Sleep, Women and Cardiovascular Disease

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Areas to Discuss

• Women and their Sleep
• Specific Diseases
  – Insomnia
  – OSA
• Cardiovascular Risk
  – Hypertension/MI
  – Congestive failure
  – Coronary Artery Disease
• Stroke
• Specialty topics:
  – Menstrual periods
  – Pregnancy
  – Menopause

http://www.cagle.com/sex/annoyance/annoyance.asp
National Sleep Foundation Poll 2007

- 25 minute telephone survey 1003 women age 18-64
- 84% post partum women insomnia
  - 47% no help with childcare at night
  - 20% drove drowsy with child
  - 42% rare to “never” good night sleep
  - 19% post partum blues
Many women report good sleep for only a few nights/month
  - 24% child bearing age good sleep a few nights / month or less
  - 40% pregnant women
  - 55% post partum
  - 25% peri menopausal and 30% post menopausal

Sleep Profile

- Part of our personality
- Larks versus Owls- normal low point 530 AM, lark 430 AM, owl 7 AM
- Sleep Needs
  - Toddlers 12-14 Hr
  - Children 10-11 Hr
  - Teen 9-10 Hr
  - Adult -7 Hr age 40 and 6.2 Hr age 60
- Sleep need does not change in elderly
- Family history affects sleep
- Microsleeps and Automatic behavior
Cost of Poor Sleep

- Prescription MEDS $3 billion 9 months/06
- $362 million on ads
- Dove-calming night soap and body wash
- Boots from Target sleep aromatherapy
- Canyon Ranch sleep specialist
- $100 Billion annually in lost productivity, medical expense sick leave, property and environmental damage

Excessive Daytime Sleepiness

- We average 6.9 hours sleep but need 7.5-8 hours last changed 1870’s
- Sleep debt accumulates-the longer we lack sleep the worse we perform
- Sleep deprivation affects driving NHTSA estimates 20% drivers have slept at the wheel
Drowsiness is Dangerous

• Being awake 20 hours equals blood alcohol concentration of 0.08% = drunk
• Short sleep in 8098 adults (National Comorbidity Study) - increased suicide thoughts and attempts
• Megan’s Law in New Jersey it is a felony to drive and kill someone sleep deprived
• Truck drivers limited to 11 hours duty

Drowsy Driving Close to Home

• Dr. F in MA treated a patient with asbestosis, bronchitis, lung CA, emphysema 6 times/year
• Patient told he was unsafe to drive due to meds, but resumed 1 year later and after several months LOC and killed a child (meds included oxazepam, oxycodone, paroxitene), no cause accident found. The driver and his doctor were sued.
• Dec 2007 supreme court ruled it was not malpractice, but does the physician owe a duty to the people his patient could injure? Need written evidence of warning
• Charles Czeisler estimates 600 sleep related car crashes in MA/year
• A death in MA in 2002 caused by a teenager up all night playing video games led to restriction of juniors from 1230-5 AM.
Long Term Sleep Loss

- 2004 women with 5 hours sleep 39% more likely to develop heart disease compared to women with 8 hours sleep
- NY Times 2/1/07 - YELO West 57th -7- private chambers- 12$/20 minutes, recliner dim light music, cashmere, (reflexology-65$) - “corporate wellness center”

Siesta

- 28,571 patients 5 years European prospective investigation into cancer and nutrition
- Never nap -3/week- or less often & <30 mins
- Mediterranean diet score 0-9
- Global activity score, include exercise
- Remove pt with serious disease CHD, stroke CA
- Siesta lowered mortality, 85 deaths men, 48 women reduced stress
- Age, smoking, central obesity, education, activity, diet
- Arch Int Med Feb 12,
What is Insomnia?

