

SleepServices
Australia

Sleep disturbance in menopause

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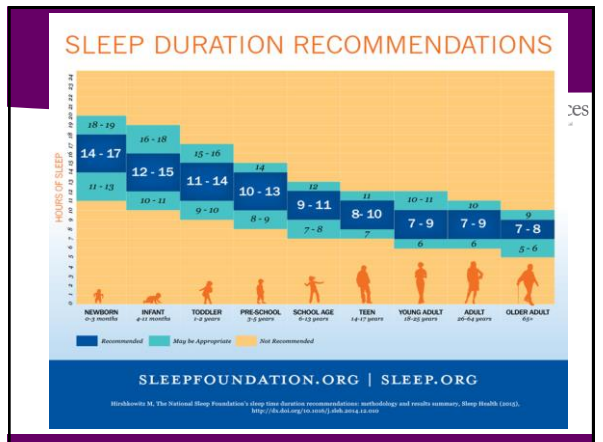
Conflicts of interest

- Medical director – Sleep Services Australia (Australia wide home diagnostic sleep service)

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A good night's sleep....

- Enough sleep....
- Good quality sleep
- Sleep in one block
- Ideally sleep at night
- No sleep disorders
- Few arousals
- Regular sleep wake cycles



Stages of sleep

Stage 1 4-5% Light sleep. Muscle activity slows down. Occasional muscle twitching.

Stage 2 45-55% Breathing pattern and heart rate slows. Slight decrease in body temperature.

Stage 3 4-6% Deep sleep begins. Brain begins to generate slow delta waves.

Stage 4 12-15% Very deep sleep. Rhythmic breathing. Limited muscle activity. Brain produces delta waves.

Stage 5 20-25% Rapid eye movement. Brainwaves speed up and dreaming occurs. Muscles relax and heart rate and blood rate increase. Breathing is rapid and shallow.

Wake REM Stage 1 Stage 2 Stage 3 Stage 4

first cycle second cycle third cycle fourth cycle fifth cycle

▲ ATLAS™ Cycle ■ Deep Sleep (SWS) ■ Dreaming (REM)

HOW SLEEP AFFECTS YOUR HEALTH

SLEEP DEPRIVATION

- IMPAIRED COGNITION**
Lack of sleep slows memory and your ability to process information.
- HIGHER LEVELS OF ANXIETY**
Lack of sleep causes the brain's anticipatory reactions, increasing overall anxiety levels.
- STROKE RISK**
When you sleep 6 hours or less a night, your chance of a stroke increases 4x.
- INCREASED RISK FOR DIABETES**
Lack of sleep increases cortisol and nonresponse, both are associated with insulin resistance.
- INCREASES SYMPTOMS OF DEPRESSION**
A lack of sleep disrupts neurotransmitters in the brain which regulates mood.
- INCREASED RISK OF BREAST CANCER**
Melatonin decreases when you are exposed to light late at night. A decrease in melatonin disrupts estrogen production which can lead to breast cancer.
- INCREASED RISK FOR HEART DISEASE**
Heart pressure increases when you sleep.
- WEIGHT GAIN**
Sleep helps balance hormones that make you feel hungry and full.

Adventist Health
livingwellpdx.org

Hormones and sleep



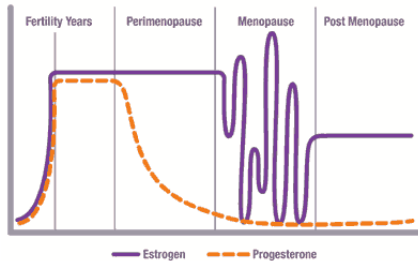
- Oestrogen
 - Direct effects - Increase REM sleep, decrease sleep latency, decrease the no of awakenings, increase TST, ↓ number of spontaneous arousals
 - Related to temperature regulation
 - Antidepressant effect – modulation of neurotransmitters including NA, serotonin (5HT), and acetylcholine metabolism
- Progesterone
 - direct sedative effect by stimulating non REM associated GABA receptors and being a respiratory stimulant
- Melatonin
 - Hormone which regulates timing of sleep and quality of sleep.
 - levels usually reduce with age, but immediately post menopause melatonin increases for up to several years

