Pain, Sex, Sleep
03/27/19

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Aims

• Provide a brief overview of the burden of chronic pain,
  – highlighting sex differences in pain prevalence and sensitivity

• Describe background on insomnia as risk factor for chronic pain
  – highlighting that sex may interact with insomnia to increase risk for chronic pain.

• Discuss sleep deprivation literature showing that sleep disruption and loss increase pain sensitivity

• Present new data on how sleep disruption may differentially impact pain modulation in women to increase risk for chronic pain
# Public Health Impact of Chronic Pain

**Years Lived with Disability (YLDs)**

<table>
<thead>
<tr>
<th>Diseases and Injuries</th>
<th>YLD Rank</th>
<th>No. of YLDs (In Thousands)</th>
<th>Median Change, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low back pain</strong></td>
<td>1 (1-3)</td>
<td>2538.00 (1771.4-3427.2)</td>
<td>24.9 (13.8 to 38.4)</td>
</tr>
<tr>
<td><strong>Major depressive disorder</strong></td>
<td>2 (1-5)</td>
<td>2142.50 (1525.2-2843.7)</td>
<td>42.7 (9.2 to 83.3)</td>
</tr>
<tr>
<td><strong>Other musculoskeletal disorders</strong></td>
<td>3 (1-4)</td>
<td>2024.40 (1664.7-2311.9)</td>
<td>28.5 (18.9 to 38.9)</td>
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<td><strong>Neck pain</strong></td>
<td>4 (2-6)</td>
<td>1652.70 (1151.0-2296.4)</td>
<td>29.1 (17.4 to 41.1)</td>
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<td><strong>Anxiety disorders</strong></td>
<td>5 (2-6)</td>
<td>1541.00 (1078.5-2172.8)</td>
<td>21.3 (4.7 to 39.5)</td>
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<td><strong>Chronic obstructive pulmonary disease</strong></td>
<td>6 (4-9)</td>
<td>1304.10 (761.3-2007.2)</td>
<td>34.1 (4.6 to 70.9)</td>
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<td><strong>Drug use disorders</strong></td>
<td>7 (6-10)</td>
<td>996.9 (722.3-1337.9)</td>
<td>29.8 (6.5 to 58.6)</td>
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<td><strong>Diabetes</strong></td>
<td>8 (7-15)</td>
<td>747.7 (506.1-1059.3)</td>
<td>56.2 (38.4 to 74.8)</td>
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<td><strong>Osteoarthritis</strong></td>
<td>12 (8-19)</td>
<td>637.6 (393.1-972.0)</td>
<td>56.1 (28.3 to 88.3)</td>
</tr>
<tr>
<td><strong>Asthma</strong></td>
<td>9 (7-19)</td>
<td>769.3 (418.1-1229.5)</td>
<td>21.2 (11.5 to 31.6)</td>
</tr>
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</table>

Sex Differences in Clinical Pain:

- Females have higher rates of most chronic pain disorders

- Is this because men go to the doctor less or are less willing to report pain symptoms?
Females demonstrate increased pain sensitivity on laboratory measures of pain threshold and tolerance.

Meta-Analysis: Results from studies of mechanical, thermal, electrical, and ischemic pain (n > 40,000 for studies of pain tolerance). Virtually no studies find lower pain threshold or tolerance among males.

Riley et al., 1998, *Pain*
Response Bias or Physiological Differences Between the Sexes?
Sex differences in pain expression in newborns

65 neonates undergoing capillary puncture; behavioral responses coded using the neonatal facial coding system.

Adapted from Guinsburg et al., 2000. “Differences in pain expression between male and female newborn infants” In: *Pain*
Insomnia and Chronic Pain are Comorbid Public Health Epidemics:
Both Differentially Impact Females

Chronic Insomnia
10-15%

Chronic Pain
11.5-55.2%

50% - 88%

O.R. = 1.41 for females to males (Zhang et al. 2006)

Insomnia X Age X SEX

O.R. = 1.44-2+ for females to males (Lamerato et al. Pain Prac, 2015; Catala EJP 2002)

Atlanta School of Sleep Medicine
How Are Sleep and Pain Inter-related?

