Sleep Disorders

Dr.Niayesh Mohebbi
Assistant Professor of Clinical Pharmacy
Clinical Pharmacy Department
Tehran University of Medical Sciences

Introduction

- Approximately one-third of the adult life is expended on sleep.
- Sleep deficiency, including insufficient sleep duration, irregular timing of sleep, poor sleep quality, and sleep or circadian rhythm disorders, is highly prevalent and threaten public safety.
- Major sleep disorders include insomnia ranging from 15 % to 35%, sleep apnea at 6% to 24% periodic limb movements in sleep (PLMS), and restless leg syndrome (RLS) ranging from 3% to 15%, and narcolepsy at 0.025% to 0.05%.
- Nightmares, nocturnal leg cramps, and snoring are more benign sleep disorders.

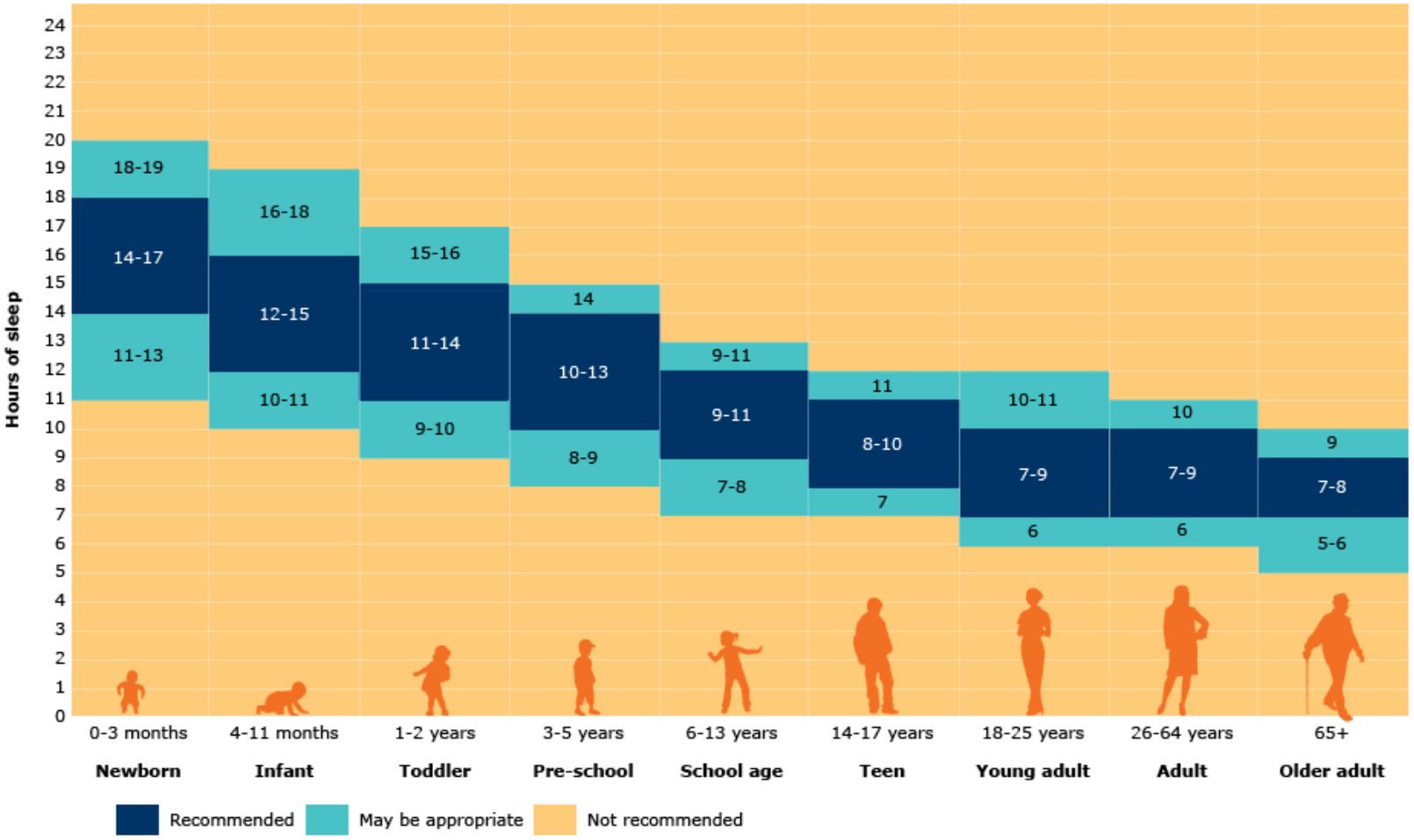
Circadian Rhythm and Sleep Cycles

- Sleep is a dynamic process with a cyclical recurrence and varying stages. The endogenous sleep-wake pattern of humans is based on the solar day-night cycle called the **circadian rhythm.**

- Circadian rhythm is controlled both by internal and external factors. Sensory input (visual and acoustic) or other external factors modify the "internal clock" to a 24 hour day through working with the internal network and signaling brain centers to either wake or sleep.

- Thus, darkness is a visual cue that prepares the brain for sleep. Similarly, bright light serves to prepare the brain for wakefulness.

Sleep duration recommendations by age from the National Sleep Foundation*



* These recommendations are very similar, but not identical to those from the American Academy of Sleep Medicine (AASM).[1,2]

1. *Paruthi S, Brooks LJ, D'Ambrosio C, et al. Recommended amount of sleep for pediatric populations: A statement of the American Academy of Sleep Medicine. J Clin Sleep Med 2016; 12:785.*
2. *Consensus Conference Panel, Watson NF, Badr MS, et al. Recommended amount of sleep for a healthy adult: A Joint Consensus Statement of the American Academy of Sleep Medicine and Sleep Research Society. J Clin Sleep Med 2015; 11:591.*

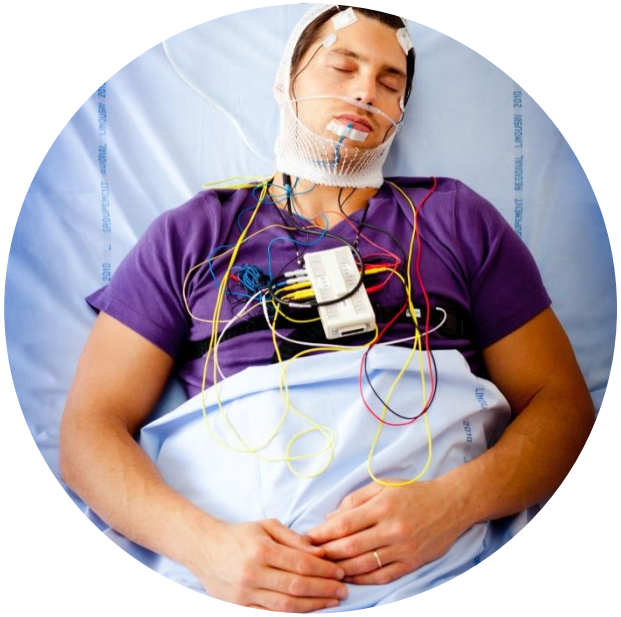
Circadian Rhythm and Sleep Cycles

- Once sleep is initiated, it alternates between the two phases of rapid eye movement (REM) and non-rapid eye movement (NREM) sleep.
- These phases vary in length throughout the sleep cycles.
- During a normal night of sleep, a person generally has four to six cycles of sleep which last an average of 90 minutes (vary 70-120 minutes).

The Sleep Stages

- Each sleep stage serves a physiologic function and can be monitored in sleep laboratories by polysomnography.