Hormones and sleep 2



- ↓ oestradiol and progesterone may have a direct effect on sleep
- ↓ Oestrogen
 - Hot flashes and night sweats
 - Slows intake and secondary production of magnesium
 - Harder to relax and fall asleep
- ↓ Progesterone
 - Decreased sleep inducing effect
 - Changes in mood and anxiety which directly affect sleep
- Melatonin
 - post menopausal women with insomnia generally have shown to have lower melatonin levels than their cohorts
 - Decreased melatonin affects ability to fall asleep, and stay asleep

Hormonal changes around menopause



Sleep issues during menopause



- Symptoms vary between women in frequency, severity and duration and may persist for several years after menopause
 - Vasomotor symptoms
 - Sleep disordered breathing
 - Insomnia
 - Restless legs syndrome
 - Mood disorders
 - Medications
 - Chronic diseases
- Causes of sleep disturbances during the peri-menopausal period are often multifactorial

Changes around menopause which affect sleep

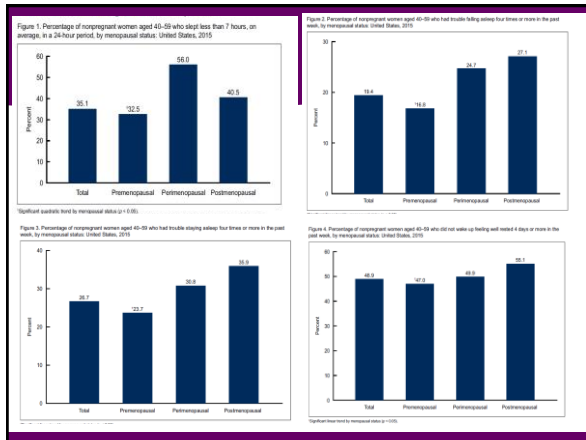


- Busy lives – demanding careers, ageing parents, raising children
- Stress
- Health issues
- Pain
- Other sleep disorders
 - sleep-related breathing
 - movement disorders
- Sleep issues are likely even without the major biological changes
- Self reported sleep difficulties ranging between 40-56% (pre-menopausal ~ 31%)

Statistics...



- > 56% perimenopausal women sleep less than 7 hours per night
- 27.1% have problems falling asleep > 4 times a week
- 35.9% have trouble staying asleep > 4 times per week
- 49.9% wake in the morning feeling tired, four or more days in a week
- Insomnia - 40.5%



Hot flashes

- Unexpected feelings of heat all over body accompanied by sweating. Usually begin around the face and spread to the chest affecting 75-85% of women around menopause.
- While sleep time may not suffer, sleep quality does. Hot flashes may interrupt sleep and frequent awakenings cause next day fatigue.
- Consistently associated with poorer self reported sleep quality and chronic insomnia
- Bothersome HF but not HF alone associated with sleep issues
- Effective treatment of HF is associated with improved sleep quality

- ~80% of HFs interfere with sleep
- HF's were linked with more PSG awakenings, more WASO, more Stage 1 sleep
- Few HFs occur in REM sleep
- HF-associated wake time was responsible for 27% of WASO time

Prevalence of sleep apnoea

Figure 1: Prevalence of sleep-disordered breathing (SDB) indicated by apnea-hypopnea index (AHI) of 5 or greater for premenopausal women and perimenopausal plus postmenopausal women by age. Values represent a 5-year moving average.

Age	Pre-menopause	Peri- and postmenopause
30	0.10	0.10
35	0.10	0.10
40	0.10	0.10
45	0.10	0.15
50	0.10	0.20
55	0.10	0.25
60	0.10	0.30
65	0.10	0.35

Figure 2: Prevalence of SDB indicated by an AHI of 5 or greater for premenopausal women and perimenopausal plus postmenopausal women by body mass index (BMI). Values represent a 5-unit moving average.