1) Traditional Linear View

PAIN → AROUSAL → Sleep Disruption

2) Reciprocal View: Moldofsky’s Paradigm Shift

(Moldofsky, 1975); Replicated in women Lentz and Landis (1999)

- Multiple Forms of Sleep Deprivation ↑ Pain Sensitivity
  (e.g., Roehrs et al. 2006; Kundermann 2004; Haack 2005; Ablin & Clauw 2006; Smith et. al. 2007; onen 2001)

- Sex Differences Largely Ignored (Small Ns)
What do the longitudinal clinical data show?

• At least 5 prospective epidemiological studies controlling for psychosocial risk factors show that over 1-3 years poor sleep [Gupta (2007); Mikkelsson (1999); Bonvanie (2016); Sanders (2016); Harrison (2014);] Smith et. al. (2008)

  1) Confers 2-3 fold risk of new onset chronic pain (pain free to start)
  2) Linked to persistence and progression of emergent musculoskeletal pain
  3) Predicts progression from regional to widespread pain disorder

• Restorative sleep linked to 3- fold pain remission rate [Davies (2008)]

• Effects of poor sleep on developing chronic musculoskeletal pain and pain severity are more pronounced in females (Bonvanie (2016) ; Zhang (2012))

OPPERA Study (N=2453)
Sanders, Maixner, et al., JOP, 17(6) (2016)
How does sleep disturbance increase risk for chronic pain?

Does it alter central pain modulation?

- Sleep and pain systems share overlapping neurobiology
- Does sleep disturbance alter descending pain modulatory systems associated with Central Sensitization and chronic pain pathophysiology?

1) Pain Inhibition (Conditioned Pain Modulation)
2) Pain facilitation (Temporal Summation)

DeLeo, 2006
Higher Order Measures of Pain Inhibition

Conditioned Pain Modulation (aka DNIC)

• “Pain inhibits pain”
• Simultaneous application of 2 noxious stimuli
  - Phasic (Pressure Pain Threshold—algometry)
  - Conditioning stimulus administered at distant site
    • Cold pressor task: 45 secs (contra lateral side)
• ↑ Pain threshold (↓ pain sensitivity) during tonic painful stimulus from baseline
• Supraspinally mediated inhibition of wide dynamic range neurons in dorsal horn (LeBars, 1992)
  - Cervical transection studies
• Meditated by endogenous opioids? (blocked by naloxone)
  • Willer, 1990; Julien N, 2006; Anderson; 2002
  • Not simply distraction—thalamic lesion (Broucker, 1990)
Impaired CPM Is Associated with Several Chronic Pain Disorders and Predicts Development of Post Surgical Pain

- **Fibromyalgia (FM)**
  - Luatenbacher, 1997
  - Kosek & Hansson, 1997

- **Temporomandibular J / D (TMD)**
  - Maixner, 1995
  - Kashima, 1999

- **Irritable Bowel Syndrome**
  - Wilder-Smith, 2004

- **Low Back Pain**
  - Peters et al., 1992

- **Tension headache**
  - Pielsticker, 2005

THE ABSENCE OF CPM

- CPM predicts chronic post surgical pain [Wilder-smith J. of Pain & palliative care pharma (2010); Granovsky, current pain and headache (2013)]

Sex Differences in Pain Inhibition (CPM):

The Nociceptive Flexion Reflex (RIII) Test:

polysynaptic spinal reflex elicited by electrical stimulation of the sural nerve. It can be supraspinally modulated, but is considered a measure of spinal nociceptive processes.

- Generally, Males demonstrate greater pain inhibitory capacity (CPM) (Bartley & Fillingim, BJA, 2013)

Adapted From: Serrao et al., 2004. In: Pain
Does Sleep Fragmentation and/or Sleep Restriction Alter CPM?

