported more pain ($p < .01$) at the pain tolerance level.

- Higher trait anxiety scores were associated with higher pain report in men only ($r [89] = .22, p = .04$).

**Results:** gender differences in pain perception exist among the Chinese population in Hong Kong

General Differences

- Painful experimental stimuli are generally reported to produce a greater intensity of pain in women than in men.
- Clinical pain is often reported
  - With higher severity and frequency
  - Longer duration
  - Present in a greater number of body regions in women than in men

Factors Contributing to Gender Difference in Experiencing Pain

- **Stimulus specific**: type, timing & spatial aspects of the stimulus

- **Biological factors**
  - Quantitative as well as qualitative differences in the endogenous pain inhibitory systems have been implicated
  - Neural differences: differences in receptor populations or pain neuromodulators
  - Influence of gonadal hormones

- **Psychosocial factors**
  - Sex role beliefs
  - Pain coping strategies
  - Pain related expectancies

- **Exposure to repeated painful visceral events** (e.g. menses, labor) during life may contribute to an increased sensitivity to, and greater prevalence of, pain among women


Stimulus Variables

- **Thermal**
  - Show greatest variability
  - Rate of rise in temp determines which type of fiber is evoked
  - Slow rates of temp. rise evoke C-fiber responses, faster rates evoke Aδ fibers.
  - Sex differences in heat pain are more robust when threshold is determined via the method of levels with a slow rate of rise\(^1\)
  - Sex differences in pain threshold and tolerance are more frequently observed when C fibers are evoked\(^2\)

- **Pressure:** sub maximal tourniquet test (ischemia)
  - ↑ lactate & K+ → peripheral nerve ending activation
  - Stimuli may also cause nerve damage → release of neuromodulators: prostaglandins, histamine serotonin, bradykinin, leukotrienes & substance P
  - Gender affects synthesis and/or release of some of these factors (e.g. substance P\(^3\))
  - Stimulus method per se may not be as important in determining gender differences, as the stimulus-specific elicitation of neuronal/non-neuronal events, such as neurotransmitter release


Sex-role Expectations...

- Sex-role expectations begin in childhood: Boys are expected to be “heroic and uncomplaining”; girls are encouraged to show “emotions” = dissimilar environmental clues
  - ♂ willingness to report pain as adults

However:

- Women are more susceptible to both acute and chronic pain and suffer greater pain with the same objective pathology

Pupillary Response to Pressure Pain

- **Methodology:** 20 subjects exposed to 4 levels of tonic pressure to fingers. Pain threshold, tolerance and pupillary dilatation were measured.
- No differences (male vs. female) at low pressure levels.
- Females showed at high pressure:
  - Greater pain (verbal scale).
  - Greater pupillary dilatation.
- **Authors conclusions:** “pain perception using an autonomic indicator – pupillary dilation - beyond voluntary control suggest that these differences reflect low-level sensory and/or affective components of pain rather than attitudinal or response-bias factors.

Psychological Factors

- Women utilize health care service more than men: attend to pain more readily and manage pain more aggressively than men\(^1\)
- Anxiety & depression may ↑ pain severity, esp. in ♀\(^2\)
- Paradox:
  - Depression & anxiety thought to be caused by relative deficiency of 5-HT
  - 5-HT is a pain producing neuromodulator
  - 5-HT uptake inhibitors (antidepressants) successfully used as analgesic adjuncts in pain therapy.

\(^{1}\text{Unruh Am. Why can’t a woman be more like a man? Behav Brain Sci 1997; 20: 467-68.}\)

Neural Differences...

- **Premise:** nociceptive excitatory activity (ascending) is balanced by inhibitory activity (descending) (at both physiological and psychological levels)
- **Women suffer more painful conditions**
- **Postulate:** Variability in pain sensitivity may be due to sex differences in the descending inhibitory pathway

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1 Berkley KJ Sex differences in pain (Review), *Behav Brain Sci* 1997; 20:371-80
...Neural Differences

- **Testing** via stress-induced analgesia (SIA)
  Exposure to stress prior to noxious stimulation
  expect $\downarrow$ pain sensitivity $^1$

- **Results:**
  - Female rodents display lower levels of SIA than males$^2$
  - Quality of endogenous analgesia differs
    - ♂ higher level of opioid mediated analgesia than ♀$^2$
    - In ♂ mice non-opioid mediated paradigms are mediated via NMDA receptors$^3$
    - ♀ mice exhibit naloxone and NMDA antagonist insensitive$^4$

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$^2$Romero MT, Bodnar RJ. Gender differences in two forms of cold water swim analgesia. *Physiol Behav* 1986; 37: 893-97


Sex Hormones

- Some pain syndromes are aggravated by exogenous hormones (TMJ)\(^1\)

- Endogenous sex hormones alter some pain syndromes
  - Fibromyalgia\(^2\)
  - Rheumatoid arthritis\(^3\)
  - Irritable bowel syndrome\(^4\)


Menstrual Cycle Variation in Pain Perception:

Meta-analysis of 16 published studies examined relationship between experimentally induced pain and menstrual cycle phase in healthy females

- During follicular phase (lowest progesterone levels) human females exhibited highest pain threshold and the greatest tolerances to pain (except electrical pain, highest in luteal phase)1

- Contrast to rodents where injection of progesterone resulted in deep anesthesia


Other Biological Differences

• Sex hormones influence sensitivity to noxious stimuli: pain threshold and tolerance vary with the stage of the menstrual cycle
• Imaging of the brain show differences in men/women in the spatial pattern and intensity of response to acute pain.
• Mu-receptors in the healthy female brain are activated differently than in healthy males
• Melanocortin-1 receptor gene is different in each sex and mediates response to kappa-opioids.

