Pain and Pain Management in Women - The Impact of Sex and Gender

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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?

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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
Deaths from opioids increased 5 fold for women vs 3.6 times for men (1999-2010)

Percentage increase in deaths is higher for women (115% vs 85%)

ED visits related to misuse or abuse of opioids doubled between 2004 and 2010

Hospitalizations for opioid overdoses more frequent among women

MMWR July 5, 2013
Opioid Prescriptions

- Women are more likely to be prescribed opioids than men
- At higher doses for longer periods of time (this difference may be less, if controlling for expressed pain level)
- More likely to be prescribed opioids and benzodiazepines
Current Questions

- Are women (females) more likely to have pain?
- Is it perceived differently?
- Are they more likely to complain of pain?
- Are there differences in response to medications?
We’ve Been Here Before…

- Latter half of 19th century
- Limited ability to assess or treat sources of pain
- Patent remedies available without prescription
- Contained opioids used to treat adults and children (e.g., pain, diarrhea, “female complaints”)
- Up to 80% of opium users were women during late 1800s
- “Women were more prone to opium addiction because of their ‘more nervous organization and tendency to hysterical and chronic diseases’” (physician cited in Kandall)
What are Sex and Gender?
Institute of Medicine Report
2001

- Every cell has a sex
- Sex = genetic (gonadal) complement
- Gender = social interactions, available resources
- Both impact all areas of health
So Where Do We Start?
Sex and Gender-Based Differences: It’s Not Just Hormones

- Anatomy
- Physiology (especially immune system)
- Effect of sex hormones
  - local
  - systemic
- Environmental influences
- Women are more likely to have conditions that lead to pain
- Response to pain signals and opioids?
Chronic Pain

- Higher incidence in women, especially after menopause (e.g., low back pain, joint pain)
- Reflect higher incidence or progression of painful conditions?
- Are women more likely to seek care for pain?
- Differences in pain perception/sensitivity?
- Victims of ACE or more recent trauma (leading to pain-generating conditions, depression, changed pain perception?)
- Differing response to treatment?
Chronic Pain Conditions

Women
- Migraine
- Inflammatory conditions (e.g., rheumatoid arthritis)
- Osteoarthritis
- Neck pain
- Low back pain (DDD, stenosis)
- TMD
- IBD
- Fibromyalgia

Men
- Cluster headache
- Pancreatitis
- Ulcer
- Post-herpetic neuralgia
Osteoarthritis Sex/Gender Differences

Female/male OA per 100

- Radiographic
  - hand 9.5/4.8
  - feet 2.7/1.5
  - knee 1.2/0.4
  - hip 1.4/1.4

- Symptomatic OA
  - hand 8.9/6.7
  - feet 3.6/1.6
  - knee 13.6/10.0

CDC data
Sex/Gender-Specific Osteoarthritis Risk Factors

- Acquired injury patterns of overuse
- Inherent impact of estrogen muscle strength anatomy
Sex/Gender Differences in Pain and Opioid Use/Abuse

- Pain generators: objective
- Amount of pain perceived or complained of: more subjective
- Depends on perception of pain: may be sex-based
- Expression: may be gender-based (e.g., history of prior pain, depression, prior interactions with health care system)
- Treatment of pain: also depends on perceptions, prior experiences, and interactions with health care professional
Perception of Pain

- May be different between the sexes
- Anatomic differences (in rat models) in organization of brain circuits that process pain signals
- fMRI and PET imaging of brains different between men and women with chronic pain
- Are these differences primary, leading to increased risk of developing chronic pain or are they changes that occur as a result of chronic pain?
Women are more sensitive to other sensory input

- Heightened visual color discrimination (tend to have more retinal photopigments)
- Can be more sensitive to noise (adaptive?)
- Sensitive to temperature changes
- Increased tactile sensation (e.g., use of touch screens)
- Better sensory discrimination of pain?
Differences in Pain Perception

- Women are thought to be more “sensitive” to pain
- Research is challenging to interpret
- Typically use healthy subjects without prior pain
- Differ in their perceptions of pain?
- May lack decreased estrogen levels, seen in women with chronic pain
- Differences in estrogen status among women with chronic pain?
Human Models of Pain

- Experimental models of pressure, temperature, etc.
- No consistent sex-based results
- Depends on type of stimulus and study design
- Usually use healthy volunteers
- Do these results translate to typical pain-generating conditions? To people with chronic pain?
Pain studies in humans

- 122 articles retrieved and analyzed
- Suggested that females and males have comparable thresholds for cold and ischemic pain, while pressure pain thresholds are lower in F than M.
- Strong evidence that F tolerate less thermal (heat, cold) and pressure pain than M.
- Ischemic pain is comparable in both sexes.
- The majority of the studies that measured pain intensity and unpleasantness showed no sex difference in many pain modalities.
- “10 years of laboratory research have not been successful in producing a clear and consistent pattern of sex differences in human pain sensitivity, even with the use of deep, tonic, long-lasting stimuli, which are known to better mimic clinical pain.”