Insomnia Analogue (sleep continuity disturbance)
Forced Awakening Sample Timeline- 8 Hour Period

<table>
<thead>
<tr>
<th>PM</th>
<th>10:00-11:00</th>
<th>11:00-12:00</th>
<th>AM</th>
<th>12:00-1:00</th>
<th>1:00-2:00</th>
<th>2:00-3:00</th>
<th>3:00-4:00</th>
<th>4:00-5:00</th>
<th>5:00-6:00</th>
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= 20 minute block of time during which participants are kept awake

Total Possible Sleep Time = 280 minutes

Smith et al., Sleep, 2008
Results: CPM (Pain Inhibition) in women

Sleep Fragmentation, But Not Sleep Restriction Impairs Endogenous Pain Inhibitory Processes

Replication of FA finding in 11 Women with ischemic pain (Iacovides et al. JOP, 2017)

Replication of RSO finding

Matre et al. 2016; EJP (n=22; male and female)

• 2 nights of RSO improved CPM
Are the Effects of Sleep Loss on Pain Inhibition / Sex Dependent?

Total Sleep Deprivation (36 hours) Versus Healthy Undisturbed Sleep N=36]

Total Sleep Deprivation: Impairs CPM in Females but not Males

Eichhorn, Treede & Schuh-Hofer., Neuroscience 2017
Do experimental forced awakenings decrease the effects of morphine analgesia (.08 mg/kg, I.M.)? 
N= 79, 46 females

- Findings replicate pre-clinical data (Alexandre et al., Nat. Med., 2017)

No Sex Differences observed

Sleep Condition X Drug Interaction = .06 (Morphine effect @ US; P<.001; Morphine effect at FA; P=.39)

Results controlling for menstrual phase, race, age, bmi
What About Measures of Central Pain Facilitation?

TEMPORAL SUMMATION

• ↑ Pain due to repeated noxious stimulation of same intensity
• Sensitization of second order dorsal horn C-fibers in spine
• ↑ Idiopathic chronic pain [e.g., fibromyalgia, TMD (Staud et al. 2001; Price et al. 2002)]
• Predicts development of chronic pain (e.g., Petersen et al. Pain 2015)

SEX DIFFERENCES in TS (Bartley et al. BJA, 2013; Racine et al. Pain 2012)

SLEEP CONSOLIDATION and TS

• Associated with insomnia and poor sleep efficiency (Bulls et al. 2017)
• Total sleep deprivation did not induce ↑TS (Eichhorn, et al., Neuroscience (2017))
• No studies have evaluated whether sleep disruption alters TS in humans

TS is Enhanced in Women

Data courtesy of Roger Fillingim, Ph.D.
Experimental Data Testing Whether Sleep Disruption Enhances Temporal Summation

[N = 79 Healthy Young Adults (46 females); R01 DA0329922: Smith]

Quantitative sensory testing protocol, 2 nights post sleep condition

Measure of Temporal Summation:

- Weighted pin prick stimulator
- 10 Pain ratings of a train of 10 pricks (512N, 1 second ISI)
- Wind up Ratio = Peak pain rating / first prick pain rating
Do experimental forced awakenings increase mechanical temporal summation? (weighted pin prick stimulator (512N, 1 second ISI)

And if so, does the effect differ by SEX? (N=79, 46 females)

Recent Study demonstrated that Chronic sleep restriction to 4 hours / night for three weeks induced enhanced TS to cold pain in the last two weeks [Simpson & Haack, Pain (2018)]

Results controlling for menstrual phase, race, age, bmi

Smith & Irwin et al. IN PRESS Sleep (2018)
Does sleep disruption alter general measures of pain sensitivity in a sex dependent manner?

  - No sex effect for suprathreshold cold sensitivity, or mechanical pain threshold
  - Except TSD Reduced heat pain threshold in females only.

Results controlling for menstrual phase, race, age, bmi

Smith & Irwin et al. *IN PRESS Sleep* (2018)
Take Home Messages

1) Poor sleep (insomnia) and chronic pain differentially impact women.