A complaint of:
- Difficulty falling asleep
- Difficulty staying asleep
- Poor quality sleep

Associated with:
- Distress
- Impaired function

Hints for Good Sleep

- Exercise enhances sleep
- Maintain a healthy diet (avoid caffeine and alcohol)
- Keep your room restful, dark, and quiet
- Not too hot or cold
- Avoid tobacco
- Sleep is affected by everyone in the room
- Regular sleep and wake hours
- If you cannot sleep get up and distract yourself
GET RID OF THE ?!&$#@ CLOCK UNLESS YOU LIKE TO REMIND YOURSELF YOU ARE AWAKE EVERY HOUR
DO NOT WORRY ABOUT NOT SLEEPING, CHANCES ARE YOU ARE SLEEPING MORE THAN YOU THINK

Sleep remedies

- Alcohol
- Benadryl
- Trazadone
- Antidepressants
- Pain meds
- Valium like sedatives
- Newer sleep meds – Lunesta and Ambien
- Melatonin and Rozerem
Other Causes of Sleepiness

- Narcolepsy: rare sleep attacks with sleep paralysis, cataplexy, hallucinations
- Snoring in 40% men: vibration, loud wakes
- 5% of men and 3% of women have sleep apnea
- Decreased muscle tone, obesity, small chin, sedatives, nasal congestion
- Frequent wake ups with restless legs
- PAIN fibromyalgia

Obstructive Sleep Apnea
Pathophysiology of OSA

Apnea Patterns

- Obstructive
- Mixed
- Central

Airflow
Respiratory effort
Assessment: Polysomnography

- Not routinely indicated for the evaluation of insomnia
- Indications
  - Suspect other sleep disorder
  - Poor treatment response
  - Atypical clinical presentation

Practice parameters for the evaluation of chronic insomnia. SLEEP 2006.

Sleep Apnea in Women

- Costly to health care – Manitoba 5 years before apnea diagnosis and 2 after = 414 women
  - CPAP (231) patients or weight loss alone (55)
  - Utilization up with Diagnosis
  - After CPAP
    - Respiratory and somatic complaints down after
    - Costs of utilization decreased
  - Weight loss group decrease utilization but not sig
  - Not include costs of decreased productivity or accidents

Banno, K and Kryger M Sleep
29;10-2009 1307-1311
Gender differences in OSA health care utilization

- 289 women and men – match age, AHI, BMI-more depression, hypothyroid, insomnia (UARS) than men
- Increased health care cost 5 years prior to diagnosis more vitamins, 2.7 X more anxiolytics & antidepressants
- 93% women moderate – severe OSA not diagnosed
- Most costly 25% consumed 65% services
  - Hyperlipidemia, CVD, arthropathy, asthma
- Women BMI >40 poorest health status used 1.4 times more health care
  - AHI and 02 sat not affect utilization
- Women more non specific complaints,

OSA Risk factors Women

- **Menopause**-In a Canadian population OSA increased from 21 to 47% after menopause despite BMI 30
- Weight gain and neck size increases risk

- **Leptin** a hunger suppressing adipokine stimulates breathing
- With abdominal obesity, you lose leptin or can become leptin resistant

- **Estrogen** improves sleep apnea, **progesterone** worsens apnea
- **Hypothyroid** disease may increase sleep apnea
• OBESITY

– In 2003-2004
  » 19% of children and
  » 17% teens are obese
  » 40 years ago = 4% children

• Obese children 10 times more likely OSA

• 60-70% of sleep apnea patients are obese, body 20% above ideal, upper body

• Weight loss can cure or improve snoring and sleep disordered breathing.

Snoring and Sleep Apnea Therapy

• Sleep on the side- tennis balls velcro pad
• Weight loss
• Snore pillow
• Decongestant
• UPPP -50-%
• Jaw reconstruction
• Dental devices
• CPAP
Treatment OSA with CPAP

Mask
• nose or nose and mouth and may fit in nostrils

CPAP
• humidity, ramp feature, memory
• CFLEX
• variable pressure
• BIPAP

Lifestyle changes
Oral Appliance: Mechanics

Swift™ LT for Her

First fit with her in mind

The Swift™ LT for her is the first mask designed especially for women, combining the revolutionary design of the Swift LT with personalized features for women's unique preferences:

- Light touch: Nasal forehead support and weighs only 2.3 oz (65 g), sealing softly and securely to ensure a comfortable night’s sleep.
- Easy fit: Rotating barrel allows her to customize her best seal, while the simple design makes it easy to fit and clean.
- Soft and stable: 95% smaller mask frame width, making it perfect for side sleeping.
- Whisper-quiet comfort: Quietest nasal pillow system on the market (72% quieter than the Mirage Swift™ III—25 dB or less).
- Innovative headgear design: Adjustable backstrap can be worn over or under the hair to accommodate a wide range of hair styles in a soft, feminine print and light blue color.

