Sex Differences in Pain and Opioid Addiction

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Disclosures

• None
Questions

• Is there evidence for sex differences in brain pathways?
• Does pain perception differ between women and men?
• How does opioid addiction differ between women and men?
• What are the special issues affecting women with opioid addiction?
Key points: Brain, pain, opioid addiction

• Rate of opioid addiction in U.S. is higher in men than women, but rising more rapidly in women
• Sex differences in brain pathways and responses to hormones affect pain perception and sensitivity to opioids
• Women have more diseases associated with chronic pain and a greater sensitivity to painful stimuli
• Women are prescribed opioid analgesics more often than men
• Women get addicted when taking lower doses of opioids for shorter periods of time
• Women are more likely to obtain opioids from family or friends
• Childcare responsibilities may limit participation in treatment programs
• Pregnancy confers risk of neonatal withdrawal syndrome
What are opioids?

- Hydrocodone, oxycodone
- Oxymorphone
- Morphine
- Codeine
- Fentanyl
- Heroin
Dopamine Reward System
Drugs increase dopamine which triggers desire

Ventral tegmental area, dopamine production

Ventral tegmental area, dopamine production

Neurons stimulated by memories, eg memories of cravings and pleasure

Dorsal striatum, neurons help form habits by identifying enjoyable patterns

Amygdala, neurons stimulated by learned emotional responses such as memories of cravings and pleasure


From National Geographic
Jason Treat and Ryan Williams,
Art: Daniel Hertzberg,
Source: Kebt Berridge,
U Michigan

Connie Newman, MD
March 3, 2019
Rates for drug overdose deaths and drug misuse or abuse related ED visits among women in US 2004-2010


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Overdose rates for women: cocaine/heroin and prescription opioids U.S. 2010

National Vital Statistics System and Drug Abuse Warning Network


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Age adjusted death rates for drug overdose deaths (including prescription drugs) among women; US 2009-2010

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New York State: Number of opioid deaths


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Hospital discharges involving any opioid overdose in New York State counties 2012-2014
Ages 45-64 yrs
Crude rate per 100,000 population


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Sex differences in the brain affect sensitivity to pain and opioids

- Sex steroids (estrogen, testosterone) have nuclear and membrane receptors throughout the entire brain
- Receptors in neurons and glial cells
- Estrogen and testosterone have different effects on signaling pathways and gene expression
- Sex differences in mood, cognition, blood pressure regulation, motor coordination, pain sensitivity and opioid sensitivity are established by hormones and genetic factors


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Sex differences in CA1 steroid hormone receptor distribution

In females and males, nuclear and nonnuclear steroid receptors are found in different cell types and/or cellular location. Both F and M have membrane receptors on dendrites and dendritic spines. In F, estrogen receptors are in GABAergic neurons; in males androgen receptors are in pyramidal cell neurons. Estrogen receptors also exist on cholinergic (Ach) afferents.

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Pain model

Blue – sensory/discriminative lateral pain pathway (thalamus, SI, SII)

Orange – affective/motivational medial pain pathway (ACC, INS)

Green - one component of the cognitive/evaluative pain system (dIPFC).

Arrows show cortical connections between regions and systems

ACC anterior cingulate cortex, INS insula, dIPFC dorsolateral prefrontal cortex, SI primary somatosensory cortex, SII secondary somatosensory cortex

Monroe TB et al Biol of Sex Diff 2015; 6:25
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On average women reported higher pain scores for 47 diagnoses (>11,000 patients; 56% women)

Diagonal line represents average pain score difference of 1 unit between the sexes.


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Differences in pain scores between men and women (>11,000 patients)

Differences in pain scores between men and women (>11,000 patients)


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Women experience back and musculoskeletal pain more frequently than men

Each blue bar shows excess prevalence of pain in women reported in each study.

Data are self-reported, from large, general population studies (surveys or telephone interviews). Definition of pain varied by study, and included current pain, 1-12 month pain duration or chronic pain.