What Genes/Proteins have been Implicated in Sex Differences in Pain/Analgesia?

1. Estrogen Receptor
2. Mu/Kappa/Delta Opioid (MOR, KOR, DOR) Receptors
3. GABAA Receptors
4. N-methyl-D-aspartate (NMDA) Receptor
5. Melanocortin-1 Receptor (MC1R)
6. Orphanin FQ/Nociceptin (OFQ/N) Receptor
7. Protein Kinase A/C
8. G-protein coupled Inwardly Rectifying Potassium Channel (GIRK2)
9. Acid Sensing Ion Channel (ASIC)
10. Alpha-2-Adrenergic Receptor

IASP Fact Sheet: Sex Differences in Pain – Basic Science Findings, Sept. 2007
Gender Differences in Brain Activation
PET Study of Brain Activation by Heat..

Methodology:

Normal right-handed subjects were asked to discriminate differences in the intensity of innocuous and noxious heat stimuli to the left forearm.

Results:

Both ♂ & ♀ rated 40° C as warm but not painful.

Both rated 50° C as painful, but ♀ rated 50° C significantly more intense than did ♂.

PET Study of Brain Activation by Heat

- Both showed bilateral activation of premotor cortex and the posterior insula, anterior cingulate cortex and the cerebellar vermis.
- Females had significantly greater activation of the contralateral prefrontal cortex and of the contralateral insula and thalamus.
- Pain related differences may be due to gender, perceived pain intensity or both.

PET Scans in IBS based on perceived rectal distension

- The female brain showed greater activity in limbic regions, which are emotion-based centers. In men, the cognitive regions, or analytical centers, showed greater activity.

- Study of volunteers demonstrated
  - *Anticipation of the pain generated the same brain responses as the actual pain stimulus.*

Some Differences in How Men and Women Experience Pain...

A 2003 UCLA study of people with irritable bowel syndrome shows that different parts of the brain respond to pain depending on a person’s sex.

In the men, some of the cognitive regions, or analytical centers, showed greater activity. Here, the prefrontal cortex is activated, leading to the mental labeling, judging and categorizing of pain.

Some differences in how the brain is ‘wired’:
- Male and female hippocampi differ in their anatomical structure, neurochemical makeup and reactivity to stressful situations.
- The amygdala in each hemisphere functions differently in men and women.

In men experiencing pain, the right amygdala is activated. It has more connections with regions of the body involved with responding to the external environment, like the visual cortex.

In women experiencing pain, the left amygdala is activated. It has more connections to regions whose activity relates more to the internal functions of the body, such as the hypothalamus.
Gender Differences in Endogenous Mu-Opioids...

- Methodology:

  Study participants were scanned as they received a pain-causing but harmless injection of salt water in their jaw muscle. (Simulates TMJ pain)

  Study 1:

  - 14 ♂ scanned before and during jaw pain showed increases in endorphin release in certain brain areas during the painful state

  - Most of the 14 ♀ studied actually showed a reduction in endorphin release.

  - The ♀ reported feeling more intense pain, and more pain-related negative emotions, than the ♂.

  All the ♀ were studied at a time in their menstrual cycle when levels of estrogen and progesterone were lowest.

Endogenous Mu-Opioids

Study 2:

- Women were scanned once during their early follicular phase, and again during that same phase in another month - after they had been wearing an estrogen-releasing skin patch for a week.
- The patch made their levels of estrogen rise to levels normally seen during later parts of the menstrual cycle. (Allowed estrogen's effect to be studied without the effects of other hormones, such as progesterone, that normally increase along with it.)

Instead of the low or absent activation of the mu-opioid system seen in women during low-estrogen conditions, the same women under high-estrogen conditions showed a marked increases in their ability to release endorphins and activate the receptors.

Results similar to men!

The colorful areas in these brain scans show the areas of the brain where higher estrogen levels made a difference in the availability of mu-receptors.