*Testing per ISO 3744:1994 Acoustics determination of sound power levels of noise using pressure at 10 cm H2O. Quoted percentage companions are calculated by converting sound power values from a logarithmic scale to a linear scale.
Cardiovascular Function During Sleep

- Sleep (NREM) is a time of rest for the heart
  - Decreased heart rate
  - Decreased blood pressure
  - Decreased systemic vascular resistance
  - Decreased sympathetic activity
  - Decreased epinephrine
  - Decreased cortisol (till early am)
  - Decreased heart rate variability
CV Response to Arousal

Blood Pressure

Heart Rate

Sleep Disordered Breathing and Cardiovascular Disease

- Peppard and Young - Wisc Sleep Cohort Study
- There was a dose response association between sleep disordered breathing AHI >15 at baseline and high blood pressure 4 years later independent of other factors
  - Increased atrial fibrillation, increased MI
  - Increased TIA and stroke, increased mortality

Peppard PE et al NEJM
342;1378 May 2000
Hypertension
Common in association with OSA
40% OSA pts with hypertension (Pepperell et al Lancet 2002)
40% hypertensive pts have OSA (Rauscher et al Chest 1992)

Causal relationship supported by:
1. Mechanistic studies
2. Epidemiology from large cohort studies
3. Intervention data from randomized, controlled trials

Hypertension and Sleep Apnea

- Intermittent hypoxia
- Sympathetic over activation
- Vascular endothelial dysfunction
- Inflammation
- Common in association with apnea and treatment of sleep apnea can reduce hypertension
Hypertension


Hypertension & OSA: Dog Mode
Hypertension & OSA: Dog Model

Hypertension & OSA: Epidemiology

Nieto et al., JAMA 2000;283:1829-36.
Hypertension & OSA: Intervention

Therapeutic vs. Subtherapeutic CPAP

Pepperell et al. Lancet 2002; 359:204
CHF

- SDB in 45-75% of patients with LVEF < 45
- Both OSA and CSA
- CSA predicts poor outcome
- CANPAP 258 patients EF <40
  - 5 year follow up no difference in mortality
  - Did not use adaptive servo-ventilation
  - Cardiac function, central apnea, sympathetic activity and exercise tolerance were improved

Central Apnea:
Cheyne-Stokes Respiration

Courtesy: A. Malhotra
CHF: Distribution of Severity of SDB

![Graph showing distribution of severity of SDB](image)


CHF: Effect of CSA on Mortality

![Graph showing effect of CSA on mortality](image)

- n = 62
- EF < 35%
- NYHA II - III
- CSR 36 %

Lanfranchi et al. Circulation 1999; 99:1435
CHF & CSR: Treatment Options

- Optimize medical therapy of CHF
- Oxygen
- CPAP
- Theophylline
- Acetazolamide
- CO2
  - Inhalation
  - Dead space
- Adaptive servo-ventilation

CAD: Inflammation

- Inflammatory mediators elevated in OSA
- Reduced with CPAP

Yokoe et al. Circ 2003; 107:1129
Sleep Apnea Affects Mortality - CVD

He J et al. Chest 1988;94 (Untreated, age<50)

Sleep and Stroke

- Women 50-79-Womens health Initiative
  - Sleep > 9 hours 70% more risk CVA
  - Sleep <6 hours 14% more risk CVA
- Long sleep more illness and death
- Snoring risk factor for stroke in 110 snorers without OSA; measure carotid atherosclerosis
  - 20% mild snorers
  - 32% moderate snorers
  - 64% heavy snorers
- Adjust age, sex, smoking hypertension

Lee et al Sleep 2008. 31;9 p1207
Stroke and OSA Risk Factors

- Hypertension, lose autoregulation
- Elevated fibrinogen
- Increase AM blood viscosity
- Changes cerebral blood flow
- Cardiac arrhythmia
- Paradoxic embolys
- Increased risk atherosclerosis