From Mogil, JS Nature Reviews Neuroscience 2012, 13:859-866

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Chronic Pain More Prevalent in Women

- Epidemiological data show more women than men have chronic pain
- Some chronic pain syndromes only occur in women
  - Endometriosis, menstrual pain
- Some common chronic pain syndromes that occur in both men and women, occur more often in women
  - Chronic fatigue, fibromyalgia, interstitial cystitis, temporomandibular disorder


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Experimental studies of pain sensitivity

- Experiments using various noxious stimuli (e.g., heat, pressure) - over 100 studies of sex differences
- Review of all studies show that women are more sensitive to pain than men
  - Although size of the effect is not clear
  - And some debate the clinical importance
- Study results have been variable, but when there are differences in women and men, these almost unanimously show that women compared to men:
  - Have a higher sensitivity and lower tolerance to pain
  - Report higher pain ratings
  - Have greater ability to discriminate among varying levels of pain


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Different pathways for opioid analgesia and hyperalgesia in rats

- NMDAR (NMDA type glutamate receptors) pathway used by males
- MC1R (melanocortin 1 receptor) pathway used by females
- Depending upon hormonal levels, females can access male pathways when their own is not working properly

NMDA N methyl D-aspartate


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Pain intensity varies across phases of the menstrual cycle

• Women have higher threshold for pain and therefore higher tolerance in the follicular phase $^1$
  - Except for electrical pain-higher tolerance in luteal phase $^2$

• Increased reactivity to pain peri-menstrually and mid cycle $^3$

$^1$ Sherman JJ and LaResche L. Am J Physiol Regul Integr Comp Physiol 2006; 291: R245-R246;

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How does pain in women relate to opioid addiction?

- Women experience pain more frequently than men (due to disease) and more intensely.
- Women are more commonly prescribed prescription opioid analgesic than men and at higher doses.
- Women become addicted to opioids when taking lower doses for shorter periods of time (telescoping).
Women more likely to be prescribed opioids for pain management

• Death rate for opioid pain reliever (OPR) overdose is higher among men than women

• However since 1993, hospitalizations for OPR overdoses are higher in women

• Compared to men
  o Women more likely to be prescribed OPR
  o Women more likely to use OPR chronically
  o Women more likely to receive higher doses of OPR


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Special issues for women with opioid addiction

- Depression, intimate partner violence associated with opioid addiction
- Caregiver responsibilities (children, elderly relatives) affect participation in treatment programs
- Risk of neonatal opioid withdrawal syndrome

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Neonatal drug withdrawal (abstinence) syndrome

- Drug withdrawal due to in utero exposure to opioids
- Hypertonia, autonomic instability, irritability, poor sucking reflex, poor weight gain
- Seizures less common
- 2001-2009 prenatal maternal opioid use increased 5 fold from 1.2 to 5.6 per 1,000 hospital births per year

Substance Abuse and Mental Health Services Administration, Advancing the Care of Pregnant and Parenting Women with Opioid Use Disorder and their Infants. Rockville Maryland, 2016


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Admissions to neonatal ICU increased 4 fold 2004 to 2013


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Opioid addiction in elderly women

• 40-50% of adults 65 and older report chronic pain disorder (11 countries Europe) \(^1\)

• US Patients 65 yrs and old, 23% women and 19% men take 5 or more prescription drugs

• The use of opioid prescriptions long term is greater in US women age 65 older then women < 65 and men in all age groups \(^2\)
  
  - Substance use disorders often unrecognized in people 65 and older

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CDC Guideline for prescribing opioids for chronic pain 2016

• Opioids are not first line or routine treatment for chronic pain
  o Combine with nonpharmacologic therapy and nonopioid pharmacologic therapy

• Establish and measure goals for pain and function

• Before treatment and periodically during treatment discuss benefits and risks and availability of non opioid therapies with the patient

• Evaluate risk factors for opioid harms

www.cdc.gov/drugoverdose/prescribing/guideline.html
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CDC Guideline for prescribing opioids for chronic pain-2

- Use immediate release opioids when starting
- **Start with lowest effective dose and consider benefits and risks of increasing dose**
- Prescribe no more than needed
- Do not use ER/LA opioids for acute pain
- Evaluate benefits/harms after 1 to 4 weeks or dose increase
- Continue to evaluate benefits/harms every 3 months or more frequently
- Reduce dose, or taper or discontinue when needed

www.cdc.gov/drugoverdose/prescribing/guideline.html

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CDC: assessing risk and addressing harms of opioid use