- Polysomnography is the term used to describe three electrophysiologic measures: the electroencephalogram (EEG), the electromyogram, and the electro-oculogram.

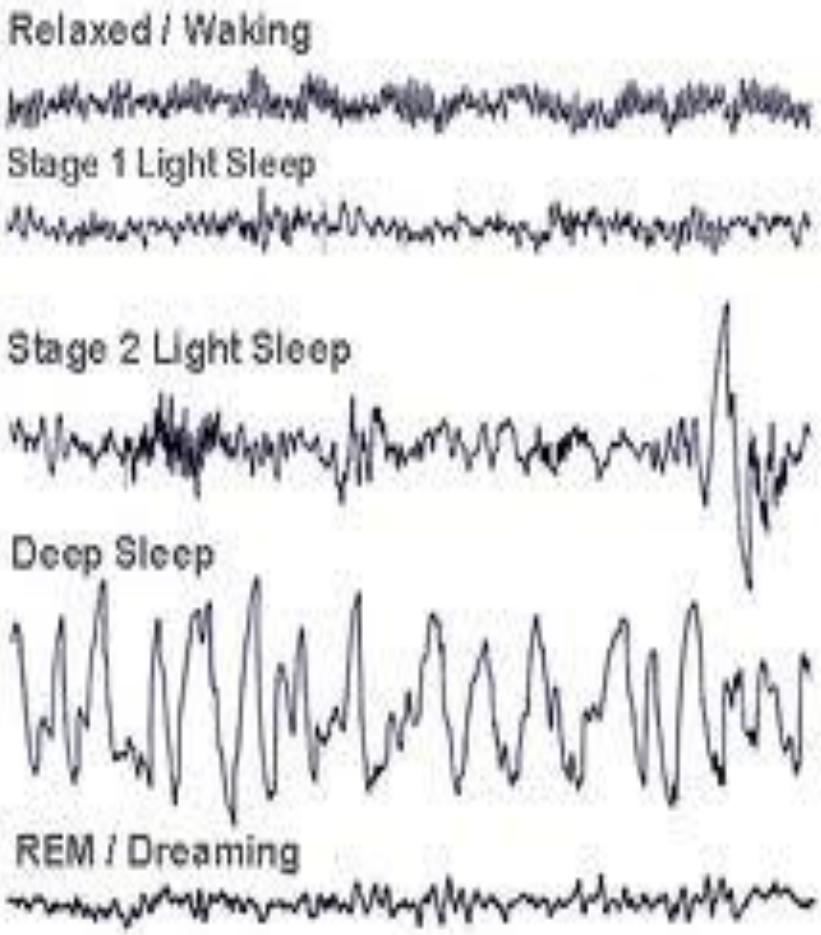


Non-Rapid Eye Movement Sleep

- NREM sleep → 4 stages
- Stage 1 is a transition between sleep and wakefulness known as *"relaxed wakefulness"*, which generally makes up approximately 2% to 5% of sleep.
- Approximately 50% of total sleep time is spent in stage 2, which is rapid-wave (alpha) or lighter sleep.
- Stages 3 and 4 are slow-wave (delta) or deep sleep. Stage 3 occupies an average of 5% of sleep time, whereas stage 4 constitutes 10% to 15% of sleep time in young, healthy adults.

Non-Rapid Eye Movement Sleep

- At sleep onset, the brain quickly passes through stage 1 and moves to stage 2.
- Muscle activity shuts down, and brain waves become less active.
- After a brief REM period, the brain moves into slow-wave sleep (NREM stages 3 and 4) approximately 1 to 3 hours after a person falls asleep.
- The body continually moves through all of the sleep stages over the course of the night.
- REM periods become longer, and deep sleep lessens during the last half of the night.


Relaxed / Waking
Stage 1 Light Sleep
Stage 2 Light Sleep
Deep Sleep
REM / Dreaming

Non-Rapid Eye Movement Sleep

- The function of stage 1 is to initiate sleep.
- Stage 2 provides rest for the muscles and brain through muscle atonia and low voltage brain wave activity.
- Arousability from sleep is highest during stages 1 and 2.
- In contrast, it is difficult to awaken someone during stages 3 and 4, or delta sleep. Delta sleep, also known as *restorative sleep,* is enhanced by serotonin, adenosine, cholecystokinin, and IL-1.

Non-Rapid Eye Movement Sleep

- Deep sleep is most abundant in infants and children and tends to level off at approximately 4 hours a night during adolescence.

- At age 65, deep sleep accounts for only 10% of sleep, and at age 75, it often is nonexistent.

