Objectives:

- Understand which sleep disorders commonly impact women's health.
- Describe differences in sleep and sleep disturbances between women and men.
- Outline evaluation and management strategies for treating women veterans with sleep disorders.

Why is Sleep Important?

1. Memory consolidation and improving Brain plasticity for learning - REM sleep particularly important for memory.
2. Immune regulation - sleep helps boost the immune system:
   a. With sleep deprivation, increased risk of infection.
   b. Can live without food for 10 days but with no sleep for 10 days, high risk of death from sepsis.
Importance of Sleep, continued

3. Restorative theory: Sleep is required for muscle growth, tissue repair, protein synthesis, and growth hormone release occur mostly or entirely during sleep.

4. Adaptive theory - evolutionarily helpful to have periods of decreased metabolic demands and rest such as sleep.

Sleep is Critical for Quality Health because with Sleep Disturbance, there is an increased risk of:

- Obesity/diabetes
- Hypertension
- Cardiovascular events
- Stroke
- Depression, Anxiety and PTSD
- Substance abuse
- Cancer
- All cause mortality

Sleep Disturbance = increased risk of some Cancers

- Decreased Sleep may lead to increase in Breast, Prostate and Colorectal cancers
- Increased Breast Cancer risk in Women with poor sleep quality:
  - 2016 article in Genes and Cancer: Melatonin blocked growth of some Breast Cancer Cells.
  - 2012 article in Breast Cancer Research: Women who chronically lacked good quality Sleep (on average < 6 hours per night) were at increased risk of developing more aggressive Breast Cancers.
Women and Sleep Disorders

• 28-64% of peri-menopausal/menopausal women report sleep disturbance and especially insomnia.

• Sleep complaints are twice as prevalent in women yet 75% of research on sleep conducted on men.

Common Sleep Disorders in Women:

1. Obstructive Sleep Apnea (OSA)
2. Insomnia
3. Hormonal changes affecting sleep
4. Restless Leg Syndrome

Obstructive Sleep Apnea: Repetitive complete collapse (APNEA) of the upper airway during sleep, or partial collapse associated with 4% oxygen desaturation (HYPOPNEA)

Associated conditions
• Obesity
• Cardiovascular disease
• Stroke
• Diabetes
• Mood disturbance
• Neurocognitive dysfunction
• Motor vehicle accidents, 5 x more in patients with untreated OSA
**OSA risk factors**

- Obesity
- Advancing age
- Male gender—but need more studies in women to really ascertain this gender bias
- Menopause
- Craniofacial/upper airway abnormalities
- Nasal congestion
- Smoking
- Family history
- Pregnancy
- Other medical conditions: End stage renal disease, congestive heart failure, chronic lung disease, stroke

**OSA in Women: Underdiagnosed and Undertreated**

1. Sleep apnea is underdiagnosed in women. Wisconsin Sleep Cohort Study suggests 90% of women with moderate to severe OSA were not diagnosed.

2. Women are more likely to be treated inappropriately than men with the same severity of OSA.

3. Women are 2-3 times less likely than men to report classic OSA symptoms: the usual screening questions or tools may not be accurate for women.

**Screening for Symptoms of OSA in Women:**

1. Classic symptoms more often reported in men:
   - Loud snoring
   - Witnessed apnea
   - Excessive daytime sleepiness

2. Atypical symptoms more often reported in women:
   - Insomnia (20%)
   - Morning headache
   - Unrefreshing sleep
   - Fatigue
   - Depression and anxiety
   - Memory loss and poor concentration
   - Decreased libido
   - Irritability
OSA, TBI and Brain health

White matter structural integrity appeared more negatively affected in female OSA patients compared to male patients (Macey, Sleep 2012)

• This could suggest OSA may be more problematic and need earlier treatment in women, especially for cognitive function and brain health

• Implications for Women Veterans who suffered Traumatic Brain Injury.

Home Sleep Testing for OSA

• Benefits: convenient, comfortable, Home sleep environment, provides more data than nocturnal oximetry alone

• Excellent for picking up on Moderate to Severe Apnea

• Draw backs: Test for evaluating Sleep Apnea ONLY - cannot assess sleep architecture or sleep movements (parasomnias, etc.)