- Consider offering naloxone when high risk of overdose
- Check Prescription Data Monitoring Program for high dosages and prescriptions from other providers
- Urine drug testing as needed to identify prescribed substances and undisclosed use
- Avoid concurrent benzodiazepines
- Arrange treatment for opioid use disorder if needed

www.cdc.gov/drugoverdose/prescribing/guideline.html

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Pain management recommendations from CDC and Pain and Anesthesia Societies 2016

- Limit use of opioids for post operative pain
- When opioids prescribed use lowest effective dose, and short duration of treatment
- Consider non opioid alternatives including medications, physical therapy, exercise, cognitive behavioral therapy
- Educate patients about alternatives to opioids
- Reduce anxiety and depression which may accompany chronic pain and may cause women to use opioids


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US Surgeon General addresses importance of naloxone
September 2018

“I, Surgeon General of the United States Public Health Service, VADM Jerome Adams, am emphasizing the importance of the overdose-reversing drug naloxone. For patients currently taking high doses of opioids as prescribed for pain, individuals misusing prescription opioids, individuals using illicit opioids such as heroin or fentanyl, health care practitioners, family and friends of people who have an opioid use disorder, and community members who come into contact with people at risk for opioid overdose, knowing how to use naloxone and keeping it within reach can save a life.”

BE PREPARED. GET NALOXONE. SAVE A LIFE.

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AMWA Opioid Addiction in Women Task Force

Mission: to reduce the number of women addicted to opioids, and to improve the care of women with opioid addiction, by

1) Education of health care providers and the public about
   • Unique aspects of opioid addiction in women
   • Barriers to treatment for women
   • Sex differences in pain leading to addiction

2) Contributing to or commenting on draft opioid prescribing guidelines, pain management guidelines and evidence based standards

3) Dissemination of the specific needs of women in prevention and treatment of opioid addiction, and recovery services

4) Identifying knowledge gaps related to sex differences in pain and opioid addiction that would benefit from research, data and specific metrics


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AMWA Opioid Addiction in Women Task Force: Educational programs for HCPs address:

- Risks of opioid addiction in women, especially from prescription medications,
- Sex differences in pain that could lead to addiction
- Differences in care of women and men with similar conditions associated with pain (ex. Orthopedic procedures)
- Possible solutions such as using non-opioid alternatives to manage pain without having to compromise daily activities, and offering LARCs to reproductive age women with opioid addiction at the time of hospitalization (with Medicaid coverage)
- Need for training in medication assisted treatment with buprenorphine, methadone and other medications


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AMWA Opioid Addiction in Women Task Force:
Educational programs for the public:

• Administration of Naloxone
• Use of non-opioid alternatives (medications, physical therapy, acupuncture, and other non-pharmacological alternatives) for management of patients about addiction
• Education of women of reproductive age and pregnant women about opioid addiction and risks to the fetus


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HHS Meeting on Best Practices Pain Management Task Force, Sept 25-26, 2018

Recommendations from AMWA

1) Elimination of Pain control as a measure of quality of care as this drives increased prescribing of opioids

2) Education of providers, medical students and the public about
   - Sex-based differences in pain frequency and intensity,
   - Associated increased risk of addiction to prescription opioid analgesics in women, and
   - Benefits of non opioid alternatives, which include medications and other treatments – physical therapy, exercise, etc
   - Safe storage and disposal of prescription opioids

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3) Providers should be encouraged to speak with patients about all options for pain management, including non-opioid alternatives, in order to develop a treatment plan that provides optimal pain relief and function, with minimal risk.

4) Providers should be encouraged to assess women with chronic pain for depression and PTSD.

5) Discussions of family planning should be part of medication assisted treatment for addiction. Women who are treated for an overdose or addiction should be offered all options for contraception.
HHS report (draft Dec 2019) management of chronic pain
Unique issues related to pain management in women
(consistent with AMWA comments)

• Data & literature suggest “Women experience more pain than men, have higher sensitivities to painful stimuli compared with men, and report experiencing greater intensities in pain.”