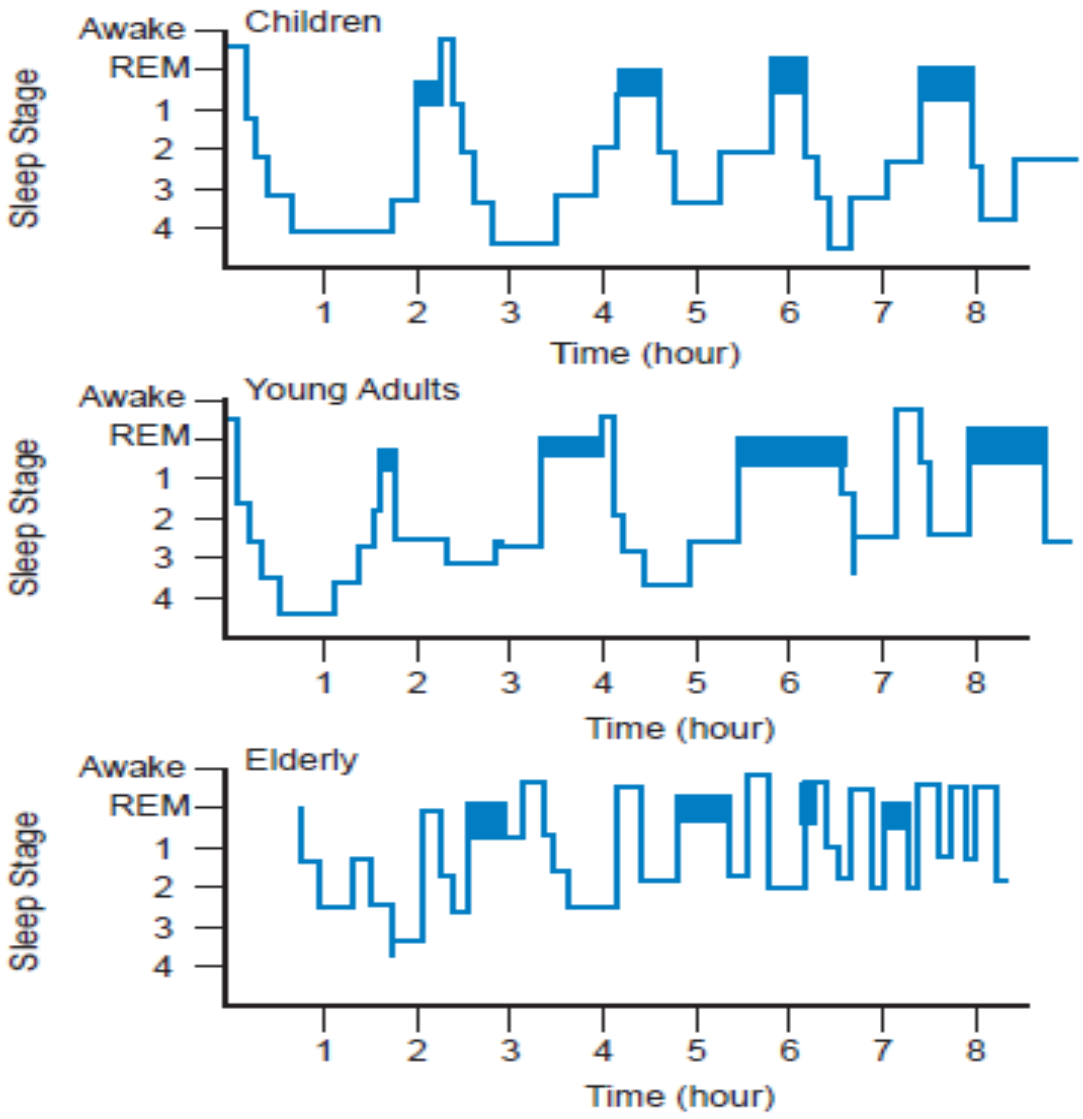


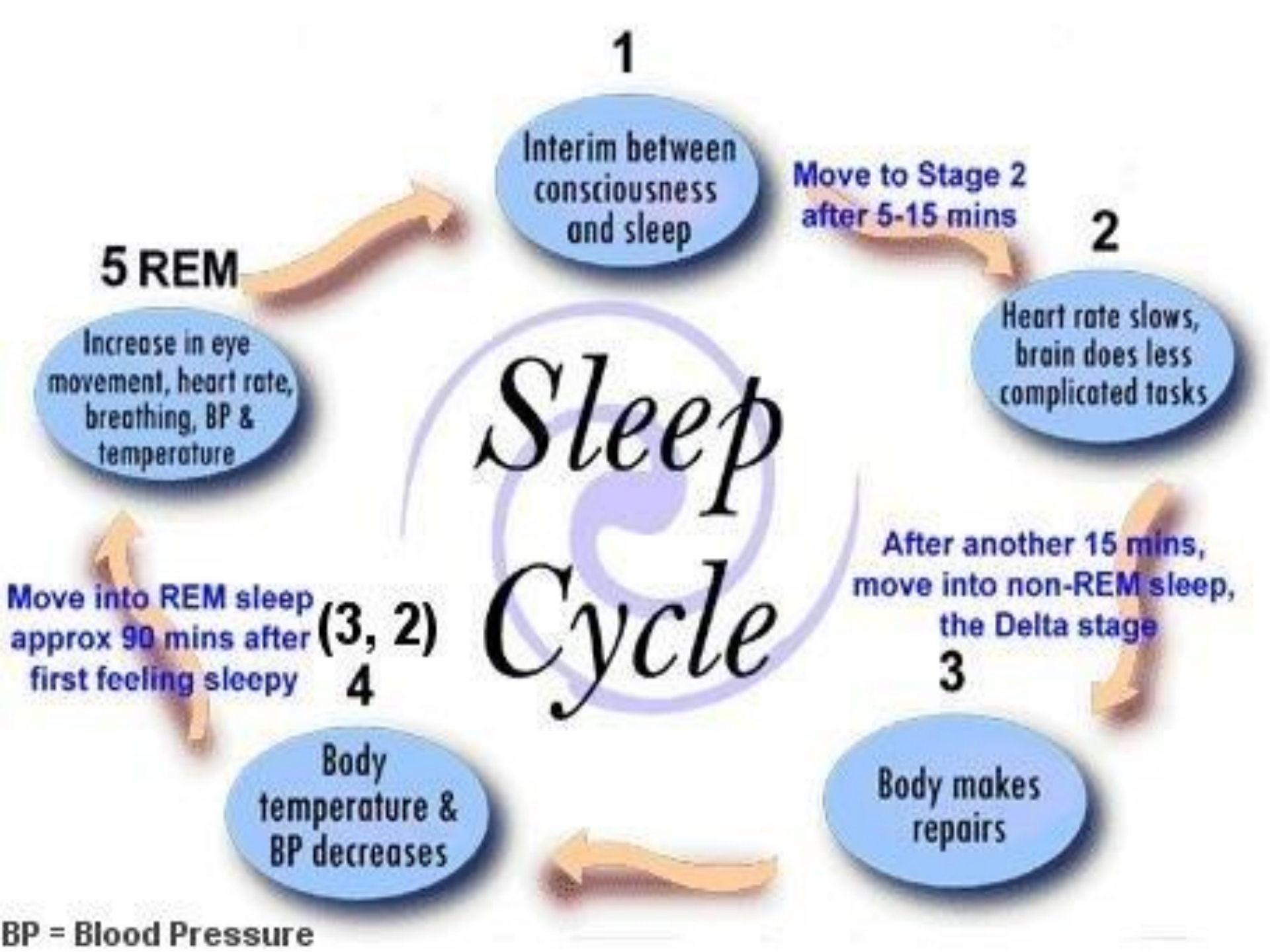
FIGURE 81-1 **Normal sleep cycles.**

Rapid Eye Movement Sleep

- REM sleep is also called paradoxical sleep because it has aspects of both deep sleep and light sleep.
- Body and brainstem functions appear to be in a deep sleep state as muscle and sympathetic tone drop dramatically.
- In contrast, neurochemical processes and higher cortical brain function appear active.
- Dreaming is associated closely with REM sleep, and when a person is awakened from REM, alertness returns relatively quickly.

