Women and Opioids

- 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 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
Women’s Health

- “Wandering womb”
- 1843: Mechanism of conception clarified; previously, it was assumed that men created life and that women served as incubators
- Women’s health defined by adding female reproductive system to male model
“The principal causes of the diseases of women are:

1. Imperfect development of the sexual organs
2. Gonorrhea
3. Septic inflammation following childbirth
4. Lacerations due to childbirth
5. Miscellaneous causes, including constipation, erroneous habits of life, and errors of dress…”
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
Where are the Differences?

- Identified in all organ systems
- More than 200 conditions (so far)
- See in risk for diseases, etiology, prevention, presentation, response to treatment
- Differences in sex hormones are just the start....
Concussions

- Women report more prolonged symptoms after sports-related concussions.
- Differences in physiologic response (sex) vs pressure for male athletes to return to sport (gender)?
- Older women at higher risk of continued axonal loss, higher risk of post-concussion syndrome.
- Different long term symptoms: women- drowsiness, sensitivity to noise; men- amnesia, disorientation.
Ischemic Heart Disease

- High LDL risk factor in men, low HDL and high triglyceride risk factors in women
- Women more likely to present with fatigue, SOB, diaphoresis, N/V
- Women more likely to have unstable angina, microvascular disease
- Coronary angiography less diagnostic in women
Musculoskeletal System

- Anterior knee pain (syndrome)
- Hallux valgus (bunion)
- Osteoporosis (primary more common among women, secondary among men)
- Low impact fractures (vertebral compression fractures and back pain)
Musculoskeletal System

- Trochanteric bursitis
- Iliotibial band syndrome
- Morton neuroma
- Breast carcinoma metastatic to bone
- Adhesive capsulitis ("frozen shoulder")
- Low back pain
- ACL injuries
- Osteoarthritis (especially knee and 1st CMC)
Degenerative Disc Disease

- More common among women after menopause
- Progressive loss of disc space on MRI for the first 15 years after menopause in cohort with LBP
- Response to loss of estrogen (ER found on annulus)?
- Related to changing BMI?
- Related to BMD?
- Relationship to LBP?

Lou et al 2014
Spinal Stenosis

- Incidence increases with age for both men and women
- Plateaus in men at age 70
- Continues to increase in women over age 70
- Differing etiologies?
- Low back and/or LE pain
Degenerative Spondylolisthesis

- 4-5 times more common among women
- Hormonal influences?
- Pelvic morphology?
- Facet joint orientation?
- Low bone mass?
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
Joint Injury

- Significantly higher risk of OA in younger people after knee injury due to initial cartilage damage.
- Earlier among women than men with ACL injuries.

Roos Current Opinion in Rheumatology 2005
Hip OA: Anatomic Differences
Femoroacetabular Impingement

- Acetabular dysplasia higher in women
- Cam vs pincer
- Pincer more common in women
- Acetabular retroversion and/or overcoverage
- Repetitive impaction of acetabular rim and femoral head/neck leading to OA
Knee OA: Anatomic Risk Factors

- Large Q-angle
- Foot pronation
- Increased femoral anteversion
- Genu valgum
- External tibial torsion
- Tibia vara
- Patella alta
- Shallower femoral notch
- Narrower patella
Treatment Non-Surgical

- Women more likely to be treated in the 12 months prior to surgery with opioids, non-opioids, injections, and physical therapy.
- More rapidly progressive disease? Differences in pain perception? Usual modalities not as effective in women?

Bawa et al 2016
Metal Hypersensitivity

- Women had higher levels of pain after joint replacement
- Women had higher rates and severity of metal sensitization
- Cause of pain?

Caicedo et al 2017
Chronic Pain Conditions

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

**Men**
- Cluster headache
- Pancreatitis
- Ulcer
- Post-herpetic neuralgia
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?
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?
Sensitivity to Stimuli

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
Pain Studies in Humans

- 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

Hashmi et al
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
Psychology - Depression

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
Depression and Abuse/Violence

- Almost half were above the cutoff score for PTSD and almost 2/3 above scores for depression
- Only 7% of women, 31% a diagnosis of depression, and 3.6% had both diagnoses
- Either clinicians are not identifying these diagnoses or women are not bringing them up
- This impacts the ability to adequately treat chronic pain and to identify those early at risk for OUD

Wuest et al 2007
Abuse/Violence

- 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?

Smith et al 2012
OUD and Victimization

- 2 large national epidemiologic studies
- Opioid use disorders were positively associated with an increased risk of victimization in women
- This may indicate that opioid disorders increase the likelihood of victimization for women (e.g., financial, impacting relationships) or that victimization leads to opioid use for women (e.g., to self-medicate physical pain or depression) - which comes first?
- Female victims of PIV tend to experience more injury and psychological distress than men, which might account for the significant association of opioid use disorders and victimization among women but not among men

Smith et al 2012
Abuse/PTSD

- Research has documented a high incidence of comorbid posttraumatic stress disorder (PTSD) and substance abuse, including opioids.
- Women substance abusers, in particular, show high rates of this dual diagnosis (30% to 59%), most commonly deriving from a history of repetitive childhood physical and/or sexual assault.
- Rates for men are two to three times lower and typically stem from combat or crime trauma.
- Patients with both disorders are characterized by high severity on a multitude of psychological and treatment variables.

Najavits et al 1997
Abuse and PTSD

- May lead to chronic health conditions, including pain, through effects on:
  - inflammatory system
  - neuroendocrine system
  - hypothalamus-pituitary-adrenal axis
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/Gender Bias in Pain Treatment

- **Outpatient opioid use**
  - Studies show both sexes being given more
  - VA study showed women got more short and long-acting opioids
  - Greater risk of polypharmacy and polypharmacy-related deaths in females

- **Emergency Room studies**
  - Both sexes have been found to either be over or under-treated
  - Oligoanalgesia and delayed analgesia in female abdominal pain ER patients
Responses to Medications

- Differences in pharmacokinetics (related to body weight?) and pharmacodynamics
- Drug absorption, excretion, and bioavailability
- 8 of 10 medications removed from the market were removed due to unforeseen adverse reactions in women
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 ovariectomized 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)
Non-prescription Use

- 24 (12 men and 12 women) non-treatment seeking individuals at least 18 years of age with current (i.e., past 12 months) prescription opioid dependence

- Women were approximately six years older when they initiated prescription opioid use, but were only three years older when they began to use prescription opioids regularly (i.e., weekly), suggesting an accelerated course of dependence among women

- Women were significantly more likely than men to be motivated to use prescription opioids in order to cope with interpersonal stress

- Support other studies that have noted women become dependent on opioids more quickly than men

Back et al 2011
Opioids for Chronic Pain

- Issues with misuse, abuse, diversion
- 938,586 UDS from pts treated with opioids and/or benzo for chronic pain
- Males more likely than females to have illicit drug noted
- Women more likely to obtain non-prescribed opioids from family/friends
- Men are more likely to obtain these or other opioids from the street

- Couto et al 2009

![Graph showing urine test results in patients testing positive or negative for illicit substance(s)](image)
Females account for almost two-thirds of MPE rates

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?
Summary of Gender Bias in Pain Treatment

- 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 presentations differ so that men being offered physiotherapy, radiologic studies, surgery, analgesics?
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 | 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
Thank you!!