• Some diseases associated with pain have a higher prevalence in women (endometriosis, migraines, abdominal and pelvic pain

• Gender differences in non-medical use and abuse of prescription opioids

• Research shows women more likely than men to use and abuse prescription opioids

• From 1999 to 2010, rate of increase in opioid-related deaths was higher in women vs men

• Women face unique pain management challenges in pregnancy and post partum


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HHS report (draft Dec 2019) Pain management

Recommendations for women

• Increase research to gain improved understanding of mechanisms driving sex differences in pain responses and mechanism based therapies that address these differences

• Raise awareness in public and health care areas to unique challenges women face during pregnancy and postpartum period, including various pain syndromes and psychosocial comorbidities

• Include OB-GYNs as part of multidisciplinary care teams because they are likely to play an important role in the treatment of pain for women

• Develop pain management guidelines for pregnant and postpartum women with national specialty societies

• Counsel women of childbearing age on risks of opioids and other medications in pregnancy, including risks to the fetus and newborns.


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Summary and Key points: Brain, pain, opioid addiction

- Rate of opioid addiction in U.S. is higher in men than women, but rising more rapidly in women
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- Women have more diseases associated with chronic pain and a greater sensitivity to painful stimuli
- Women are prescribed opioid analgesics more often than men
- Women get addicted when taking lower doses of opioids for shorter periods of time
- Women are more likely to obtain opioids from family or friends
- Childcare responsibilities may limit participation in treatment programs
- Pregnancy confers risk of neonatal withdrawal syndrome
Thank you

Please feel free to contact me
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Additional slides
Recommendations for reducing opioid use

• Educate providers and the public about non-opioid alternatives to pain
• Limit opioid use post operatively to lowest dose for shortest period of time
• Conversations between providers and patients about non-opioid alternatives, including medications, physical therapy, exercise, behavioral therapy for treatment of pain
• Remove extra opioid prescription bottles from medicine cabinets
• Increase reimbursement for non-opioid medications for use intra- and post-operatively
• Increase availability of naloxone and instructions for using it

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New York State: Opioid deaths per 100,000 persons


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Etiologies of differences in pain sensitivity in women and men

• Genes on X and Y chromosomes
  ○ In females one X chromosome is inactivated

• Mitochondrial genes from the mother

• Epigenetics (interaction between genes and experiences)

• Entire brain, not just hypothalamus, is affected by sex steroids which differ in women and men
Spinal Toll-like receptor 4 mediates allodynia in male but not female mice

Sorge RE Spinal cord toll-like receptor 4 mediates inflammatory and neuropathic hypersensitivity in male but not female mice J Neurosci 2011; 31 (43): 15450-15454

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Medication use in neonatal abstinence syndrome 2004-2013

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HHS 5 point strategy for opioid crisis 2018

1. Addiction prevention, treatment, and recovery services
2. Better data on the epidemic
3. Health, evidence based methods of pain management
4. Increased availability of overdose-reversing drugs
5. Cutting edge research on pain and addiction

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Sex hormones act in the brain

- Sex hormone receptors found in nuclei and near cell membranes and associated with presynaptic terminals, mitochondria, post-synaptic densities
- Effects on signaling pathways in many areas of the brain
- Direct and indirect effects on gene expression

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Estrogen plays a role in synapse remodeling in hippocampus, and remodeling varies across estrus cycle.


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Sex differences in pain pathways occur in younger and older adults

• Neuroimaging studies in younger adults show sex differences in processing of painful stimuli. These differences may contribute to disproportionate pain in women

• One study in 12 cognitively healthy older women and 12 cognitively healthy older men, age 65-81, median 67
  o Compared to men, women reported feeling mild and moderate pain at a lower stimulus intensity (greater pain sensitivity) but did not report pain was more unpleasant
  o Increased sensitivity to mild pain in older women was associated with less brain deactivation in specific pain regions

Monroe TB et al Biol of Sex Diff 2015; 6:25
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Estradiol enhances motivation to obtain cocaine in rats

Becker JB and Hu M. Front Neuroendocrinol 2008; 29: 36-47

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