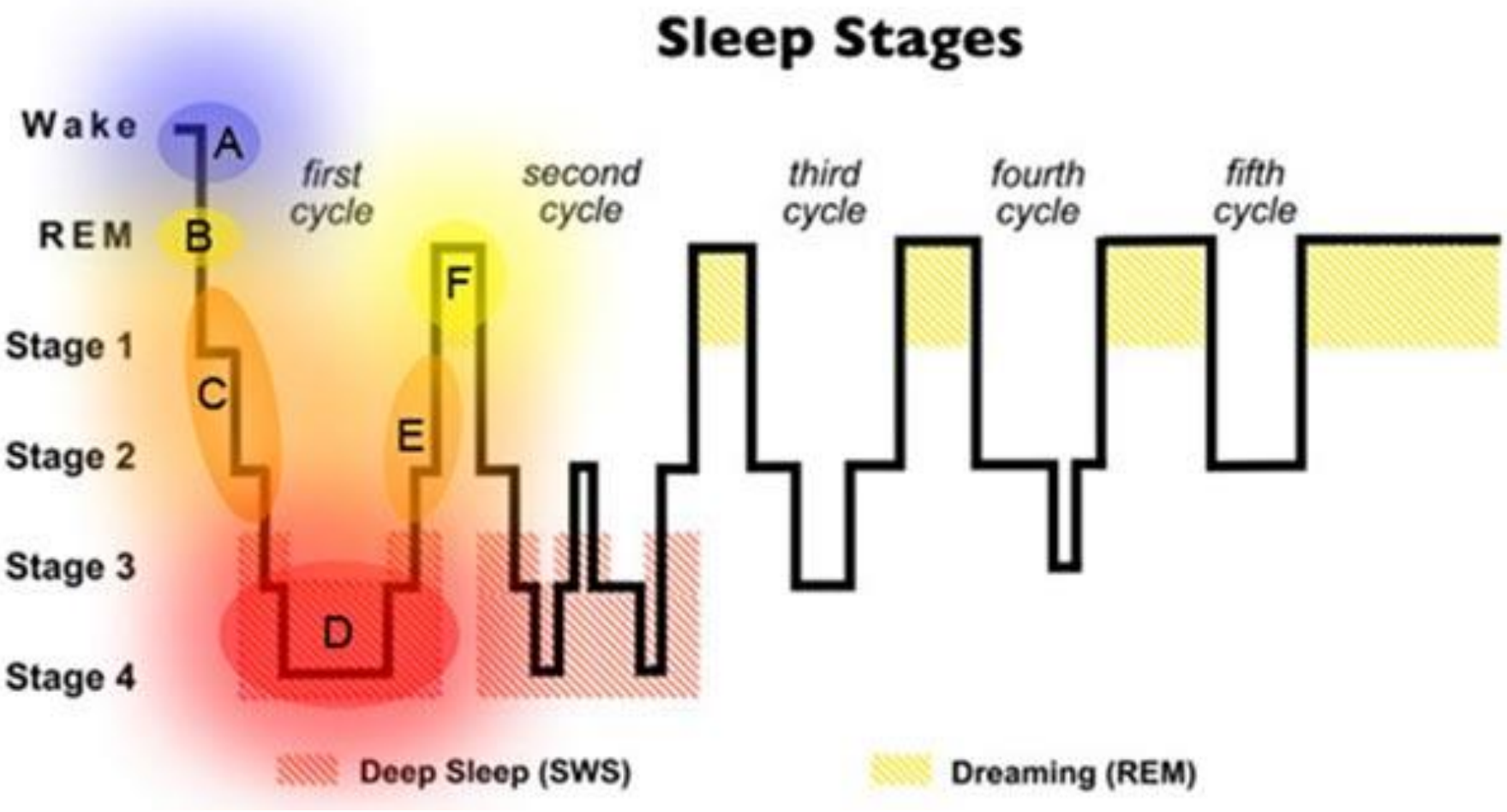
Rapid Eye Movement Sleep

- Breathing is irregular, (sudden changes in respiratory amplitude and frequency).
- Variability in heart rate, blood pressure (BP), cerebral blood flow, and metabolism
- REM periods cycle approximately every 90 minutes.
- Duration of REM increases in the last half of the night.

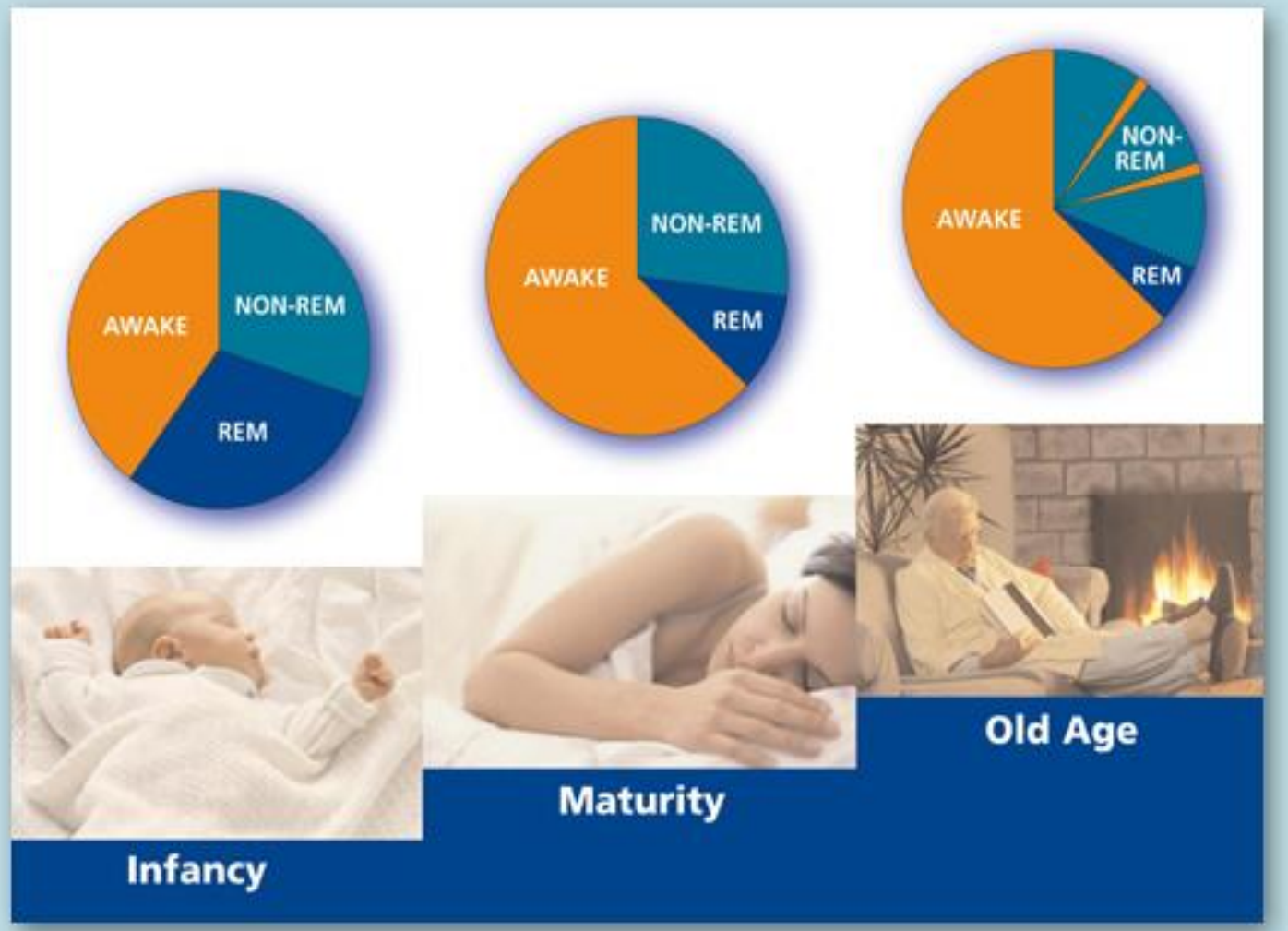


BP = Blood Pressure

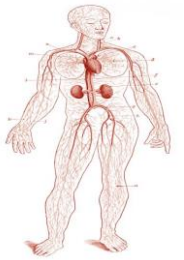
Sleep Stages



Normal Sleep and Normal Aging: Less Deep Sleep



BENEFITS OF SLEEP AND POTENTIAL CONSEQUENCES OF DEPRIVATION

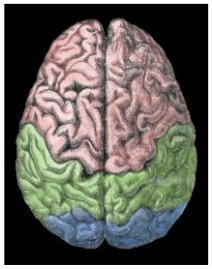


Delta sleep

- Essential for restoration and repair of body tissues
- Secretion of growth hormone

Consequences of deprivation

- Musculoskeletal tenderness
- Increased sensitivity to pain



REM sleep

- Essential for brain restoration and growth
- Memory, creativity, emotional balance, mood, sexuality
- Psychophysiology growth and personality development

Consequences of deprivation

- Agitation and aggression

REFERENCES

Billiard M. Sleep. Physiology, investigations and medicine. Springer US publishing, 2003

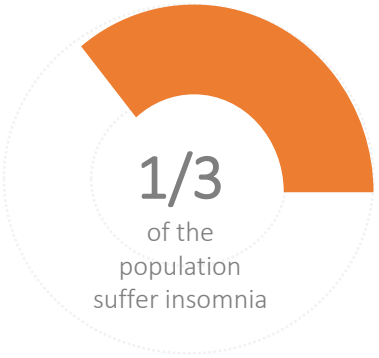
Insomnia

- During the course of a year, approximately one-third (30%-36%) of the population will experience insomnia, and 10% to 15 % will consider the problem severe due to daytime consequences.

- Decades of scientific findings associate sleep deficiency with increased disease risk, including cardiovascular and metabolic disease, psychiatric illness, substance abuse, pregnancy complications, and impaired neurobehavioral and cognitive impairment.