Body Mass Index	Pre-menopause	Peri- and postmenopause
21	0.05	0.05
25	0.05	0.05
29	0.05	0.05
33	0.05	0.05
37	0.05	0.05
41	0.05	0.05
45	0.05	0.05

- 2.6 times more likely than pre-menopausal women to have mild OSA
- 3.5 times more likely to have severe OSA

Young, T et al. Am J Respir Crit Care med
Vol 167. pp 1181-1185, 2003

Assessing sleep disturbance

- Main symptoms – insomnia, nocturnal awakenings, unrefreshing sleep, excessive daytime sleepiness
- Past history - pre-existing sleep issues
- Symptom onset – is there a relationship between the onset of the sleep symptoms and menopausal symptoms
- Symptoms – frequency, duration, impact on daytime fn
- VMS – frequency, severity and the number of night-time awakenings attributable to these
- Other important symptoms – new onset snoring, apnoeas, weight gain, restless legs

Assessing sleep disturbance

- Medications
- Social factors – relationship difficulties, workplace issues, work/life balance, smoking, alcohol & caffeine intake
- Mood – symptoms of depression or anxiety. Past history of psychiatric illness
- Past history - pre-existing sleep issues

Investigation of sleep related symptoms

- Comprehensive history
- Sleep questionnaires
- Sleep diaries
- Actigraphy
- Polysomnography – inpatient & home
- Sleep apnoea screening tests

Treatment



- Sleep hygiene
- Treatment of other disorders which affect sleep
 - Pain, GER,
- Management of stress
- Treatment of mood / depression / anxiety
- Meditation
- Medication
 - OTC, herbal medicine, hormonal, sleeping tablets, other
- Treatment of other sleep disorders

Improve sleep hygiene

-
- Getting back in sync with your body's natural sleep-wake cycle—is one of the most important strategies for achieving good sleep
 - Set a regular bedtime & wake up at the same time every day
 - When possible, do your intense training sessions early in the day rather than in the evening to reduce sleep onset latency
 - Stay away from large, fatty meals at night
 - Cut down on caffeine
 - Avoid drinking too many liquids in the evening
 - Turn off your television
 - Take a hot shower or leisurely warm bath before bedtime
 - Reserve your bed for sleeping
 - Eat and drink correctly
 - Deep breathing
 - Tense all the muscles as tightly as you can, then relax
 - Close your eyes and try taking deep, slow breaths
 - Keep noise down
 - Keep your room dark and cold
 - Make sure your bed is comfortable
 - Make your bedroom more sleep friendly
 - Get anxiety & stress in check

Management of Stress / Anxiety



- Mindfulness
- Relaxation techniques
 - Progressive muscle relaxation
 - Abdominal breathing
 - Isometric relaxation exercises
- Cognitive behavioural therapy
 - Focuses on changing patterns of thinking and beliefs that are associated with, and trigger anxiety
- Exercise
- Avoidance of nicotine, caffeine and stimulants
- yoga/tai chi
- Medication
- Support groups

Hormone replacement therapy – HRT



- Found to help relieve menopausal symptoms in women with concomitant HF's
 - Most studies have been done using combined therapy; however benefit has been shown with oestrogen alone
 - Recent big studies stopped due to safety concerns re cardiovascular disease and dementia
 - Recommended that HRT be prescribed at the lowest effective dose and used for only brief periods and when no contra-indications
- Oestrogen increasing homeostatic drive, decreasing hot flushes,
- Progesterone exerting a direct hypnotic effect
- Independent effects of oestrogen vs progesterone / progestin compounds need further evaluation
- Follow guidelines, ie when the balance of potential benefits and risks is favourable for the individual
- Abrupt discontinuation of HT is associated with hot flash relapse which could lead to insomnia

Treatment



- Benzodiazepines
 - Acute situational sleep problems
 - Side effects, addictive nature, withdrawal symptoms & tolerance
 - Primarily modulate GABA receptors
- Non benzodiazepine hypnotics – zolpidem & eszopiclone
 - Improved sleep onset & sleep maintenance in randomised trials
 - Also reduced self reported hot flushes
- Gabapentin
 - used for its sedative effects
 - Reducing hot flushes in post menopausal women

Treatment ...2



- Antidepressants
 - SSRI and SNRI have been shown to effective in treating hot flushes
 - Tetracyclic antidepressants / mirtazapine – increase the release of noradrenaline and serotonin. Positively impact on insomnia
- Circadian rhythm
 - Maintaining a fixed sleep / wake cycle with adequate sleep duration
 - Melatonin / Ramelteon (selective melatonin receptor agonist)
 - Light therapy – maintain wakefulness

