Sex Differences in Pain Perception & Treatment

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SO CLICHÉ!
NOT NICE!
MAYBE ACCURATE BUT SEXIST!?!
Objectives

- Why is this concept important?
- Discuss differences in prevalence, perception, severity of pain between sexes & genders
- Explore how sex can influence pain treatment
  - Both scientifically and clinically
- Discuss differences in how pain patients are perceived based on the sex of the pain provider
**WHAT ARE THE UPDATES?**

1. **UPDATES TO RESEARCH STRATEGY GUIDANCE**
   - The research strategy is where you discuss the significance, innovation, and approach of your research plan. Let's look at an R01, for example:
   - The new research strategy guidelines require that you:
     - State the strengths and weaknesses of published research or preliminary data crucial to the support of your application
     - Describe how your experimental design and methods will achieve robust and unbiased results
     - Explain how biological variables, such as sex, are factored into research design and provide justification if only one sex is used

2. **NEW ATTACHMENT FOR AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES**
   - From now on, you must briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies.
   - These include, but are not limited to:
     - **Cell lines**
     - **Specialty chemicals**
     - **Antibodies**
     - **Other biologics**
   - Standard laboratory reagents that are not expected to vary do not need to be included in the plan. Examples are buffers and other common biologicals or chemicals.
   - **DO NOT** put experimental methods or preliminary data in this section.
   - **DO** focus on authentication and validation of key resources.

3. **NEW REVIEWER GUIDELINES**
   - Here are the additional criteria the reviewers will be asked to use:
     - **Is there a strong scientific premise for the project?**
     - **Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?**
     - **Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed?**
   - Reviewers will also be asked to comment on that new attachment (see Update 2!!)
Incorporation of Sex as a Biologic Variable in NIH Research

Consider
Design studies that take sex into account, or explain why it isn’t incorporated

Collect
Tabulate sex-based data

Characterize
Analyze sex-based data

Communicate
Report and publish sex-based data

Do you mean sex or gender?

**SEX**

**GENDER**

<table>
<thead>
<tr>
<th>GENDER IDENTITY</th>
<th>GENDER EXPRESSION</th>
<th>GENDER PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>(How you feel on the inside)</td>
<td>(How you present yourself to others)</td>
<td>(How the world sees you)</td>
</tr>
<tr>
<td>MAN (FTM)</td>
<td>ANDROGYNOUS / NON-BINARY</td>
<td>MAN</td>
</tr>
<tr>
<td>GENDERFLUID AND TRANS*</td>
<td>MASCULINE</td>
<td>TRANSGENDER / GENDERQUEER / NON-BINARY</td>
</tr>
<tr>
<td>TRANSGENDER / GENDERQUEER / NON-BINARY</td>
<td>FEMININE</td>
<td>WOMAN (MTF)</td>
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</table>

*Note: Trans* refers to transgender.
Sex Differences in Pain Prevalence

- Pain is more prevalent in females
- Many pain syndromes only occur in women
- A majority of pain conditions in both sexes are more prevalent in women

Sex Differences in Pain Severity

- Some studies show that women report greater subjective pain severity than men
- Some studies show that no differences exist between sexes
- Potential for bias
  - Less severe pain under-represented
  - Sex differences in pain treatment and effectiveness

- Women report higher subjective severity of pain in acute pain settings
- To explore further, objective pain thresholds have been investigated

Bartley EJ and Fillingim RB. BJA. 2013.
Sex Differences in Experimentally Induced Pain

- Many modalities have been used for quantitative sensory testing (QST)
- Across most modalities in healthy adults women found to have more pain sensitivity than men

Modalities used:
- Mechanical
- Electrical
- Thermal
- Ischemic
- Chemical
- Temporal Summation
- Conditioned Pain Modulation

Bartley EJ and Fillingim RB. BJA. 2013.
Fig 1. Z-scores for multiple pain measures in a sample of healthy young adults (166 female, 167 male). Z-scores were computed such that the mean for the entire sample is 0. Higher Z-scores reflect lower pain sensitivity and lower Z-scores reflect higher pain sensitivity. Sex differences were statistically significant for all pain measures ($P < 0.05$); however, the effect sizes ranged from small to large (Cohen's $d$ in parentheses below), with a mean effect size in the moderate range ($d=0.62$). HPTH = heat pain threshold ($d=0.48$), Hpto = heat pain tolerance ($d=0.98$), IPTH = ischaemic pain threshold ($d=0.24$), IPTO = ischaemic pain tolerance ($d=0.52$), CPTH = cold pain threshold ($d=0.41$), Cpto = cold pain tolerance ($d=0.55$), PPTtrap = pressure pain threshold at the trapezius muscle ($d=0.90$), PPTmass = pressure pain threshold at the masseter muscle ($d=0.89$). Details regarding pain testing methods have been reported previously.\textsuperscript{25, 26}
Sex Differences in Experimentally Induced Pain