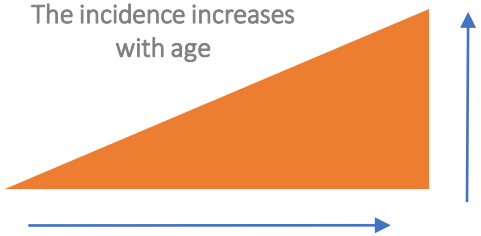
- Insomnia and excessive daytime sleepiness (EDS) in the elderly are leading predictors of institutionalization.

EPIDEMIOLOGY

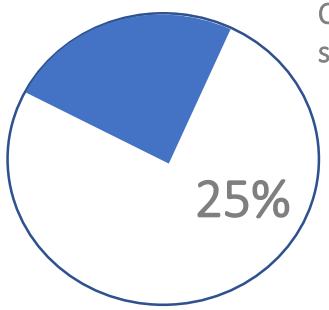


The most common health complaint

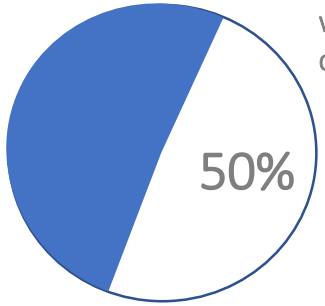
The incidence is higher in women than in men



Sleep maintenance particularly problematic in people >65 years



Co-morbidity with somatic disease



Co-morbidity with psychiatric disease

Diagnosis

- To meet the criteria for insomnia disorder according to **ICSD-3** and **DSM 5,** the sleep disturbance must cause significant distress or impairment in important areas of functioning (i.e., social, occupational, educational, academic, behavioral) and occur at least three nights per week over a 3-month period despite adequate opportunity for sleep.

- The insomnia disorder can be further classified based on duration as follows:
  - Episodic (1-3 months)
  - Persistent (>3 months)
  - Recurrent (two or more episodes in 1 year)

- Insomnia with duration less than 1 month, previously referred to as transient insomnia, would be classified as "other specified insomnia disorder."

Definitions

- **Difficulty Falling Asleep:** Requiring longer than 30 min to fall asleep
- **Difficulty Maintaining Sleep:** Awakenings throughout the night without immediate return to sleep
- **Early-morning awakening:** At least 30 minutes prior to the desired time
- Total sleep time decreased to less than 6 hours

Are You a Healthy Sleeper?

Patient Assessment

- First determine whether the sleep problem is:
  - Difficulty falling asleep
  - Difficulty maintaining sleep
  - Early-morning awakening
  - Poor-quality sleep
  - Excessive day-time sleepiness (EDS)

- Answers to the questions, "How long does it take you to fall asleep, and how many hours do you sleep?"
- Questions such as "How do you feel during the day: well rested, sleepy, or something else?" can help assess functional impairment.

- Not all patients need the same amount of sleep. Approximately 7 to 9 hours of sleep is optimal for most people.

Patient Assessment

- The next step in patient assessment involves investigating the possible causes of the sleep disorder and any concomitant conditions.
- All medical, psychiatric, drug, environmental, and social causes must be considered and treated along with the sleep disorder.
- The degree of functional impairment should be assessed to evaluate the severity of the disorder.

Etiology of Insomnia

Drug Induced

- Alcohol
- Bupropion
- SSRI's
- MAOI's
- Thyroid Supplements
- Decongestants
- Appetite Suppressants
- Theophylline
- Corticosteroids
- Dopamine Agonists
- Ca^{2+} Channel Blockers
- Diuretics

Etiology of Insomnia

Situational

- Financial Stress
- Occupational Stress
- Major Life Events
- Jet Lag
- Shift Work

Psychiatric

- Mood Disorders
- Anxiety Disorders
- Psychotic Disorders
- Substance Abuse

Etiology of Insomnia

Medical

- Cardiovascular
- Respiratory
- Chronic Pain
- Gastrointestinal
- Neurological
- Arthritis
- Cancer
- Endocrine Disorders
- Pregnancy

Table 84-4

Potential Causes and Contributing Factors for Each Chronic Sleep Complaint[5,28,65]

Difficulty Falling Asleep (DFA)
Learned or conditioned activation (primary insomnia): restless legs syndrome (RLS)
Medications: methylphenidate, modafinil, fluoxetine, bupropion, steroid, β-blocker
Substances: caffeine, guarana, alcohol
Psychiatric disorders: schizophrenia, depression, anxiety disorder, bipolar disorder
Medical disorder: chronic pain, neuropathy, gastrointestinal disorder, cardiopulmonary disorders (particularly if in recumbent position)
Difficulty Maintaining Sleep (DMA)
Excessive time in bed
Psychiatric disorder: major depression, anxiety or bipolar disorder, substance abuse
Sleep-disordered breathing: sleep apnea, acute respiratory distress syndrome
Cardiac disease: atrial fibrillation, heart failure, angina
Neurologic disorder: dementia, Parkinson disease, multiple sclerosis
Early Morning Awakening (EMA)
Major depression
Advanced sleep phase syndrome: learned or conditioned activation (primary insomnia)
Forced to get up because of family or work obligations
Excessive Daytime Sleepiness
Medications: clonidine, antihistamines, antipsychotic, antidepressant, benzodiazepine, chloral hydrate, opioid, anticonvulsant, α_1-adrenergic blockers
Obstructive sleep apnea, central sleep apnea, narcolepsy
Chronic sleep deprivation

Setting Treatment Expectations

- When patients seek treatment for insomnia, it is important that appropriate expectations are set.
- Unlike what many patients expect, normal sleep is NOT immediate unconsciousness that lasts 8 hours without interruption every night.
- Rather, normal sleep is more appropriately viewed as some nights when sleep latency is a little longer, some nights with occasional interruptions in sleep, and some nights of 5, 6, or 7 hours rather than 8 hours of sleep.
- Attempts to treat sleep complaints will fail unless the patient understands that normal sleep means a return to a pattern of natural variations in sleep.

Insomnia Treatment Modalities

- Nonpharmacologic treatments
- Pharmacologic treatments

BEHAVIORAL STRATEGIES

Sleep hygiene

- Good sleeping habits
- Keeping a regular schedule, exercising, and avoiding naps

Stimulus control

- Form a positive and clear association between bed and sleep
- Establishes a stable sleep-wake schedule

Sleep restriction

- Limit time in bed to total sleep time

Cognitive behavioral therapy – insomnia (CBT-I)

- A combination of cognitive therapy and behavioral treatments
- To change unrealistic expectations and negative thoughts about sleep

Nonpharmacologic Treatment

- The first-line treatment for chronic insomnia should be psychological and behavioral therapies.
- Cognitive-behavioral therapies (CBTs) are effective, long-lasting interventions for insomnia and considered the standard of care.
- They may be more effective than pharmacotherapy for sleep onset latency and sleep efficiency.
- The sleep benefits of these interventions are not immediate and can take several weeks to successfully implement.

Behavioral Therapy

- **Sleep hygiene**
- **Stimulus control**
- **Relaxation**
- **Sleep Restriction therapy**
- **Cognitive behavioral therapy (CBT)**

Sleep Hygiene

- Sleep as long as necessary to feel rested and then get out of bed
- Keep a regular sleep schedule (e.g. a wake-up time in the morning)
- Try not to force sleep
- Avoid caffeinated beverages after lunch
- Avoid alcohol near bedtime (eg, late afternoon and evening)
- Avoid smoking or other nicotine intake, particularly during the evening
- Adjust the bedroom environment as needed to decrease stimuli
- Avoid prolonged use of light-emitting screens before bedtime
- Resolve concerns or worries before bedtime
- Exercise regularly, preferably more than four hours prior to bedtime
- Do not go to bed hungry

Stimulus control therapy rules

1. Go to bed only when sleepy.
2. Do not watch television, read, eat, or worry while in bed. Use bed only for sleep and sex.
3. Get out of bed if unable to fall asleep within 20 minutes and go to another room. Return to bed only when sleepy. Repeat this step as many times as necessary throughout the night.
4. Set an alarm clock to wake up at a fixed time each morning, including weekends.
5. Do not take a nap during the day.