Broadley 2006, J Clin Neuroscience

Autoregulation is Impaired in Stroke

- Average age 47 no stroke or cardiac disease but had Obstructive sleep Apnea
  - Lower cerebral blood flow velocity
  - Lower blood oxygen level in sleep
  - Took longer to recover from drop in BP
  - Took longer to normalize blood flow to the brain

Urbano F et al J Applied Physiology 2009
OSA Risk Stroke and Death

- 697 patients with OSA (AHI 35 vs 2 in controls)
- Age >50, questionnaire and PSG, suspect OSA 1022
- 31% lost 10% weight, 58% used CPAP 4 hrs, 15% UPPP

- Follow 3 years.
- Stroke or death from any cause 88 pt (hazard ratio 2.24)
- Then adjust age, sex, race, smoking, ETOH, BMI, hyperlipidemia, diabetes, a-fib, and hypertension (hazard ratio 1.97)
- Dose response relationship between sleep apnea at baseline and end point of stroke or death
  Yaggi et al NEJM 353; 2034-46, 2005

OSA after Stroke

- 55 patients studied within 3 days of CVA and 29 had AHI>10
  Mean BMI 27, Modified Barthel 53
- AHI pts had pre stroke sleepiness, snoring but not more hypertension, or post stroke dysphagia
- Mechanism ?
  - Central respiratory depression
  - Pharyngo-laryngeal dysfunction
  - Immobility and paralysis respiratory muscles
- 16 patient offered CPAP, 13 used it, well tolerated in 8, symptomatic improvement in 5
- Repeat PSG 6 weeks confirmed OSA (AHI>10)
- Broadley
Menstruation

- Bloating, tender breasts, headaches, cramps during pre- and peri-menstruation
- Lethargy reported pre-menstrually in 16-25% of women and in 25-32% of during menstruation
- Increased likelihood for depression in days leading up to menses
- Sleep disruption pre and perimenstrual

Menstrual Cycle

Fig. 1: Female sex hormone concentrations across the menstrual cycle (Schmidt-Matthiesen, 1992, modified).

Dzaja et al., 2005
Polycystic Ovarian Syndrome

- Ovaries produce too much testosterone
- Low FSH and poor follicle development
- Associated with:
  - Hirsuitism
  - Obesity (larger waist-hip ratio)
  - Fertility problems / Amenorrhea

- 44% had OSA (AHI > 5 and EDS) [Avg RDI 40] compared to 5.5% BMI and age-matched controls (Fogel et al., 2001)

- Relationship to OSA may be related to insulin resistance (Vgonmtzas et al, 2001)

Menopause

[Image: http://www.aperfectworld.org/cartoons/menopause.png]
Menopause=Disrupted Sleep
25-50% of women

- Vasomotor symptoms associate with arousal and disrupt sleep architecture
- Progesterone
  - sedative stimulate GABA receptor
  - respiratory stimulant
  - apnea protection pregnancy
- Estrogen
  - Increase REM cycle affect NE, 5HT, Ach.
  - Decrease sleep latency and WASO
  - Temperature regulation, hot flash (catechols, LH up)
  - Regulates time of lowest body temp, pushing later and shallower
  - May have antidepressant effect (5HT agonist, increase NE, GABA agonist)

Sleep and Menopause

- HRT taken years after onset menopause may improve sleep
- Women 50-69 on HRT versus placebo
  - Hot flashes
  - Sexual function All Improved
  - Sleep problems
- 23-68% of women have insomnia
- REM latency is longer and sleep efficiency less
**Menopause 2**

- **Cortisol**
  - Estrogen affects cortisol with higher level earlier in sleep
  - Estrogen regulates AM cortisol and may stabilize night sleep
- **Melatonin**
  - Suppresses estrus in animals with seasonal reproduction
  - Males regress testicular tissue (high)
  - Keeps humans asleep in dark
  - Tamoxifen, oopherectomy, decreases melatonin
  - Estrogen may have reciprocal melatonin support function
- **Testosterone**
  - Minor effect on sleep but exogenous worsen sleep apnea,

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**Hormone Replacement for Sleep**