Biological Differences: Rodent Studies

- Females more sensitive to noxious stimuli and have lower levels of stress-induced analgesics
- Male rodents have stronger analgesic response to mu opioids
- Transgenic mice show males a higher level of activity in the endogenous analgesic system

Mu Opioid Analgesics

- Mu opioid agonist were more potent in one sex than another, but SPECIES specific.
  - Mice & rats: ♂ > ♀
  - Humans: ♀ > ♂

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<tr>
<td>Human</td>
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<td>4 (29%)</td>
<td>10 (71%)</td>
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Possible Mechanisms Underlying Sex Difference in Mu Opioid Analgesia

• Pharmacokinetics: Opioid metabolism
  – Rodents\(^1\): sex difference in ratio of M-3-G to morphine
  – Human\(^2\): M-3-G/Morphine = in \(\sigma\) & \(\varphi\)

• Pharmacodynamics (opioid receptor density, in affinity of opioids for opioid receptors or in opioid receptor-mediated signal transduction)
  – Ex: PET scan showed women of reproductive age had greater mu opioid receptor binding\(^3\)

Dental Pain Model: Tooth Extraction

- **Methodology:** Extraction of third molars by the same surgeon; evaluation of effectiveness of analgesics on post-surgical pain

- **Results:** *Kappa opioids* (pentazocine*, nalbuphine* and butorphanol*) eased pain better in women than men

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* All of these agents are mixed agonist-antagonists and act at both kappa and mu-receptors

Kappa-Opioids: Why the Differences in Response

- Multiple mechanisms may explain sex differences in opioid analgesia:
  - Gonadal hormonal effects
  - Pharmacokinetics
  - Pharmacodynamics
  - Genetic influences
  - Balance of analgesic/antianalgesic processes
  - Psychological factors

- Disparity of results obtained from different pain models
  - Animals versus humans
  - Clinical pain versus experimental pain in humans
  - Suggests that the models themselves are mechanistically different

Kappa-Opioids: Why the differences in Response?

• Disparity of results obtained from different pain models
  – Animals versus humans
  – Clinical pain versus experimental pain in humans

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Case Study: Gender Differences in Side Effects

32 yr. treated 4-5 yrs for fibromyalgia and chronic low back pain (Worker’s Compensation) with multiple modal therapy including physical therapy, ultrasound, counseling, acupuncture and NSAID and opioid (ibuprophen 400mgs q8h and morphine SR 60 mgs q8h)

Presented with infertility to her family doctor. Hx of scant, sporadic periods beginning about 3 yrs ago; menstruation cessation for 4 months. Laboratory results: normal except for low HB (95), low FSH and LH and high PR.

↑ Prolactin
- ? Anterior pituitary adenoma

Sex differences in (side) effects of opioids other than analgesia may limit their therapeutic use!
Gender Differences in Over-the-Counter Medication Usage…

- Women who take OTCs for pain are more likely than men to take these medications often
- Men are more likely than women to admit to risky attitudes or behaviors
- Men are less likely to worry about potential side effects

Humphrey Taylor: Over-The-Counter Pain Medications sponsored by the National Consumers League, Harrisinteractive market Research
When reading the labels on their OTCs, women tend to be more thorough than men, although both genders fail to adequately read the entire label.

Gender Differences in Over-the-Counter Medication Usage…

Humphrey Taylor: Over-The-Counter Pain Medications sponsored by the National Consumers League, Harrisinteractive market Research
Gender Differences in Over-the-Counter Medication Usage…

Furthermore, men are more likely than women to say that they don’t have to worry about serious side effects – as long as they follow the label.

As long as I take the recommended dose, I don’t think there are any serious risks of stomach, kidney, or liver damage associated with over-the-counter pain medicines.

Humphrey Taylor: Over-The-Counter Pain Medications sponsored by the National Consumers League, Harrisinteractive market Research
Men are more likely than women to think that it is “okay” to mix medications.

If taken according to the directions, it’s okay to take an over-the-counter pain reliever while taking an over-the-counter product for cold or sinus condition.

Base: All respondents
Psychological Factors & Pain Perception

- Influenced by personality, emotional state, and socialization factors
- Chronic pain
  Patients perceive thermal stimuli normally but find these stimuli less unpleasant
- Emotional state:
  - Depression has been related to pain perception: ex.: a relationship between depressed mood and the perception of anginal pain during exercise treadmill testing
  - Anxiety state levels have been found to correlate with pain tolerance

4 Wall PD. On, the relationship of anxiety to pain. Pain 1979; 6: 253–64.
Chronic Spinal Pain

- **Opioid use** was associated with greater self-reported disability and poorer function in both women and men.

- Opioid use with affective distress: The women using opioids showed lower affective distress, whereas the opioid-using men reported greater affective distress.

- **Opioid use was not associated with pain severity**, although the women reported greater pain than men.

Pain Related
Health Care Use and Disability$^{1,2}$

- Health Care:
  - Women (♀) are more likely to seek health care for pain than men (♂) are,
  - Result: a high proportion of women in many pain treatment settings.
  - Reason: The higher rate of treatment seeking among women may be due to the fact that pain is often more severe for women than for men.

- Employment disability:
  - It is unclear whether women or men are more likely to experience employment disability associated with pain conditions; numerous factors such as type of work and family responsibilities influence employment disability rates.
  - When disability is defined in terms of limitations in activities of daily living as well as work absence, women have higher rates of pain related disability.

- School: Although rates vary across populations, a median of about 20% of girls report missing school days due to dysmenorrhea.

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