• Not helpful with treatment/PAP titration or advanced therapies

• Cannot assess Respiratory related arousals which are not associated with a 4% oxygen desaturation so can underestimate disease

HOME SLEEP APNEA TEST (HSAT)
In-Lab Testing: Polysomnography

- 12 channels of data
- Can assess Sleep stages as well as Sleep movements
- PAP titration
- Evaluates more than just Apnea

The Gold Standard

- 0-4 Normal
- 5-14 Mild
- 15-29 Moderate
- >30 Severe

AHI or Apnea/Hypopnea Index: Apnea + Hypopneas per hour. By definition, these pauses in breathing must last for at least 10 seconds.

POLYSOMNOGRAM (PSG)

OSA treatment

- Positive airway pressure therapy (PAP) most effective IF used – 80% of patients who used PAP had some improvement in symptoms
- Compliance always a challenge
- 65-83% in one study, same between sexes but one prospective study showed female patients used CPAP more
PAP works! OSA Treatment Has a Major Impact on Comorbidities

After one year, patients surveyed state OSA treatment delivers:

- **Hypertension**
  - 41% report blood pressure improvement
  - 17% report decrease in medication usage

- **Diabetes**
  - 31% report improved HbA1c
  - 1.6x increase in "good-quality" sleep

- **Asthma & Breathing Conditions**
  - 54% report improved respiratory function
  - 90% increase in patients reporting symptoms as mild
  - 6.4x increase in "good-quality" sleep

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OSA Treatment Has a Major Impact on Treating and Preventing Illness

After one year, patients surveyed state OSA treatment delivers:

- **Insomnia**
  - 7x increase in good quality sleep
  - Decline from 54% to 1% reporting "very bad" quality sleep

- **Depression, Anxiety and Mental Health**
  - 12x increase in "good-quality" sleep
  - 4x reduction in reported life threatening mental health condition
  - 48% report improved mental health

- **Heart Disease**
  - 56% report reduced heart disease risk
  - 5x decrease in self-reported life-threatening heart disease
  - Decline from 52% to 3% reporting "very bad" quality sleep
  - Increase from 0% to 26% reporting "very good" quality sleep

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OSA treatment results

- Most treatment trials have been conducted in male patients
- Few trials have included enough women to define differences in efficacy of various modalities
Other Therapies for OSA

1. Positional therapy
2. Weight reduction
3. Alcohol and sedative avoidance
4. Smoking cessation
5. Oral appliances
6. Surgical therapy

Insomnia: Definition

1. Repeated difficulty with sleep initiation, duration, maintenance, consolidation, or quality of sleep. Symptoms last > 1 month.
2. Occurs despite adequate time and opportunity for sleep.
3. Results in some form of daytime impairment.

“I have a theory about your insomnia...”
Differences in Sleep Architecture Between Women and Men

- Women have a longer sleep latency than men.
- Women have increased Slow Wave Sleep (also called Stage 3 "Deep" Sleep or Delta sleep) as compared to men at any particular age.
- SWS decreases in age more so in men than women. Women "preserve" delta sleep into old age more so than men.
- This ability for deeper sleep would suggest a sense of improved sleep quality for women but that is not the case.

Insomnia in Women

- Women are 40% more likely to experience insomnia than men.
- Women report poorer sleep quality in general even when the quantitative comparison of Polysomnographic sleep is similar to men.

Insomnia in Women, continued

- Hormonal status seems to play a major role as increased rates of insomnia during:
  - Menopause/perimenopause
  - Late-luteal phase of the menstrual cycle
  - Third trimester of pregnancy
- Chronic insomnia prevalent among cancer patients, and especially women with breast cancer.
Healthy Sleep Habits = FIVE THINGS ALL PEOPLE WITH INSOMNIA SHOULD DO

- KEEP a very regular sleep schedule
- QUIT smoking
- QUIT caffeine – Stimulant and delays Melatonin secretion
- QUIT alcohol – Sedative but when wears off rebound awakening and Changes REM sleep
- QUIT screen time within 1 hour of bedtime and affect of blue light = delays Melatonin secretion