- Double blind, crossover study of 63 post-menopausal women (Polo-Kantola 1998)
  - Improvement in sleep quality
  - Including vasomotor, somatic (tachycardia) and mood symptoms
- Contrasting study (Purdie 1995)
  - No effects of HRT on PSG sleep in 33 women
Other Therapies

- Micronized progesterone, may have less effect on vessels, improve WASO and efficiency
- Herbals black cohosh moderate effect, soy isoflavones (phytoestrogen) red clover, vit E, dong quai
- Clonidine 34-44% decrease symptom
- Gabapentin 300-900 mg reduce sx 66%
- SSRI fluoxetine, venlafaxine

Hot Flushes / Night Sweats

- Study of Women’s Health Across the Nation (Kravitz 2003)
  - Multiethnic study of 12,603 women
  - 38% of women reported difficulty sleeping within 2 weeks of the survey
  - The highest rate was in the late perimenopausal (45%) and surgically postmenopausal groups (48%)
- Hot flushes are relieved by estrogen in 90% of pts (if willing to take it)

http://www.redhotflush.co.uk/
Hormone Replacement for OSA

• Incidence sleep apnea women approaches men after menopause

• Short term hormone replacement (estrogen and progesterone) in 15 post-menopausal women does not seem to improve sleep apnea symptoms. (Cistulli 1994)

• Contrastingly, a Swedish study looked at 5 women (4 postmenopausal, 1 peri-menopausal) given estradiol and trimgeston for 6 weeks. Reduction in RDI was 75% (AHI mean 14.9 to 3.6). (Wesstrom 2005)

Pregnancy
Normal Pregnancy

- 1998 NSF poll – almost 80% of women reported more disturbed sleep during pregnancy
  - Increased urination
  - Tiredness
  - Pelvic pressure
  - Insomnia
  - Lower back pain
  - Restless sleep
  - Leg Cramps
  - Frightening Dreams
Sleep Architecture

Table 1. Characteristics of Sleep in Pregnancy*

<table>
<thead>
<tr>
<th>Stage of Pregnancy</th>
<th>Subjective (Surveys and Sleep Logs)</th>
<th>Objective (Polysomnography)</th>
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<tbody>
<tr>
<td>First trimester</td>
<td>Increased total sleep time due to naps (3, 51)</td>
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<tr>
<td></td>
<td>Increased daytime sleepiness (3, 51)</td>
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<td></td>
<td>Increased nocturnal insomnia (3, 51)</td>
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<tr>
<td>Second trimester</td>
<td>Normalization of total sleep time (51)</td>
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<td></td>
<td>Increased awakening (3)</td>
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<tr>
<td>Third trimester</td>
<td>Decreased total sleep time (3, 51)</td>
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<td></td>
<td>Increased insomnia (3, 51)</td>
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<tr>
<td></td>
<td>Increased nocturnal awakening (53, 54)</td>
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<td></td>
<td>Increased daytime sleepiness (3, 51)</td>
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<td></td>
<td>Increased total sleep time (56)</td>
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<td>Decreased stage 3 and 4 non-REM sleep (56)</td>
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<td>Decreased REM sleep (56)</td>
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<td>Decreased REM sleep (56)</td>
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* Numbers in parentheses are reference citations. REM = rapid eye movement.

Fibromyalgia

- Perimenopause, women:men = 7:1
- Simple sleep deprivation will increase pain enhance trigger points
- Alpha Intrusion
  - Simultaneous with delta 50% chronic
  - Throughout NREM 20%
  - Low alpha 30%
- Decreased spindles increased CAP
- High incidence depression
- Na Oxybate increased slow wave sleep, decreased alpha intrusion, reduced trigger points
Conclusions

• Sleep is an important part of our 24 hour level of alertness
• We need to respect our natural need for sleep (Siesta cultures) as we are chronically sleep deprived
• Sleep disturbances have effects on cardiovascular disease
• Sleep apnea is a risk factor for hypertension, coronary artery disease, congestive heart failure, transient ischemic attacks, and stroke
• The common mechanisms are sympathetic activation, hypoxia, endothelial dysfunction and inflammation
Sleep Disorders in Women Are

- Dangerous
- Common
- Diagnosable
- Treatable