Pain and Sleep
Can’t Fix One Without the Other
Pain and Sleep – Can’t Fix One Without the Other

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I have the following relevant financial relationship(s) with one or more commercial interests to disclose:

- **Pfizer**
  - Speaker’s Bureau

- **Sanofi Aventis**
  - Consultant
Outline

• Sleep variations and pain in patients
  – chronic pain patients
  – patients undergoing elective surgery
• Sleep deprivation/restriction in volunteers
  – Total/partial deprivation and fragmentation
  – sleep stage specific
• Treatment of sleep disturbance and pain
  – behavioral/medical
  – pharmacological
• Comorbidities in pain patients complicating treatment
  – depression
  – addiction/illicit drug use
Prevalence of Sleep Disturbance in Common Chronic Pain Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic back pain</td>
<td>50%-70%</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>80%-96%</td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
<td>87%-93%</td>
</tr>
<tr>
<td>Headache</td>
<td>50%</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>11%-88%</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>17%-60%</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>84%</td>
</tr>
</tbody>
</table>

*Includes known primary diagnoses; peripheral nerve injury; spinal nerve root origin; postherpetic neuralgia.

# 30 days of self-rated sleep and pain in 50 women with Fibromyalgia

**TABLE 1**

<table>
<thead>
<tr>
<th>Sequential daily process</th>
<th>$\beta$</th>
<th>$t$</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last night’s sleep quality predicting</td>
<td>-0.05</td>
<td>-3.22</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Today’s pain intensity$^a$</td>
<td>-0.01</td>
<td>-1.13</td>
<td>ns</td>
</tr>
<tr>
<td>Last night’s sleep quality predicting</td>
<td>-0.09</td>
<td>-4.15</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Today’s pain focus$^b$</td>
<td>-0.05</td>
<td>-2.63</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Today’s pain intensity predicting</td>
<td>-0.10</td>
<td>-2.10</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Tonight’s sleep quality$^a$</td>
<td>-0.01</td>
<td>-1.00</td>
<td>ns</td>
</tr>
<tr>
<td>Today’s pain focus predicting</td>
<td>-0.11</td>
<td>-3.17</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Tonight’s Sleep Quality$^b$</td>
<td>-0.10</td>
<td>-2.36</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

$^a$Bottom figure controls for today’s attention to pain.

$^b$Bottom figure controls for today’s pain intensity.

Affleck et al, 1996
Sleep EEG arousal disturbances are typically present in patients with chronic pain.

Alpha-delta EEG sleep (mixture of delta waves combined with relatively large amplitude alpha-like rhythms) is more likely to have increased post-sleep tenderness and subjective pain, poor sleep efficiency, and less slow wave sleep.

Morning stiffness, diffuse pain and discomfort after awakening are common in fibromyalgia patients with phasic alpha sleep.

Phasic alpha sleep is associated with longer duration of pain symptoms, perception of poor sleep, and morning pain.
Roehrs et al, 2013
Self-reported and Objective Sleepiness in Chronic Pain

Roehrs et al, 2013
Fatigue versus Sleepiness in Chronic Pain

Roehrs et al, 2013
Total Sleep Deprivation

Threshold for heat pain

Dep vs Cnt p<.04, both mornings

Kundermann et al, 2004
Finger Withdrawal and Stimulus Intensity

Steinmiller et al, 2010
Finger Withdrawal and Codeine

p < .01 Dx x Grp

Steinmiller et al, 2010
Sleep Restriction and Pain Sensitivity

Roehrs et al, 2006
Sleep Fragmentation (1 awakening/hour)

DNIC = diffuse noxious inhibitory controls > 1 noxious stimulus inhibits a 2\textsuperscript{nd} noxious stimulus

Base DNIC = 29%
Avg FA DNIC = 5%

Figure 4—Pressure Pain Threshold Values for the DNIC Procedure in the Forced Awakening (FA) Group (mean ± SEM)

Smith et al, 2007
Selective Slow Wave Sleep Deprivation

• Moldofsky et al, 1976 – selective stage 4 deprivation in healthy college students reduced pain threshold measured by dolorimetry
• Older et al, 1998 – selective stage 3 & 4 deprivation in young normals had no effect on pain threshold measured by dolorimetry
• Lentz et al, 1999 - selective stage 3 & 4 deprivation in middle-age women reduced pain threshold measured by dolorimetry
• Onen et al, 2001 – selective slow wave sleep interruption in young adults had no effect on mechanical pain thresholds, while 40 hr total reduced thresholds
Individual Variation in Rapid Eye Movement Sleep Is Associated With Pain Perception in Healthy Women: Preliminary Data

Michael T. Smith, PhD; Robert R. Edwards, PhD; Gregory L. Stonerock, BA; Una D. McCann, MD

1Johns Hopkins University School of Medicine, Department of Psychiatry, and Behavioral Sciences, Baltimore, MD; 2University of North Carolina, Department of Psychology, Chapel Hill, NC

Study Objectives: Sleep-deprivation experiments suggest that sleep loss increases pain sensitivity. It is unclear from preliminary studies, however, whether sleep-related processes are directly associated with pain perception or whether hyperalgesia is due to the secondary effects of sleep deprivation and/or demand characteristics. Consequently, we sought to evaluate relationships between sleep architecture and laboratory measures of pain processing in healthy women, sleeping under normal conditions.

Design: Correlational, 2-night polysomnographic study with laboratory pain testing conducted on subsequent days.