Racine et al 2012
Articles published between 1998 and 2008 were retrieved, analyzed, and synthesized. 129 articles examined various biopsychosocial factors that may contribute to differences in pain sensitivity between healthy women and men. The involvement of hormonal and physiological factors is either inconsistent or absent. The evidence to support less efficient endogenous pain inhibitory systems in women is mixed and does not necessarily apply to all pain modalities. "Depression may not mediate sex differences in pain perception, while the role of anxiety is ambiguous." Cognitive and social factors appear to partly explain some sex-related differences. Past individual history may be influential in female pain responses. "Some factors/mechanisms remain understudied in the field." "There is also a need to assess and improve the ecological validity of findings from laboratory studies on healthy subjects, and perhaps a change of paradigm needs to be considered at this point in time to better understand the factors that influence the experience of women and men who suffer from acute or chronic pain." Racine et al. 2012.
Animal Models of Pain

- Used to decrease impact of psychologic or societal/gender issues
- Animal studies (to control for the last 2) primarily among males
- Most have identified sex-based differences in pain response depending on modality

Hashmi et al
Differences in pain perception start early

- Study of pain perception with use of EEG in neonates with necessary procedures
- Female demonstrated more widespread brain activation than did males
- Similar differences not noted when only assessing touch
- Indicates that sex-based differences in pain perception are hardwired into brain function
- Lessens impact of gender noted in adult human studies
- Impact of changes in brain during development and other areas of maturation (e.g., production of sex hormones)

Verriotis et al 2018
The Role of Estrogen in Pain Perception
Testosterone

- Much easier....
- Primarily inhibits transmission of pain signaling pathways in the brain and spinal cord
Estrogen

- Receptors found in almost all cells/tissues
- Includes spinal cord and areas of the brain that perceive and interpret pain
- Studies have found that estrogen:
  - Increases response to pain (visceral pain)
  - Decreases response to pain (somatic pain)
  - Has no effect
- Depends on human vs animal model, reproductive/estrogen status of model, etc.
- Affects transmission of pain signals? Promotes signals to block this transmission?
- Increases or decreases pain in chronic pain conditions, in pre-menopausal women
- Data is even more mixed in post-menopausal women
Estrogen

- Serum levels tend to decrease in patients with chronic pain.
- Women using opioids chronically or with OUD have a higher incidence of amenorrhea and infertility.
- Are these related to side effects from the medications or reflect changes due to chronic pain?
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

- Sociocultural beliefs
  - Masculinity vs femininity

- Exposure to stress in early life

- Family history
Symptoms of Low Serotonin differ by sex
More common among women

- Women respond with sadness, withdrawal, low self-esteem
- Men more often display anger, aggression, impulsivity and substance abuse

Impact perception of pain?
Risk Factors for Opioid Use Disorder

- Daily dose >100 MME (morphine milligram equivalents)
- Long term use (>3 months)
- Depression
- History of abusing other substances (e.g., alcohol)
- Adolescents
Impact of Depression on Pain Perception?

- Meta-analysis of experimental studies investigating pain response in depressed participants versus healthy control participants using established pain outcome measures
- For high-intensity pain stimulation, overall pain tolerance was similar across depressed and control groups ($P = .71$, studies = 10)
- For low-intensity stimulation, a small, but statistically significant higher mean sensory threshold ($P = .01$, studies = 9) and pain threshold ($P = .02$, studies = 25) was observed in depressed participants, suggesting diminished pain
- Considerable heterogeneity in the direction and magnitude of effects was observed, indicating a likely condition-specific effect of depression on pain
- Subgroup analysis found that pain threshold/tolerance was increased in depression for cutaneous stimulation but decreased for ischemic stimulation, but that substantial heterogeneity remained
- Results provide some support for altered pain processing in depression, but suggest this link is dependent upon modality and additional, unidentified factors

Thompson et al 2016
30% for women, 16% of men report at least one episode of abuse or intimate partner violence during their lifetimes.

Opioid disorder (and binge drinking) significantly more common among women victims of IPV.

Cause or result of opioid use?

Self-medicating depression, PTSD, physical pain?

Depression and/or PTSD frequently not identified among pts with chronic pain.

Smith et al 2012
Sex/Gender Bias in Pain Treatment

- Gender bias can come from patients and/or providers
  - Can favor either gender
- Physicians more likely to provide opioids to patients of the same gender
- Female pain MD more likely to prescribe pharmacologic therapy first line
- 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-Based Differences in Opioid Response?