Data from: Bootzin RR, Perlis ML. Nonpharmacologic treatments of insomnia. J Clin Psychiatry 1992; 53:37.

Sleep restriction rules

1. Determine the patient's average sleep time from a sleep diary.
2. Use this average sleep time as the new time allowed in bed each night.
3. Set a consistent wake time based upon the type of insomnia and patient need.
4. Have patient avoid daytime naps.
5. If sleep efficiency increases above 90 percent (85 percent for patients over 65 years of age), then increase time in bed by 15 to 30 minutes.
6. If sleep efficiency decreases below 85 percent (80 percent for patients over 65 years of age), then decrease time in bed by 15 to 30 minutes.

Adapted from: Spielman AJ, Yang CM, Glovinsky PB. Insomnia: Sleep restriction therapy. In: Insomnia Diagnosis and Treatment, Sateia MJ, Buysse DJ (Eds), Informa UK Ltd, London 2010.


Comfortable mattres and bedding
Drink water
relaxation exercises
Spend time outside
Go to bed and get up at the same time every day
Helps you sleep
Read a book in bed
Avoid caffeine and alcohol at night
Have an early light dinner
SLEEP HYGIENE
Coffe and chocolates after dinner
Poor quality bedding
Stay indoors all day and do no exercise
stress and anxiety
Hot bedroom with no air circulation
Keeps you awake
Use a tablet or phone in bed
Go to bed when you're not tired
Lie in bed for hours getting stressed
www.nosleeplessnights.com

Pharmacologic Treatment

- Pharmacotherapy is indicated for a variety of reasons, including when:
  - Nondrug interventions fail or cannot be implemented
  - Sleep disturbances produce significant distress or impairment and immediate symptom relief is required
  - Patient preference is for drug therapy
  - Insomnia is comorbid with another medical, sleep, or psychiatric disorder
- Combination therapy involves initially prescribing both CBT and a medication (usually for four to eight weeks), then tapering the medication off or to an as-needed schedule while continuing CBT.

Ideal Hypnotic

- Has a rapid onset of effect (within 20 minutes)
- Helps the patient sleep throughout the night
- Does not cause daytime impairment
- Carries no abuse potential

- Currently, there are **NO ideal hypnotics.** Hypnotics that are benzodiazepine receptor agonists come closest to the ideal.

Pharmacologic Treatment

- Available agents vary in onset, duration, and potential for daytime impairment, mostly because of their individual pharmacokinetic profiles.
- The selection of an appropriate hypnotic should consider the type of insomnia to be treated and the physiologic characteristics of the patient.
- For example, if someone cannot fall asleep but has no trouble staying asleep and wants to prevent next-day carryover effects, a rapid-acting hypnotic with short half-life and no active metabolites is desirable.
- Age, sex, socioeconomic status, and comorbidities also influence the hypnotic prescribed.

Drug Classes

- Benzodiazepines (Triazolam, Estazoalm, Temazepam, Lorazepam, Quazepam, Flurazepam)
- Nonbenzodiazepine BDZ receptor agonists (Z-drugs) (Zaleplon, Zolpidem, Eszopiclone)
- Melatonin agonists (Ramelteon)
- Orexin receptor antagonists (Suvorexant)
- Other medications:
  - Antidepressants (Doxepin, Trazodone, Mirtazapine, …)
  - Diphenhydramine
  - Antipsychotics
  - Barbiturates
  - Over-the-counter (Herbal products, Melatonin, …)

Choice of an agent

- **DFS: sleep onset insomnia** a short-acting medication: zaleplon, zolpidem, triazolam, lorazepam, and ramelteon

- **DMS: sleep maintenance insomnia**, a longer-acting medication : zolpidem extended release, eszopiclone, temazepam, estazolam, low dose doxepin, and suvorexant: risk for hangover sedation.

Choice of an agent

- **Awakening in the middle of the night**, zaleplon and a specific sublingual tablet form of zolpidem, at least **4 hrs** of time in bed remaining after administration

- **History of alcohol or recreational drug dependence**, non-controlled medications such as **ramelteon, doxepin, antidepressant or anticonvulsants**

Choice of an agent

- **Consider drug interactions**: sertraline/zolpidem, fluoxetine/zolpidem, fluvoxamine/ramelteon, doxepin/ramelteon
- Medications should ideally be used for **no longer than 4-5 weeks**

- **R/O Secondary causes of insomnia** such as depression, pain, BPH, substance abuse disorders and other sleep disorders

Table 84-3

Sedative-Hypnotic Agents FDA-Approved for Treatment of Insomnia[36–38,61]

Generic[a] (Brand Name)	Dose (mg)		Onset (minutes)	Half-Life (hours)	Duration of Action[b]	Insomnia Indication
	Healthy Adults	Elderly Hepatic Impairment				
Benzodiazepines						
Estazolam (generics)	1–2	0.5–1	60–120	10–24	Intermediate	Sleep onset and sleep maintenance[f]
Flurazepam (generics)	15–30	NR	60–120	>100[c]	Long	Sleep onset and sleep maintenance[f]
Quazepam (Doral, generics)	7.5–15	NR	30–60	47–100[c]	Long	Sleep onset and Sleep maintenance[f]
Temazepam (Restoril, generics)	7.5–30	7.5	60–120	3.5–18.4	Intermediate	Sleep onset and sleep maintenance[f]
Triazolam (Halcion, generics)	0.125–0.25	0.125	15–30	1.5–5.5	Short	Sleep onset[f]
Nonbenzodiazepine Receptor Agonists						
Zaleplon (Sonata)	10–20	5–10	30	1	Short	Sleep onset[f]
Zolpidem						
Oral tablet (Ambien)	5–10[d]	5	30	1.4–4.5	Short	Sleep onset[f]
ER oral tablet (Ambien CR)	6.25–12.5[d]	6.25	30	1.62–4.05	Intermediate	Sleep onset and sleep maintenance[g]
Sublingual tablet[e] (Intermezzo)	1.75–3.5[d]	1.75	20–38	1.4–3.6	Short	Middle-of-the-night-awakening[h]
Sublingual tablet[e] (Edluar)	5–10[d]	5	30	1.57–6.73	Intermediate	Sleep onset[f]
Mucous membrane spray (Zolpimist)[i]	5–10[d]	5	10	2.7–3	Short	Sleep onset[f]
Eszopiclone (Lunesta)	1–3 (start with 1 in all patients)	1–2	30	6	Intermediate	Sleep onset and sleep maintenance[g]
Melatonin Agonist						
Ramelteon (Rozerem)	8	8	30	1–5[c]	Short	Sleep onset[g,j]
Orexin Receptor Antagonists						
Suvorexant (Belsomra)	10–20 (5–10 with moderate CYP3A4 inhibitor)	Elderly—Not specified Severe hepatic dysfunction = NR	30	12	Intermediate	Sleep onset and maintenance[g]
Antidepressants						
Doxepin (Silenor)	6	3	30	15.3 (31[c])	Intermediate	Sleep maintenance[g,j]

[a]Dispense with a product-specific Medication Guide.
[b]Time the patient feels the effects after a single dose; usually approximates half-life with multiple doses; individual variability exists; and tolerance may develop with continued use, lessening the duration; short = 1 to 5 hours; intermediate = 5 to 12 hours; long = >12 hours.
[c]Half-life includes the parent compound and its active metabolites.
[d]In women start with the lower dose.
[e]To be dissolved under the tongue and not swallowed whole.
[f]FDA approved for short-term (7–10 consecutive days) treatment of insomnia.
[g]Not limited to short-term use.
[h]Take only if 4 hours remaining before planned wake time.
[i]To be sprayed over the tongue immediately before bedtime
[j]Not a controlled substance.