2) Poor sleep is a modifiable risk factor for the emergence, progression and persistence of chronic pain.

3) Multiple forms of sleep disruption / loss increase pain sensitivity and central sensitization of nociception.

4) Sleep disruption differentially impairs pain inhibition and heightens temporal summation of pain (but not general pain sensitivity) in women compared to men.

5) Are sex differences in chronic pain risk due in part to the impact of poor sleep?

6) Would treating insomnia improve and or prevent chronic pain in women?
Hormones Matter:
Ischemic Pain Responses at Different Menstrual Cycle Phases

Data courtesy of Roger Fillingim, Ph.D.
**Sex differences in pain anatomy?**

**Methodology:** Cadaver study of the density of nerve fibers innervating facial skin. Twenty cadaver skin specimens (1 cm$^2$) were harvested, prepared using immunohistochemistry, and counted using high-powered microscopy.

Adapted from: Mowlavi et al., 2005. “Increased Cutaneous Nerve Fibers in female Specimens” In: *Plastic & Reconstructive Surgery*
Sex Differences-Hormonal Influence?

Thermal Pain as a Function of Sex & HRT Use

* HRT group differs from other groups, p < .05

Pain is a major contributor to the opioid crisis
(Pain increases relative risk of opioid use disorder by 41% Blanco et al. AJP, 2016); Amari et al. 2011)

• Women are twice as likely to be prescribed opioids than men (Simoni Wastila et al. 2000)
• Women report higher life time use (55% versus 42%) (Serdarevic et al. 2017)
• Men have higher rates of Opioid Use Disorder and overdose deaths (Blanco, 2016)
• Overdoses have increased in woman more than men (Unick et al. 2013)
Experimental Sleep Disruption or Loss Enhances Pain Sensitivity in Healthy Adults

(Summary of General QST findings Thermal & Pressure)

1) **Sleep apnea phenotype (TST preserved):** (e.g., Moldofsky, 1975, Lentz & Landis, 1999)
   - Selective sleep stage deprivation primarily SWS vs. REM

2) **Insomnia phenotype** [prolonged multiple forced awakenings (e.g., Smith et al., 2007; Roehrs, 2006)]

3) **Insufficient Sleep Syndrome Phenotype** (restricted sleep opportunity)
   (e.g., Ablin & Clauw et. al., Roehrs (2006), Haack (2005).

4) **Medical School Phenotype** (total sleep deprivation)
   (e.g. Roehrs, 2006), Kundermann, 2004, Onen, 2001)
   - Testing involves static measures of pain sensitivity – not measures of central pain processing
   - Effects are pain specific - no change in touch / warmth detection (Kundermann, 2004)
   - Possible Sex Effects Largely Ignored (small Ns)
Poor Sleep Subsequently Linked to Impaired Pain Inhibitory Capacity (CPM) In Pain Disorders and in Primary Insomnia

<table>
<thead>
<tr>
<th>Name</th>
<th>Disorder</th>
<th>N</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Monica Haack (2011), Euro. Jo. of Pain</td>
<td>Primary Insomnia</td>
<td>17</td>
<td>Insomnia ↓ CPM compared to control</td>
</tr>
<tr>
<td>2. Edwards RR. (2009), Euro. Jo. of Pain</td>
<td>TMJ/D (chronic Jaw pain)</td>
<td>53</td>
<td>↓ PSG Sleep Efficiency, ↓ CPM</td>
</tr>
<tr>
<td>3. Paul-Savoi E (2012), Open Rheumatology</td>
<td>Fibromyalgia</td>
<td>89</td>
<td>↓ Sleep quality, ↓ CPM</td>
</tr>
<tr>
<td>5. Petrov ME. (2015), Jo. of Pain</td>
<td>Knee Osteo-Arthritis</td>
<td>137</td>
<td>↑ Insomnia sev. (ISI), ↓ CPM, especially in Whites</td>
</tr>
</tbody>
</table>