- Opioids act through mu and kappa receptors
- Post-mortem studies indicate higher mu opioid receptor density in women
- Hormonal status? Pain status?
- Estrogen increases or decreases density of mu receptors
- Kappa may be more significant for women
- Differences in response not clear
- Many studies indicate that morphine produces more and longer lasting analgesia in men
- Onset of pain relief may be faster in men
- Women may be more sensitive to respiratory depression
Animal Studies

- Rat thermal and inflammatory pain model (hindpaw withdrawal)
- Effect of morphine significantly greater among male rats
- Longer lasting relief in male rats

Wang et al 2006
Impact of Estrogen

- In animal models, estrogen decreases the number of mu opioid receptors available for binding.
- Could explain decreased opioid potency with high estrogen levels. OR
- Increases mu opioid receptor concentrations in ovarectomized mice.
- Male rat midbrains have a higher expression of mu opioid receptors than do female rats.
- Morphine suppresses activation of pain signaling pathways in males but not in females.
Sex-Based Differences in Humans

- Tolerance develops more quickly and at lower doses than seen in men.
- Longer time to onset—more likely to misuse?
- Due to increased number of opioid prescriptions (vs other inventions for men).
- Other factors that increase risk of abuse? (e.g., depression)
- Social acceptance of expressing pain?
- Seen at all ages (can contribute to cognitive issues in older adults).
Data from Kansas PDMP

Females account for almost two-thirds of MPE rates

Age-adjusted MPE Rate per 100,000 Population

- Female MPE Patients
- Male MPE Patients

<table>
<thead>
<tr>
<th>Year</th>
<th>Female MPE Rate</th>
<th>Male MPE Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan-Jun 2011</td>
<td>51.2</td>
<td>23.7</td>
</tr>
<tr>
<td>Jan-Jun 2012</td>
<td>63.4</td>
<td>28.4</td>
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Data Source: Kansas Board of Pharmacy, Kansas Tracking and Reporting of Controlled Substance (2010-2012, 2015). Kansas population was based on the U.S. Census County Vintage 2015 post-censal estimate of the resident population of the United States by single year of age, bridge-race category and age-adjusted to the U.S. 2000 standard population. Credit: Images created by Iconarray.com, Risk Science Center and Center for Bioethics and Social Sciences in Medicine, University of Michigan. Accessed 2016-08-19. Comparison of indicators do not imply statistical significance. Each point estimate may include the same patients.
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 addressing prior pain generator or depression/PTSD?
Neonatal Abstinence (Withdrawal) Syndrome

- Result of in utero exposure to opioids (prescribed, illicit, for addiction treatment) and sudden withdrawal
- No clear correlation between amount of maternal opioid use and risk for NAS
- Can occur in 55-94% of newborns whose mothers were addicted to opioids during pregnancy
- Increase in incidence of at least 5 fold (2.8/1000 live births in 2004 to 14.4/1000 in 2014 - Winkelman et al Medicaid data)
- May be related to polysubstance use
- Diagnosis, measurement, and treatment not fully defined or standardized

McQueen et al 2016
NAS- Range of Presentations

- Impacts on metabolic, vasomotor, respiratory, GI, CNS systems (as in adults)
  - Fever
  - Yawning
  - Sweating
  - Increased respiratory rate
  - Projectile vomiting
  - Diarrhea
  - Poor feeding
  - Weight loss/failure to thrive
  - High-pitched crying
  - Tremors (seizures rare)
  - Irritability
  - Difficulty sleeping
NAS-Initial Outcomes

- Low birth weight
- Time spent in ICU
- Prolonged hospitalization (avg 17 days)
- Maternal-baby bonding issues

McQueen et al 2016
NAS- Longer Term Outcomes

- Less well-defined
- Motor deficits
- Cognitive delays
- ADHD
- Behavioral problems
- Ophthalmologic issues (e.g., nystagmus)
- Failure to thrive
- Short stature
- Continued maternal substance abuse
NAS-Costs

- Related to
  - longer hospitalization (unknown outcome of outpt weaning)
  - ICU stay for some children
  - transfer to other hospital for care

- Initial costs among Medicaid patients (82% of NAS-related births in 2014), after adjusting for inflation
  - $65.4 million in 2004
  - $462 million in 2014

Winkelman et al 2018

- Improved access to substance use disorder treatment among younger women? Access to family planning for women of childbearing age using opioids or other substances or under treatment? Destigmatizing SUD so that women access treatment, contraception, prenatal care?
Summary of Sex/Gender Issues in Pain Treatment/Opioid Use

- In general, studies seem to point to:
  - Women being offered psychological or pharmacotherapy (opioids, sedatives, or both) at higher doses for longer periods of time
  - Impact of depression or prior/current abuse may not be addressed
  - Need better understanding of progression of pain generating conditions, pain, and opioid tolerance for both sexes
  - How do we deal with women of childbearing age? Pregnant women?
Thank you!!