Behavioral Therapy is Key to Insomnia Treatment

- Sleep research has shown Behavioral Therapy is the most effective treatment in reducing Insomnia long term

- Medications only FDA approved for short term use, usually not more than a few months

Insomnia Treatment:

- Cognitive Behavior Therapy for Insomnia
- Sleep Stimulus Control
- Sleep Restriction: prolonged shallow sleep as compared to deep, shorter sleep
- Being aware of a delayed Sleep schedule as the real problem rather than insomnia
Medications for Insomnia: Zolpidem and Women

• Zolpidem underscores gender differences in sleep.
• FDA recommends half the dose for women than for men due to slower metabolism in women causing 50% higher serum levels as compared to men.
• First time FDA has issued a gender specific guideline for a medication
• Indicated for SHORT term insomnia (no more than 2-3 months) and may be a useful tool while patients are working through behavior modification and improving sleep schedules.

Other Medications for Insomnia

• Trazadone is not actually a very good sleep aid as often the sedating effects wear off but if there is underlying depression, it can be helpful
• Melatonin – in some can be helpful but the KEY is HOW to take it
  • Take at a REGULAR time for a REGULAR sleep schedule - the goal is to promote a healthy circadian rhythm.
  • Take at least 2 hours prior to bedtime
  • May take 2-3 weeks to see an effect
• Melatonin – agonist – Ramelteon – expensive and ?efficacy?
• Risks may out weight benefits for the following:
  • Orexin antagonist - Suvorexant
  • Benzodiazepines
  • Anti-histamines

Sleep Health is Critical To Veteran Health

• History of TBI = worse sleep quality = increased suicide ideation Ask about Sleep quality and TBI history in suicide assessment
• Veterans with Increased Depression, Anxiety, PTSD associated with poor sleep and those conditions also add to poor sleep – Bi-directional effect.
• Military Sexual Trauma in women veterans: Approximately 1 in 4 women who use VA care have a positive screen for MST based on National VA Screening data.
• Women Veterans with a positive VA MST Screen are over 11 times more likely to be diagnosed with PTSD compared to women who don't screen positive
• Healthy Sleep requires the feeling of safety in the Sleep environment. Lack of safety in the sleep environment may increase anxiety and insomnia especially if the MST event occurred in a bed.
PTSD and Sleep

Sleep disturbance represent two of the diagnostic criteria for PTSD:
1. Recurrent Nightmares – intrusion cluster of symptoms
2. Insomnia – arousal cluster of symptoms

Non-gender specific studies have shown 92% of active duty personnel with PTSD have insomnia as compared to 28% without PTSD. 52% of combat veterans with PTSD reported significant nightmares. It stands to reason if women have an increased incidence of insomnia, then women with PTSD would have even higher incidence of insomnia.

PTSD or Nightmares

From June 2017, VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder

- Prazosin for nightmares does not help with sleep latency but can improve REM sleep continuity and decrease nightmares
- Hydroxyzine possibly can help decrease nightmares and improve sleep as compared to placebo
- The studies that supported the above findings were also not gender specific
- Clonazepam has not been effective even though widespread use
- Depakote and Anti psychotics have not been shown to be effective for sleep or nightmares in PTSD
Pregnancy and Sleep

1. Sleep disorders may be exacerbated by or occur only during pregnancy
2. 78% of women report more disturbed sleep during pregnancy
3. Changes in reproductive hormones along with physical changes in the body lead to sleep problems

Sleep Disturbance in Pregnancy
- Insomnia
- Discomfort
- GERD (30-50%)
- Nocturia
- Anxiety
- RLS - Worsens thru pregnancy and 26% report symptoms
- OSA

Pregnancy and OSA
OSA and/or hypoventilation – important to treat in pregnancy!