FDA, U.S. Food and Drug Administration; NR, Not recommended; ER, Extended-release.

Benzodiazepines

- Benzodiazepines are a class of sleep promoting medications that bind to several gamma-aminobutyric acid (GABA) type A receptor subtypes.
  - Reducing the time to the onset of sleep
  - Prolonging stage 2 sleep
  - Prolonging total sleep time
  - Reducing the relative amount of REM sleep
- In addition, they decrease anxiety, impair memory, and have anticonvulsive properties.

Benzodiazepines

- Benzodiazepines commonly used for the treatment of insomnia include **triazolam, estazolam, lorazepam, temazepam, flurazepam,** and **quazepam.**
  - Triazolam is short acting.
  - Estazolam, lorazepam, and temazepam are intermediate acting.
  - Flurazepam and quazepam are long acting.
- Benzodiazepines decrease sleep latency and the number of awakenings, while improving sleep duration and sleep quality.

Adverse Effects of Benzodiazepines

- The most common adverse effects associated with the benzodiazepines and nonbenzodiazepines are residual daytime sedation, drowsiness, dizziness, lightheadedness, cognitive impairment, motor incoordination, and dependence.

- In addition, most hypnotics are respiratory suppressants that can worsen obstructive sleep apnea (OSA) or hypoventilation.

- Risks are increased if hypnotics are combined with other central nervous system depressant drugs or alcohol.

Adverse Effects of Benzodiazepines

- **Long-term use of hypnotics** may be habit forming, and rebound insomnia may occur when some short-acting medications are discontinued.

- Less common adverse effects include **complex sleep-related behaviors** (eg, sleep walking, driving, making telephone calls, eating, or having sex while not fully awake), anterograde amnesia (particularly when used with alcohol), aggressive behavior, and severe allergic reaction.

- Lethal overdose is possible, particularly with concurrent use of alcohol or another central nervous system depressant.

Adverse Effects of Benzodiazepines

- **Physiologic dependence** on BZDs resulting in a withdrawal and abstinence syndrome, develops usually after 2 to 4 months of daily use of the longer half-life BZDs.

- Shorter half-life BZD use can result in physiologic dependence earlier (days to weeks) and may be associated with more severe withdrawal problems.

- In 2007 the US FDA issued a **black-box warning** that applies to all medications marketed for insomnia: **angioedema, allergic reaction, complex sleep behaviors.**

Benzodiazepines in the management of insomnia in adults

Benzodiazepine	Adult dose (usual)*	Dose in older adults (≥65 years)	Indication	Half-life (hours)	Potential for drug interactions¶
Estazolam	1 to 2 mg	0.5 mg	Sleep onset or sleep maintenance insomnia	Intermediate (10 to 24)	CYP3A4 to minimally active metabolite.
Flurazepam	15 to 30 mg	15 mg	Sleep onset or sleep maintenance insomnia	Long (40 to 114; 120 to 160 older adults)	Non-CYP glucuronidation in liver. No active metabolite.
Lorazepam	0.5 to 2 mg	0.5 to 1 mg	Sleep onset or sleep maintenance insomnia	Intermediate (10 to 14)	Non-CYP glucuronidation in liver. No active metabolite.
Temazepam	7.5 to 30 mg	7.5 to 15 mg	Sleep onset or sleep maintenance insomnia	Intermediate (8 to 15)	Primarily non-CYP glucuronidation in liver to minimally active metabolite.
Triazolam	0.125 to 0.25 mg	0.125 to 0.25 mg	Sleep onset insomnia	Short (2 to 5)	CYP3A4. No active metabolite.

* Initiate treatment using lowest dose shown for those with low body weight, debilitated patients, and those receiving treatment with opioid analgesics or other central nervous system or cardiorespiratory depressants.

¶ For specific drug interactions, including management recommendations and combinations that should be avoided, use Lexi-Interact drug interactions program included with UpToDate.

Nonbenzodiazepines (Z-drugs)

- NBRAs have varying degrees of selectivity for the alpha-1-subunit on the GABA-A receptor.
- This selectivity imparts hypnotic efficacy with NO significant anxiolytic, muscle relaxant, or anticonvulsant effects.
- Nonbenzodiazepines appear to improve both subjective and objective sleep outcomes.

Nonbenzodiazepines (Z-drugs)

- Nonbenzodiazepines decrease sleep latency and the number of awakenings, while improving sleep duration and sleep quality.

- Consequently, NBRAs have a lower risk of abuse, withdrawal, and tolerance compared with older nonselective benzodiazepines such as triazolam and temazepam.

- Also they have fewer reports of rebound insomnia and anterograde amnesia at recommended doses.

Nonbenzodiazepines (Z-drugs)

- Another potential advantage of NBRAs alpha-1-subunit selectivity is little to NO change in sleep architecture or sleep stages.

- Benzodiazepines increase the percentage of stage 2 sleep but can suppress REM and stage 3 and 4 deep restorative sleep.

- In contrast, **NBRAs** do not interfere with these sleep stages and have lower rates of uncomfortable REM rebound (vivid dreams, increased autonomic instability) on discontinuation.

Nonbenzodiazepines (Z-drugs)

- These attributes make NBRAs more desirable for the treatment of chronic insomnia.

- Both zolpidem controlled-release and eszopiclone are FDA-approved for chronic insomnia and are effective for up to 6 months of therapy.

Nonbenzodiazepines (Z-drugs)

- Nonbenzodiazepines commonly used to treat insomnia include **zaleplon, zolpidem, eszopiclone,** and **zolpidem extended release.**

- The NBRAs differ with respect to pharmacokinetics and adverse events.

- Zolpidem, the first NBRA, was marketed in the United States in 1991 .

Zolpidem

- **Zolpidem immediate release** – Zolpidem has a half-life of approximately 1.4 to 4.5 hours.
- It is indicated for the short-term treatment of insomnia characterized by difficulty with sleep initiation.
- Zolpidem is not approved for long-term use (NO more than 4 weeks).

Zolpidem

- For faster sleep onset, zolpidem should be taken on an empty stomach for faster absorption.
- A food-effect study demonstrated that administration of a zolpidem 10 mg tablet 20 minutes after a meal resulted in a decrease in AUC and Cmax of 15 % and 25%, respectively, and an increase in the T max from 1.4 to 2.2 hours.
- Zolpidem is metabolized by the oxidative cytochrome P-450 isoenzyme CYP3A4; therefore, drug interactions should be considered when zolpidem is coadministered with CYP3A4 inhibitors such as diltiazem or fluoxetine.

Zolpidem

- Zolpidem has NO active metabolites, and it has a low risk of residual daytime sedation in recommended doses.
- Also, gender metabolism differences exist where women metabolize zolpidem slower than men, resulting in blood levels nearly two-fold higher.
- As a result, in women or the elderly, the recommended starting dose is 5 mg zolpidem immediate-release.

Zolpidem

- **Zolpidem extended release** – Zolpidem extended release has a half-life of about 1.4 to 4 hours, but is released over a longer duration.

- It was developed to improve both sleep onset insomnia and sleep maintenance insomnia.

- Zolpidem extended release is NOT limited to short-term use and there is little evidence for abuse or dependence in most patients.

