The A to ZZZ’s of Sleep Health

Cathy Rosenbaum PharmD MBA RPh CHC CDP
Founder & CEO, Rx Integrative Solutions
Blue Ash, OH
Objectives

◦ Describe the stages of sleep and the importance of sleep to health and healing

◦ Describe causes & symptoms of sleeplessness

◦ Review sleep interventions (e.g., from Rx/OTC medications, dietary supplements, herbal teas, to mind body spirit health tips)
World Sleep Statistics

- We spend 1/3 of our life asleep

- 45% of global population has sleep deprivation

- Without adequate sleep, we run risk of dying from all causes including CV disease, increased BP; can experience weight gain, weak immune system, lack of libido, mood swings, depressions, diabetes mellitus, stroke dementia

- J Sleep Health April 2019. New York Langone Health’s School of Medicine Department of Population Health (Rebecca Robbins)
Stages of Normal Sleep

- **(0) Alpha Pre-Sleep (Drowsy)**
- **(1) Theta Light Sleep (Chatty Mind)**
- **(2) Theta Subconscious (Less Aware, Twitching)**
- **(3) Deep Delta (Restock Shelves)**
- **(4) Deep Delta (Take Out Trash)**
- **(5) Rapid Eye Movement (Dreams)**
Non-REM (NREM) to REM phases
4-6 cycles each night; one cycle can last for average of 90 minutes (70 minutes -120 minutes)
Healthy sleep can proceed from any NREM stages (N1 to N4) to REM sleep
Sleep Cycles

- Stage 1 of NREM sleep is between wakefulness and sleep (described as being awake, being drowsy, or being asleep).
- Stage 2 accounts for the majority of NREM sleep (disengaged from environment).
- During NREM Stages 3 and 4, both metabolic activity and brain waves slow (Delta sleep). Restock shelves, take out trash.
- **Delta stages are where human growth hormone is released and memories are processed. Stages important to generation of neurons, repairing muscle, restoring immune system.**
- REM Stage 5 is deepest sleep (dream, memory consolidation)
Sleep Cycles

- Brain becomes electrically and metabolically activated in REM

- REM occurs in bursts, accompanied by a 62-173% increase in cerebral blood flow, generalized muscle atonia, poikilothermia, dreaming, fluctuations in respiratory and cardiac rate

- Memory is received, locked, integrated during REM sleep (consolidation process)
Dreams

Dreams happen 4-5 times per night

We don’t remember dreams because we have not awakened and disrupted our sleep

Hitting the ‘snooze’ alarm in the morning to go back to sleep causes the body to sleep in a light quality sleep (may not dream)
Well, the census results are out, but a footnote says that the sheep count is probably inaccurate as the auditors often found themselves getting drowsy...
Circadian Rhythm

- **Newborns** sleep 20 hours a day
- 3 - 6 mos, differentiation between REM and NREM sleep
- 3 yrs, sleep-wake rhythm changes to a circadian pattern
- **Teens**, need 7-9 hours of sleep a day
- **Midlife**, gradual decline in sleep efficiency and sleep time
- **Seniors**, lighter and more fragmented sleep with intermittent arousals
- **Seniors**, shift in sleep stages and gradual reduction of slow wave sleep (NREM Stage 3 + Stage 4)
Seniors

- REM sleep is preserved

- Seniors tend to fall asleep earlier in the evening and awaken earlier in the morning (advanced sleep phase syndrome).

- Sleep efficiency (ratio of time spent sleeping to total time spent in bed) is lower in seniors. **FALSE: seniors require less sleep.**
Sleep and Memory Consolidation

- Different types of memories are consolidated at different stages of sleep.
- Use-dependent activity occurs every time you sleep (neuronal regeneration).
- Experience-dependent activity (new skill, fact, event committed to memory) occurs in memory enhancement and consolidation.
- Consolidation of memory takes an unstable bit of memory and hardwires it.
- Whole process of encoding memories, stabilizing them, and integrating them with other memories is known as memory consolidation.
- NREM needed for consolidating memory in hippocampus (stages 3 & 4).
- REM needed for synaptic plasticity used for consolidating memories in cortex (stage 5).
Sleep Hormones

- Ghrelin and leptin are **two hormones** in appetite regulation. Leptin is **anorexigenic** (i.e. appetite suppressant) while ghrelin is **orexigenic** (i.e. appetite stimulant).