Impact of antidepressants on sleep

Table	Antidepressants and their effects on sleep physiology	
Class/medication	Pharmacology	Effects on sleep
TCA	Serotonin and norepinephrine reuptake inhibition, histamine H ₁ antagonism	Decreased sleep latency, REM suppression, increased REM latency
SSRI	Serotonin reuptake inhibition	REM suppression, increased REM latency
Selective SNRI	Serotonin and norepinephrine reuptake inhibition	REM suppression, increased REM latency
Trazodone, nefazodone	Serotonin-2 antagonism	Decreased sleep latency, increased slow wave sleep
Mirtazapine	Serotonin-2 and histamine H ₁ antagonism	Decreased sleep latency, increased slow wave sleep
Bupropion	Norepinephrine and dopamine reuptake inhibition	Increased REM sleep

↑ risk of plms
Can increase sleep disturbance

- Agomelatine – agonist of MT₁ and MT₂ receptors
 - Increase in sleep efficiency, improvements in quality and quantity of sleep increase in slow wave sleep

Herbal treatments

- Soy
 - 6 trials / 4 trials inconsistent data
 - Improvements in the soy groups at 6 months, but not at 1 year
 - Percentage of women affected by sleep problems declined by 37% at 1 month and 46% at 6 months
- Phytoestrogen – a plant hormone similar to oestrogen
 - Soy products (tofu, soybeans and soy milk)
 - Also in OTC nutritional supplements (ginseng, extract of red clover, black cohosh, Regulated by FDA. Proper doses, safety, long term effects and risks are not yet known)
- Valerian
 - More beneficial in menopausal women with low level estrogens
 - Significant improvements at higher doses 530mg BD 1/12 improved sleep
 - No improvement with 100mg nocte
- Fenugreek Husk
 - 88 post menopausal women
 - 75% improvement in the insomnia group

Herbal medicines and sleep

Herbal Medicine	INSOMNIA		
	Some support via human clinical trials?	Some support via animal or test tube studies?	Evidence level for helping insomnia
Kava (<i>Piper methysticum</i>)	Yes	Yes	More research needed
Valerian (<i>Valeriana</i> spp.)	Yes	Yes	Low
Passionflower (<i>Passiflora</i> spp)	Yes	No	Low
Hops (<i>Humulus lupulus</i>)	Yes	Yes	More research needed
Sour date (<i>Zizyphus jujube</i>)	No	Yes	More research needed
Mimosa (<i>Albizia julibrissin</i>)	No	Yes	Low
Lavender (<i>Lavendula</i> spp.)	No	Yes	More research needed
California Poppy (<i>Eschscholzia californica</i>)	No	Yes	More research needed
Chamomile (<i>Matricaria recutita</i>)	No	No	More research needed

Non medication treatment of VMS

Comparison	# RCTs (Patients)	Findings	Strength of Evidence (Rationale by Domain)
Acupuncture vs waitlist	4 (503)	SMD 0.66 lower (1.06 lower to 0.26 lower)	Moderate, Low ROB, consistent, direct, imprecise
Acupuncture vs sham acupuncture	8 (644)	SMD 0.35 lower (0.70 lower to 0.01 higher)	Moderate, Low ROB, consistent, direct, imprecise
Yoga vs control	4 (157)	SMD 0.36 lower (0.65 lower to 0.07 lower)	Low, Moderate ROB, consistent, direct, imprecise
Structured exercise vs control	4 (433)	SMD 0.08 lower (0.33 lower to 0.16 higher)	Moderate, Moderate ROB, consistent, direct, precise
Paced respiration vs control	3 (163)	SMD 0.04 higher (0.73 lower to 0.82 higher)	Low, Low ROB, inconsistent, direct, imprecise
Applied relaxation vs control	2 (82)	1 RCT showed small benefit and 1 RCT showed no effect	Insufficient, Moderate ROB, inconsistent, direct, imprecise
Hypnosis vs control	3 (274)	No pooled estimate. Effect size ranged from 0.479 to 1.25	Low, Moderate ROB, consistent, direct, imprecise
Mindfulness-based stress reduction vs control	1 (110)	No reduction in hot flashes	Not rated

Abbreviations: RCT = randomized controlled trial; ROB = risk of bias; SMD = standardized mean difference

Conclusion

- Sleep disturbance is a common complaint – significant impact on QOL
- For some women, sleep problems are severe and impact daytime functions and QOL and may have long term consequences for mental & physical health
- Many causal factors including but not limited to vasomotor & hormonal factors, co-existing medical conditions, and lifestyle factors
- Number of pharmacological & behavioural treatment strategies
- Treatment needs to be tailored for the individual

Thank you

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