- Temporal Summation
  - Generally find that women have greater temporal summation of pain than men

- Conditioned Pain Modulation
  - Men display more intact inhibitory descending pain modulation → greater conditioned pain modulation than women
Mechanisms Underlying Sex Differences in Pain - Hormonal

- Sex hormones:
  - Estradiol and progesterone → pro- and anti-nociceptive
  - Testosterone → mostly anti-nociceptive
  - Low androgen levels → increased pain
    - Chronic opioid use lowers testosterone levels in males
    - Low androgen levels associated with anti-anabolic features of fibromyalgia

- Pain and the menstrual cycle
  - Increased sensitivity to most pain modalities (exception electrical)
    - During luteal phase compared to follicular phase

Mechanisms Underlying Sex Differences in Pain - Hormonal

- ↑ reports of back pain, TMD, migraine headaches at end of luteal phase
- FM patients report ↑ pain with menstruation onset or menopause
  - Importance of ↓ estradiol
- Exogenous estrogen:
  - Associated with ↑ pain related to TMD in cycling AND post-menopausal women
- Decreased estrogen availability:
  - Tamoxifen improved pain in women with cyclical mastalgia

Mechanisms Underlying Sex Differences in Pain - Hormonal

- Estrogen → analgesia OR hyperalgesia by modulating endogenous opioid system
- In ovariectomized mice – estradiol ↑ mu-opioid receptor protein concentrations, ↑ endogenous opioid peptides
- PET showed women in low estradiol state (early follicular phase)
  - Lower in vivo mu-opioid receptor availability
  - Corresponding to higher endogenous mu-opioid activation
  - Higher pain ratings, more negative affect
- High estrogen (HRT via patch) led to increased mu-opioid receptor availability and increased pain-related activation of endogenous mu-opioid neurotransmission

What about pregnancy-related analgesia?

- Gradual and steady increase in pain thresholds throughout late pregnancy
- Acute increase in pain thresholds right before delivery
Transgender changes in pain due to hormones

- Female-to-male transgendered chronic pain patients
  - Approximately half showed improvements in pain with testosterone treatment
- Much more research needed in this arena.

Summary of Hormonal Impact on Pain and Analgesia

<table>
<thead>
<tr>
<th>Hormonal milieu</th>
<th>Effects on pain state</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endogenous hormonal states</strong></td>
<td></td>
</tr>
<tr>
<td>Cycling women</td>
<td>End of luteal phase (premenstrual) vs other phases of the menstrual cycle</td>
</tr>
<tr>
<td></td>
<td>Premenstrual period</td>
</tr>
<tr>
<td></td>
<td>Onset of menstrual cycle</td>
</tr>
<tr>
<td>Postmenopausal women</td>
<td>Postmenopausal women compared to cycling women</td>
</tr>
<tr>
<td><strong>Exogenous hormone therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Cycling women</td>
<td>Cycling women administered exogenous estrogen</td>
</tr>
<tr>
<td>Postmenopausal women</td>
<td>Postmenopausal women administered exogenous estrogen</td>
</tr>
<tr>
<td></td>
<td>Estrogen replacement for postmenopausal women</td>
</tr>
</tbody>
</table>

Summary:
- High or low estrogen in cycling women tends to enhance pain.
- Testosterone generally improves pain and quality of life measures.
Mechanisms Underlying Sex Differences in Pain – Opioids

- Pharmacokinetics do not appear to underlie differences in analgesic effects.
- Many human studies have shown mu-opioids have increased potency in females.
  - Females have > MOR concentrations → ↑ response to mu agonists.
- Females greater analgesia to kappa opioids.

Mechanisms Underlying Sex Differences in Pain – Opioids

- Differences in receptor density, affinity, signal transduction
  
  - Women in high estrodiol/low progesterone state → ↓ pain sensitivity & ↑ brain mu-opioid receptor (MOR) binding
  
  - Low estradiol state → ↓ brain MOR binding/availability

Mechanisms Underlying Sex Differences in Pain – Pain Processing

- fMRI differences in CNS processing of painful stimuli and anticipation of pain stimuli
  - Varying regions of brain activated by pain
- fMRI of women on OCP with low androgen levels
  - Reduced activation of pain inhibitory regions (RVM)
- PET differences in pain-related opioid receptor binding
  - Reproductive age women ↑ mu opioid receptor binding
  - Regions activated vary between sexes
Psychosocial Mechanisms Underlying Sex Differences in Pain

- Pain coping strategies
  - Men → behavioral distraction & problem-focused tactics
  - Women → social support, emotion-focused, attentional focus, positive self-statements
- Catastrophizing & self-efficacy
Psychosocial Mechanisms Underlying Sex Differences in Pain

- Sociocultural beliefs
  - Masculinity vs femininity
- Exposure to stress in early life
- Abuse / domestic violence
- Family history
How Doctors Take Women's Pain Less Seriously

When my wife was struck by mysterious, debilitating symptoms, our trip to the ER revealed the sexism inherent in emergency treatment.