- Ghrelin, the "hunger hormone" is a peptide hormone produced in GI tract, functions as a neuropeptide in the central nervous system. Ghrelin also plays a role in regulating the rate of use of energy.

- **Sleep deprived = body makes more ghrelin and less leptin**
How Histamine Affects Sleep

- Histamine is released by mast cells (white blood cells in the immune system) and plays a role in running our internal clock.
- Histamine receptors (H1 – H4) are found in the heart, breasts, lungs, brain hypothalamus.
- H1-blocking antihistamines promote sleep (Claritin).
- H2 receptor blockers like Zantac reduce stomach acid (GERD).
- Manipulating H3 receptor can either promote sleep or wakefulness (no drugs on market).
- H4 receptors involved with serotonin receptor pathway (immune/inflammation).
- Histamine is at its highest in the very early morning (3 – 4 am) – that’s why many asthma attacks & GERD happen then, to wake you up.
Insomnia (DSM-5)

- Insomnia is an experience of inadequate or poor quality of sleep characterized by difficulty falling asleep, difficulty maintaining sleep, waking up too early in the morning, or by non-refreshing sleep.

- Daytime consequences: tiredness, lack of energy, difficulty concentrating, irritability.

- **Insomnia is NOT a normal consequence of aging!**
Insomnia Causes

- Stress, anxiety, depression from overactive hypothalamic pituitary adrenal axis (increased night-time cortisol levels)
- Medications (anabolic steroids, anticonvulsants, beta blockers (CoQ10), antidepressants, decongestants, oral contraceptives (delta sleep), beta adrenergic agonists, thyroid meds)
- Nocturia (diuretics for BP)
- GERD/reflux disease with excess stomach acid
- Menopause (changes in progesterone levels)
Insomnia Causes

- Alterations in environment, routine, schedule
- Time changes/travel
- Use of caffeine, nicotine
- Watching TV (lessens amount of dreams) or using cell phone or laptop in bed (bright blue or white light that affects melatonin production)
- Medical conditions (arthritis pain, thyroid disease, CHF, asthma, COPD, restless leg syndrome, sleep apnea)
Lack of Adequate Sleep

- We need 7-8 hours of sleep per night

- Less than 7 hours -> triggers release of pro-inflammatory cytokines and decreases body’s antioxidant defense responses

- Less than 6 hours -> increased risk for obesity, type 2 diabetes, cancer, CV disease, ischemic stroke, anxiety, depression

- Less than 5 hours -> increased risk for obesity (0.35 kg/m² increase in BMI for every one-hour reduction in sleep)
Hypnic Jerks

- Normal (Stage 2)
- Caused by brain signals getting confused
- Feels like you are falling
- Body wants to fall asleep, but you force it to stay awake (still processing emails/computer)
What Gets You Up At Night?

- Thiazide diuretics for blood pressure
- Lasix (furosemide) for congestive heart failure
- BPH untreated
Causes of Restless Leg Syndrome (RLS)

- Cause unknown, more women than men experience RLS; affects all ages
- Low ferritin associated with iron deficiency
- Magnesium deficiency
- Vitamin D deficiency (J Sleep Breath 2016)
- Low dopamine levels in the brain (fall at end of day; when nerve cells damaged; amount of dopamine decreases causing muscle spasm)
Treat Restless Leg Syndrome (RLS)