Untreated OSA in pregnancy is associated with
- Preeclampsia
- lower birth weight
- decreased APGARS
Pediatric Sleep Disturbance Affecting Maternal (and Paternal) Sleep

- Infant Sleep is not consolidated until 6 months on average leading to decreased parental sleep
  - No set schedule
  - Try to catch sleep when you can!
  - Explaining 3-6 months is normal may help new parents know this is a limited time they can get through

- Behavioral Insomnia of Childhood
  - Prevalent – 25% of children meaning affects 25% of parents!
  - Behavioral interventions are key
  - Important to ask parents about this and refer for help

Hormonal Changes Affecting Sleep

- 1/3 women complain of sleep disturbance the Premenstrual week
- Vasomotor symptoms during Peri-Menopause and Menopause
- Insomnia increases after menopause:
  - 33-36% premenopausal women
  - 44-61% postmenopausal women
- Menopause showed a negative effect on sleep with longer sleep latency and less deep sleep
- Increased RLS in Menopause
- Higher prevalence of OSA after Menopause irrespective of weight gain. Are there hormonal effects on the airway?

HRT and Sleep

- HRT in some studies has been shown to help improve sleep – unsure if this is due to control of vasomotor symptoms versus the actual affect of Estrogen on Sleep
- Prospective study compared post-menopausal women with OSA treated with either ERT + PRT or ERT alone.
  - PSG repeated at 4 weeks
  - 50% reduction in Apnea/Hypopnea index in ERT + PRT group
  - 25% % reduction in Apnea/Hypopnea index in ERT group
- HRT also helped RLS symptoms
Restless Leg Syndrome (Willis-Ekbom Disease): Symptoms occur while awake

1. Urge to move the leg, usually (but not necessarily), accompanied by uncomfortable sensations
2. Predominance of symptoms during evening or night hours
3. Presence of symptoms during rest or inactivity such as sitting or lying down
4. Improvement of symptoms with movement, such as stretching or walking

Prevalence of RLS in Women

- Prevalence 14% in women (6% in men)
  - Strongly correlate with iron deficiency which is higher in pre-menopausal women with menstrual bleeding, whether abnormal or not
  - Although this does NOT explain why RLS symptoms increase after Menopause?
- Increases with age
- 80% will have Periodic Limb Movements of sleep (PLM) which is a second disorder
- Etiology not clearly understood but believed to be dopaminergic dysfunction
- Iron dopamine hypothesis
**Risk Factors for RLS**

- Iron deficiency
- Pregnancy
- Antidepressants
- Neuropathy
- Kidney disease
- Caffeine
- Alcohol
- Smoking
- Family history

**RLS and PLM Evaluation and Treatment**

1. Check Ferritin, Tsh, Vitamin D, Magnesium and replace if low
2. Check medication list!

**RLS Increased with some Medications**

- Deserves its own slide because many anti-depressants increase RLS and PLMD symptoms especially SSRIs (Prozac, Sertraline), SNRIs like (Duloxetine, Effexor), TCAs or Trazadone.
- This is to be kept in mind for those patients being treated with depression
- Wellbutrin only anti-depressant that does not increase RLS symptoms
Treatment of RLS

- Replace iron if ferritin is low (<50mcg/L) – THIS WILL HELP A LOT
- Dopamine precursors (carbidopa/levodopa)
- Dopamine agonists (pramipexole, ropinirole)
- Anticonvulsants (gabapentin, pregabalin, carbamazepine)
- Clonidine
- Benzodiazepine or BZD receptor agonists (Clonazepam, Zolpidem) not recommended due to risk for tolerance
- Opioids – last resort, given current opioid epidemic and tolerance

Summary:

1. Sleep health is an important component of the evaluation for women's health care.
2. Sleep disorders tend to be under-diagnosed in women with potential for serious consequences.
3. Common sleep disorders do not always present with common symptoms for women for example, OSA may present as insomnia.
4. More studies needed on women and sleep disorders and efficacy of treatments.

Summary, continued:

5. Sleep complaints are twice as prevalent in women yet 75% of research on sleep conducted on men.
6. 28-64% of peri-menopausal/menopausal women report sleep disturbance and especially insomnia.
7. Women may suffer more brain dysfunction from under-treated OSA than men.
8. More women remain underdiagnosed with OSA than men.
9. Restless Leg Syndrome more prevalent in women than men.
References


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THANK YOU!