Setting: General clinical research center inpatient unit with private room

Participants: Sixteen healthy, female, pain-free good sleepers, free from centrally acting agents (mean age=24±4.5 years)

Measurement and Results: Standard polysomnographic sleep-continuity and architecture variables and subject responses to standard noxious thermal stimuli delivered to the ventral and dorsal surfaces of the forearm via thermal sensory analyzer. Ratings of thermal pain threshold as well as suprathreshold indices of central pain processing (mean/peak ratings and intensity of painful aftersensations) were obtained. Averaging across nights/days, we found significant negative relationships between rapid eye movement sleep latency and suprathreshold pain ratings, i.e., measures of heightened central pain processing ($r=-.64$ to -.73, $P<.01$). Significant positive relationships were also found between percentage of rapid eye movement sleep and suprathreshold ratings ($r=.56$ to .66, $P<.050$).

Conclusions: These data are the first to demonstrate a relationship between individual variation in rapid eye movement sleep and pain-modulatory processes. The results have implications for the etiology of pain disorders and suggest that neurobiologic substrates regulating sleep may also play a role in central pain processing.

Keywords: Sleep architecture, REM sleep, pain, temporal summation, pain threshold

Citation: Smith MT; Edwards RR; Stonerock GL et al; Individual variation in rapid eye movement sleep is associated with pain perception in healthy women: preliminary data. SLEEP 2005;28(7): 809-812.
REM Deprivation Increases Pain Sensitivity

Roehrs et al, 2006
IV Morphine (0.1mg/kg) Effects on Sleep in Normals

Figure 1—Distribution of sleep stages across treatment conditions. TST refers to total sleep time; REM, rapid eye movement; SWS, slow wave sleep; S2, stage 2; S1, stage 1.

Shaw et al, 2005
Treatment of Sleep Disturbance and Pain

- Non-pharmacological treatments
  - Sleep extension/consolidation
  - Exercise
  - Meditation
  - CBT/CBT-I
- Pharmacological treatments
  - Alpha 2 delta - Pregabalin
  - SSRIs and SNRIs
  - Sodium oxybate
  - Opiates
  - Triazolam
  - Zopiclone, Eszopiclone
  - Zolpidem
Zolpidem Reduces Pain and Analgesic Use After Knee Arthroscopy

The zolpidem group received a prescription for 40 hydrocodone/APAP bitartrate tablets (7.5 mg/750 mg), a prescription for ibuprofen (800 mg), and 7 zolpidem tartrate tablets (10 mg) for the first 7 postoperative days; control group received hydrocodone/APAP (7.5 mg/750 mg) and ibuprofen (800 mg); placebo group received hydrocodone/APAP, ibuprofen, and 7 placebo gelatin pills similar in appearance to zolpidem tartrate.

Gabapentin Reduces Postoperative Pain & Morphine Consumption After Hysterectomy

N=80.
Gabapentin Reduces Pain and Sleep Interference in Postherpetic Neuralgia

*P<0.001.
**Triazolam Improves Sleep and Reduces Stiffness in Rheumatoid Arthritis**

Behavioral Treatment of Pain
Reduced Pain and Improved Sleep

SE, sleep efficiency; SOL, sleep onset latency; TST, total sleep time.
Improving Sleep in OA Patients with Insomnia Reduces Pain at both Post-Treatment and One-Year Follow-up

Vitiello et al, 2009
Increased Bedtime in Sleepy Normals

Roehrs et al, 2012
Increased Sleep Reduces Pain Sensitivity

Roehrs et al, 2012
Apnea Treatment and Pain Sensitivity

![Bar chart showing Apnea-Hypopnea Index (AHI) before and after CPAP treatment.](chart)

*P < 0.01 vs.

Khalid et al, 2011
Apnea Treatment and Pain Sensitivity

Khalid et al, 2011
Self-rated Sleep Before Joint Replacement and Post Operative Morphine Use

$r = .56$

Roehrs et al., 2006
Prophylactic Sleep Extension in Joint Replacement

Roehrs et al, 2013
Prophylactic Sleep Extension in Joint Replacement

Roehrs et al, 2013
Pain and Depression

• Persistent pain is prevalent
• Depression is prevalent
• Chronic pain and depression often co-occur

75% of persons with depression experience chronic or recurring pain

30 to 60% of patients with persistent pain report significant depressive symptoms
Illicit Drug Use in Chronic Pain

Manchikanti et al, Pain Physician 2006;9:123-129
## Illicit Drug Use in Chronic Pain

### Table 7. Urine Toxicology Results for Three Illicit Drugs

<table>
<thead>
<tr>
<th></th>
<th>Women $(n = 521)$</th>
<th>Men $(n = 250)$</th>
<th>Total $(n = 771)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabinoids</td>
<td>18.4 (96)</td>
<td>24.0 (60)</td>
<td>20.2 (156)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>7.7 (40)</td>
<td>8.8 (22)</td>
<td>8.0 (62)</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>0.2 (1)</td>
<td>0.0 (0)</td>
<td>0.1 (1)</td>
</tr>
<tr>
<td>Any illicit substance</td>
<td>22.5 (117)</td>
<td>27.2 (68)</td>
<td>24.0 (185)</td>
</tr>
</tbody>
</table>

n = 771 subjects; no lab data obtained on 30 subjects.

Fleming et al, J Pain 2007;8:573-582
The relation between pain and sleep is reciprocal

Chronic pain patients have disturbed PSG sleep, insomnia and fatigue

Reduction or fragmentation of sleep enhances pain

Reduction of REM, but not slow wave sleep, may also enhance pain

Management of insomnia and pain using nonpharmacologic or pharmacologic methods may contribute to more effective management of pain, and provide patients with greater relief

Comorbidities such as depression or illicit drug use is likely to complicate management of pain and sleep disturbance