- Mirapex and Requip (dopamine agonists) Rx medication
- Enacarbil form of gabapentin Rx medication
- Magnesium (nuts, green veggies, seafood, supplements)
- Vitamin D (milk, fortified food, supplements)
- Iron supplements
- **Tonic water (quinine 83 mg/liter) vs Qualaquin 324 mg (Rx for malaria, lupus)**
Alcohol

- An alcoholic nightcap may make you drowsy, but causes fragmented sleep
- Alcohol relaxes the muscle in the back of your throat
- Easier for the airway to become blocked in people with sleep apnea
- Sleeping pills have the same effect of causing fragmented sleep
Foods That Keep You Up At Night

- Ketchup, tomatoes
- Soda, coffee
- Chocolate, cocoa
- Donuts, bread
- Alcohol
- French fries, fried chicken
- Dried fruit
- Hot peppers, hot sauce
- Peppermint
- High sugar cereal
- Full fat cheese, pizza
- Green tea
- Onions
- Peanut butter
- Jam, jelly
- Ice cream
- Cake, cookies
- Garlic
- Asparagus (amino acid asparagine make you urinate)
Sleep Apnea

- 18 million Americans (National Sleep Foundation)
- Snoring, anxiety, nightmares, multiple awakenings (reduces REM)
- Risk factors: obesity, > 65, post menopausal, genetic, meds; a pause of 20 seconds or more in breathing
- Partial or complete collapse of back of throat during sleep
- Poorly oxygenated blood goes to brain which responds by sending signal to heart to beat stronger and faster. Racing heart increases BP (e.g., risk of atrial fib, MI, stroke)
- AHI or RDI score $\geq$ 5
Medications That Contribute to Sleep Apnea Exacerbations – Respiratory Depression

- Benzodiazepines –
  - flurazepam, temazepam, triazolam, more

- Opioids and opiates –
  - fentanyl, morphine, methadone, heroin, more
Time To Sleep...

I'm Counting Sheep
Tips for Healthy Sleep

- **Keep your bedroom dark, quiet, and cool. Allows natural melatonin levels to rise.** If light is a problem, try a sleeping mask. If noise is a problem, try earplugs, a fan, or a white noise machine to cover up the sounds.
- Do not eat or drink within about 3 hours of bedtime unless milk/tea
- Take **diuretic medications** during the day
- Take progesterone tablets at bedtime (improved sleep during menopause)
Tips for Healthy Sleep

- **Follow a routine** to help relax and wind down before sleep such as reading a book, listening to music, or taking a bath.

- If you cannot sleep **within 20 minutes** or going to bed or don’t feel drowsy, get out of bed. Read or do a quiet activity until you feel sleepy. Then try going back to bed.
Sleep Interventions

- **Hot shower** and stretch before bedtime
- **Fresh clean bed linens**
- **Write down** ‘worries’ and unfinished business on paper then park it until tomorrow
- **Deep breathe in and out for 5 minutes upon retiring**
- **Aromatherapy** with essential oil on pillow
- **Milk** – calcium promotes melatonin (contains small amount of L-tryptophan)
Affirmations

i am loved.
i am enough.
i am strong.
Exercise

- Regular aerobic exercise has been shown to deepen sleep 5 or 6 hours before sleep time.

- In a study of seniors with moderate sleep complaints, regular moderate intensity exercise during the day was beneficial for improving subjective quality of sleep.

  (King. Moderate intensity exercise and self rated quality of sleep in older adults. A randomized controlled trial. JAMA 1997;277:32-7)
Sounds of Sleep

- **New York psychiatrist Galina Mindlin MD** uses brain music
- Rhythmic patterns of sounds derived from recordings of patients’ own brain waves
- Helps overcome insomnia, anxiety, depression
- Sounds resemble classical piano music and have a calming effect similar to yoga or meditation
- Small double blind study from 1998 (Toronto U) found 80% of those undergoing this treatment reported benefits
Sleep Restriction Therapy