Is There A Gender Bias Against Female Pain Patients?

02/08/2017 02:24 pm ET I Updated Feb 09, 2017

Provider Bias Harms Women in Pain

February 23, 2017

The Gender Gap in Pain

By LAURIE EDWARDS MARCH 16, 2013

ENORMOUS GENDER AND ETHNIC BIAS IN PAIN TREATMENT

April 6, 2016 by Lynn Webster, M.D. — Leave a Comment
Sex/Gender Bias in Pain Treatment

- Gender bias can come from patients and/or providers
  - Can favor either gender
- Female pain MD more likely to prescribe pharmacologic therapy first line
  - No difference in provider in recommending more invasive treatment

- Physical attractiveness of patients
- Trustworthiness
- Undertreatment of pain in the absence of physical findings
  - Bias of female patients with “psychogenic pain”
  - Often prescribed sedatives over analgesics
Sex/Gender Bias in Pain Assessment and Treatment

- 154 health care professionals
- Rated:
  - Pain intensity & unpleasantness
  - Likelihood of administering
    - Nonopioid
    - Opioid
- Vignette: Low back pain > 1 year
- 32 patient profiles
  - Race, sex, age, pain expressions

Results

Sex/Gender Bias in Pain Assessment and Treatment

- Younger and middle aged practitioners
  - Rated females as having higher pain unpleasantness
  - More willing to prescribe opioid analgesics to female patients compared to older practitioners
- Female practitioners
  - More likely to recommend treatment with non-opioid analgesics compared to male practitioners
  - Non-opioids to black patients compared to white patients

Conclusion: patient and provider characteristics influence assessment and treatment of pain

Sex/Gender Bias in Pain Treatment

- Outpatient opioid use
  - Studies show both sexes being given more
    - Physicians more likely to provide opioids to patients of the same gender
  - VA study showed women got more short and long-acting opioids
  - Greater risk of polypharmacy and polypharmacy-related deaths in females → concurrent sedative use

- Emergency Room studies
  - Both sexes have been found to either be over or under-treated
  - Higher pain severity reported → more treatment? More potent opioids?
  - Oligoanalgesia and delayed analgesia in female abdominal pain ER patients

In general, studies seem to point to:

- Women being offered psychological or pharmacotherapy (opioids, sedatives, or both)
- Men being offered labs, physiotherapy, radiologic studies, surgery, analgesics
Females account for almost two-thirds of MPE rates.
Comments about KS PDMP data

- Difficult to know if this is a function of patient or provider.
- Patient
  - Are females seeking out multiple providers because...
    - Not being listened to or taken seriously
    - Being fired for being “untrustworthy”
    - Being undertreated
- Providers
  - Giving more opioids to females because of pain severity?
  - Providers not giving adequate treatment?
Closing Thoughts

- Research continues to be necessary
  - Patient and provider
  - Interplay of sex and gender
  - LGBTQ research
- More education in chronic pain management
- Gender/sex issues incorporated into pain medicine training
Supporting Women in Regional Anesthesia and Pain Medicine (WRAPM): Why You Should Join the Newest ASRA Special Interest Group

- Ratio of male to female anesthesiology residents in the U.S.: 2 to 1
- Ratio of male to female pain medicine fellows in the U.S.: 4 to 1
- Number of American adults reporting pain in the previous 3 months: 126 million
- Proportion of women among them: 5 out of 9
- Difference in average Medicare payments to female pain physicians compared to their male colleagues: -43.5%
- U.S. anesthesiology department chairs named "Michael" or "Robert": 15+
- U.S. anesthesiology department chairs who are women: 11
- Age of ASRA, in years: 42
- Number of Gaston Labat Award recipients: 43
- Number of female recipients: 2
- Most recent year in which a woman received the John J. Bonica Award: 2002
- Years since then that women have been awarded the Nobel Prize in Physiology or Medicine: 2004, 2008, 2009, 2009, 2014, 2015
- Number of women who have ever served on the ASRA Board of Directors: 6
- Number of female physicians currently serving on the ASRA Board: 1

Based on these data, the assessment is clear: women are underrepresented within regional anesthesiology and pain medicine, particularly in academic careers and leadership positions.

With the creation of the newest ASRA Special Interest Group (SIG), we intend to address this problem—together. Women in Regional Anesthesia and Pain Medicine (WRAPM) is a free SIG open to all ASRA members, men and women, interested in supporting and advancing the role of women in our subspecialties and medicine in general.
Thank you!
References