- Creates sleep efficiency by decreasing the amount of time you spend in bed
- Time allowed sleeping is obtained by averaging the amount of time spent sleeping for one week
- Weekly adjustments are made in 15- to 20- minute increments depending on sleep efficiency for that week
- If patient exceeds 90% efficiency, the time spent in bed is increased; if patient falls below 80% efficiency, the time spent in bed is decreased
- One study demonstrated that sleep restriction therapy improved sleep efficiency in as little as 1 week (Morin, Cognitive behavior therapy and pharmacotherapy for insomnia: update of a placebo controlled clinical trial. Sleep Res 1995;24:303)
- Fatigue and sleepiness are seen in early treatment
Medications for Sleep

- **Ambien** (zolpidem) Class IV
- **Sonata** (zaleplon) Class IV
- Benzodiazepines (**Restoril**, **Valium**, **Ativan**, clonazepam, Halcion) Class IV
- **Trazodone** (antidepressant) Rx
- **Elavil** (amitriptyline, antidepressant) Rx
- **Benadryl** (diphenhydramine) OTC
2019 New FDA Boxed Warning

• **Lunesta, Sonata, Ambien**

• Boxed warning on Medication Guides that complex sleep behavior can increase while patient is not fully awake while taking these agents

• Fall risk, sleep walking, *sleep driving*, FDA reports from 4.30.19 -> 66 cases of complex sleep behaviors occurring with these medications over the past 26 years that resulted in serious injuries, including *death*
Antidepressants

- **Amitriptyline, doxepin, imipramine, desipramine** cause anticholinergic side effects (constipation, blurred vision, nausea, dryness of mouth, confusion), cardiac toxicity, orthostatic hypotension, sexual dysfunction.

- Tricyclics (**amitriptyline, desipramine**) and **SSRIs** like **Prozac** may worsen restless leg syndrome and periodic limb movement disorder.

- **Trazodone** – not FDA approved for insomnia, commonly Rx’ed for sleep (side effects: priapism, a metabolite **meta-chlorophenylpiperazine** causes dissatisfaction and irritability the day after trazodone is taken).
Benadryl for Sleep?

- Blocks ACh production (less ACh produced as we age)
- Taken 30 – 60 minutes prior to bedtime
- Monitor for fall risk
- Do not take more than 25 mg diphenhydramine for longer than 10 days (preferably 12.5 mg)
- Anticholinergics cause dry mouth, constipation, blurred vision, morning grogginess, urinary retention; dementia
- Contraindicated in BPH, glaucoma, emphysema, chronic bronchitis
Antihistamines

DIPHENHYDRAMINE
- Tranquil Nighttime Sleep Aid
- Tylenol Simply Sleep (25 mg)
- Sominex Maximum Strength Formula (50 mg)
- Unisom SleepGels Gelcaps (50 mg)
- Unisom SleepMelts (25 mg)

DOXYLAMINE SUCCINATE
- Unisom SleepTabs Tablets (25 mg)
- Sleep Aid (Kirklands)

*Cause cognitive impairment in seniors*
OTC Products for Sleep

- Unisom
- Sominex
- Simply Sleep
- Vicks ZzzQuil (diphenhydramine)
- Nytol
- Nature Made Sleep

www.OTCGuide.net
Dietary Supplements For Sleep

- Valerian
- Melatonin
- 5-HTP
- L-theanine
Valerian (Valeriana officinalis)

- Indications: insomnia (decreases time it takes to fall asleep), anxiety
- Takes 2 weeks to work effectively
- MOA: sedative on the brain (GABA receptors)
- Dose: 400 mg – 900 mg taken 30 to 45 minutes before bed
- Side Effects: CNS depression, vivid dreams, hepatotoxic in high doses
## Melatonin

<table>
<thead>
<tr>
<th><strong>Indications</strong></th>
<th>Reduces jet lag and resets sleep-wake cycle. Dose 1 – 5 mg at bedtime PRN.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Side Effects</strong></td>
<td>Short T1/2. Next day drowsiness, fatigue, dizziness, headache, irritability, increases and decreases in blood pressure.</td>
</tr>
<tr>
<td><strong>Natural Sources</strong></td>
<td>Porridge oats, sour cherries, banana peanuts, grape skins, walnuts, olive oil, strawberries, tomatoes. <strong>Caffeine suppresses melatonin for 10 hours.</strong></td>
</tr>
</tbody>
</table>
Melatonin Containing Products

- MidNite
- Nature Made Melatonin 3 mg
- Nature Made Sleep softgels
- Natrol Melatonin 5 mg tablets
- Nature’s Bounty Melatonin 5 mg tablets
- Schiff Melatonin Plus tablets
- Sundown Melatonin tablets
- Twinlab Melatonin tablets
- Unisom Natural
5-HTP (hydroxytryptophan)

- An amino acid produced commercially from the seeds of African plant *Griffonia simplicifolia*.

- Used for disorders such as insomnia, depression, anxiety. Produces serotonin (low serotonin levels associated with depression).

- Too much 5-HTP in your system can cause a spike in serotonin levels, resulting in anxiety, shivering, and serious heart problems. Some people can get rapid onset eosinophilia-myalgia syndrome (EMS) causing breathing problems.
The diagram illustrates various components and pathways related to serotonin (5-HT) neurotransmission. Key elements include:

- **SERT** (serotonin transporter) involved in reuptaking serotonin.
- **5-HT** (5-hydroxytryptamine) as the primary neurotransmitter.
- **CA2+** channels modulating ion flow.
- **5-HT_2A** receptor with inhibitory autoreceptor function.
- **VMAT** (vesicular monoamine transporter) for serotonin storage.
- **MAO-A** (monoamine oxidase A) enzyme involved in serotonin degradation.
- **Neurons** with multiple types of serotonin receptors such as 5-HT_1A, 5-HT_2A, 5-HT_2C, 5-HT_4, 5-HT_6, and 5-HT_7.
- **Astrocytes** and **Oligodendrocytes** interacting with serotonin pathways.
- **CA2+** channels and **K^+** channels modulating neuronal excitability.
- **Dietary factors** influencing serotonin synthesis, such as tryptophan, kynurenine, and melatonin.
- **Cytokines** and **Glia/α-Ser** influencing serotonin release.

The diagram also highlights the role of **G proteins** (G蛋白) such as Gs, Gi, and Go in modulating cellular responses via **PKA** (protein kinase A) and **Epac** pathways.

**TRENDs in Pharmacological Sciences**
L-Theanine in Green Tea

How **L-Theanine** works. **L-Theanine** is an analog to glutamic acid as well as glutamine and readily crosses the blood-brain barrier. There, it increases dopamine release in the brain and increases overall levels of the inhibitory neurotransmitter, GABA, which induces relaxation and helps prevent insomnia.
Teas

- Decaffeinated Green
- Lavender **angustifolia**
- Chamomile (**Matricaria discoidea**)
- Lemon Balm (**Melissa Officinalis**)
- Sleepy Time
Which of the following is/are contraindicated for sleep in seniors?

1) Melatonin
2) Valerian
3) Diphenhydramine
4) L-theanine
5) Chamomile tea
6) Aromatherapy
7) Ambien/Sonata
8) Valium
Which of the following is/are contraindicated for sleep in seniors?

1) Melatonin
2) Valerian
3) Diphenhydramine
4) L-theanine
5) Chamomile tea
6) Aromatherapy
7) Ambien/Sonata
8) Valium
Summary

- Sleep is essential to life
- **Sleep patterns change over our lifetime; but we still need 7-8 hours/night to heal**
- It is always good to address mind body spirit and environmental factors for optimal sleep health
- **Talk with your doctor or sleep specialist about a sleep study if you think you might have sleep apnea**