Zaleplon

- **Zaleplon** – Zaleplon has a very short half-life of about one hour. As a result, it is effective for patients who have difficulty falling asleep (ie, sleep onset insomnia), but may NOT be effective for patients who have difficulty maintaining sleep (ie, sleep maintenance insomnia).

- Due to the very short half-life, the potential for hangover sleepiness is minimal after normal sleep periods.

- It can be taken in the middle of the night as long as the individual has 4 hours left in bed.

- Zaleplon is metabolized primarily via aldehyde oxidase, CYP3A4 is a secondary route of metabolism, and there are no active metabolites.

- Zaleplon is not indicated for long-term use (NO more than 4 weeks).

Eszopiclone

- **Eszopiclone** – Eszopiclone has the longest half-life of the approved nonbenzodiazepines, approximately six hours.
- Eszopiclone is effective for both sleep onset insomnia and sleep maintenance insomnia.
- Eszopiclone has less receptor selectivity than either zaleplon or zolpidem, potentially resulting in some anxiolytic, amnestic, and anticonvulsant activity.
- Eszopiclone is primarily metabolized by CYP3A4, so drugs that induce or inhibit this isoenzyme can have an impact on metabolism and a clinical effect.

Eszopiclone

- Patients taking eszopiclone may report an unpleasant metallic taste.
- Eszopiclone is NOT limited to short-term use and there is little evidence for abuse or dependence in most patients.
- Eszopiclone maintains efficacy with no evidence of tolerance after 6 months of continuous use, resulting in FDA approval for long-term use.

Adverse Effects of Z-drugs

- The adverse effects of nonbenzodiazepine hypnotics are generally similar to those associated with the benzodiazepines.
- Common possible adverse effects include headache (30%), abdominal pain (6%), asthenia (5%), somnolence (5%), dizziness (7%), and GI disturbances (2%).
- Hallucinations, mostly visual, are more common in elderly patients, those taking high doses.
- Another rare allergic reaction is **facial swelling (angioedema).** All manufacturers of hypnotic medication are required to include this information in their package inserts.

Adverse Effects of Z-drugs

- Tolerance and withdrawal associated with NBRAs is unlikely but reported with abrupt discontinuation and patients should be counseled of this possibility, particularly at high doses.

- **Complex sleep-related behaviors,** including sleepwalking, sleep driving, eating, and other behaviors performed while not fully awake, can occur in patients taking nonbenzodiazepines.

- These events appear to be more common with zolpidem, zaleplon, and eszopiclone than other medications used for sleep.

Adverse Effects of Z-drugs

- Across studies, estimates for sleep-related behaviors of any severity related to nonbenzodiazepine hypnotics range widely, from 3 to 25 percent.
- While most events are non-serious, rare cases of injury and even death have been described.
- **Higher dose appears to be a risk factor** for complex sleep-related behaviors.

Adverse Effects of Z-drugs

- **In 2019 and by the FDA,** a **boxed warning** on the risk of rare but serious **complex sleep-related behaviors** was added to all formulations of zolpidem, zaleplon, and eszopiclone, along with the following information and guidance:

- These events can occur with just one dose of these medicines as well as after a longer duration of treatment.

- These events can occur without a prior history of such events.

- Eszopiclone, zaleplon, and zolpidem are contraindicated in patients who report an episode of complex sleep behavior after taking these insomnia medicines.

Adverse Effects of Z-drugs

- Tell patients to **discontinue** their insomnia medicine if they experience an episode of complex sleep behavior even if it did not result in a serious injury.

- When starting patients on eszopiclone, zaleplon, or zolpidem, follow the dosing recommendations in the prescribing information and start with the lowest possible dose.

Dosing Precautions of Z-drugs

- There has been increasing recognition that variability in nonbenzodiazepine metabolism may affect next-morning drug levels and side effects, especially among **older adults and women.**

- In 2013, the FDA published a safety communication that the recommended dose for zolpidem be set at the lowest dose (5 mg) for women and also be considered for men.

- In addition, a new warning was issued for zolpidem extended release, advising that individuals refrain from driving or other activities that require mental alertness the day after taking the drug.

Nonbenzodiazepine benzodiazepine receptor agonists (BZRAs) in the management of insomnia in adults

Nonbenzodiazepine	Preparation(s)	Adult dose (usual) *	Dose in older adults (≥65 years)	Indication	Half-life (hours)	Potential for drug interactions ¶
Eszopiclone	Tablet	1 to 3 mg	1 to 2 mg	Sleep onset or sleep maintenance insomnia	Intermediate (6)	Moderate Eszopiclone is metabolized in part by CYP3A4
Zaleplon	Capsule	5 to 20 mg	5 mg	Sleep onset insomnia	Short (1)	Low
Zolpidem	Tablet, sublingual tablet, oral liquid (5 mg per spray)	Men 5 to 10 mg Women 5 mg	5 mg	Sleep onset insomnia	Short (1.4 to 4.5)	Low to moderate Zolpidem is metabolized in part by CYP3A4
Zolpidem extended release	Coated tablet	Men 6.25 to 12.5 mg Women 6.25 mg	6.25 mg	Sleep onset or sleep maintenance insomnia	Intermediate (1.6 to 4Δ)	Metabolized more slowly by women, particularly with age
Zolpidem middle of the night	Dissolvable tablet (sublingual)	Men 3.5 mg Women 1.75 mg	1.75 mg	Sleep maintenance insomnia (middle of the night)	Short (1.4 to 4.5)	
Zopiclone (not available in the United States)	Tablet	3.75 to 7.5 mg		Sleep onset insomnia	Intermediate (5 to 7)	Moderate Zopiclone is metabolized by CYP2C8 and 3A4

* Initiate treatment using lowest dose shown for those with low body weight, debilitated patients, and those receiving treatment with opioid analgesics or other central nervous system or cardiorespiratory depressants.
¶ For specific drug interactions, including management recommendations and combinations that should be avoided, use Lexi-Interact drug interactions program included with UpToDate.
Δ Duration of effect longer than predicted by half-life due to sustained release.

Antidepressants

- Because of its sedating properties, trazodone has become a commonly prescribed adjunctive medication (50– 200 mg/day at bedtime) to induce sleep while awaiting the onset of the primary antidepressant's effect.
- The most common side effects of trazodone include drowsiness (29.1%), dizziness (21.9%), and dry mouth (17.7%).
- Cardiac arrhythmias are possible at doses greater than 200 mg/day
- Priapism, a painful prolonged erection that occurs in 1 of 1,000 to 10,000 men.
- Tolerance did not develop to the sedative effects of trazodone in short-term studies (<6 weeks) used adjunctively for depression; however, decreased benefit with time has been reported.

Antidepressants

- Ultra-low-dose doxepin 3-mg and 6-mg tablets are used for the treatment of insomnia characterized by difficulties with sleep maintenance.
- Doxepin is not a controlled substance, so it may be of value in patients with a history of substance abuse.
- Doxepin is well tolerated, with residual sedation and anticholinergic effects.
- Hypnotic efficacy with doxepin was demonstrated for up to 3 months.
- Mirtazapine has 5-HT2 antagonist and antihistamine effects, which impart sedation.
- Mirtazapine can cause weight gain.

Antihistamines

- Most nonprescription sleep aids contain antihistamines such as diphenhydramine.
- Antihistamines can cause drowsiness and can help patients fall asleep.
- Some patients do not feel well rested the next day after taking an antihistamine, but instead feel slow, lethargic, and not mentally sharp.
- Tolerance can develop to the sedative effects of antihistamines after 3 to 7 days of continued use.
- **Routine use** of diphenhydramine to treat insomnia is **NOT recommended**.

Melatonin

- **Melatonin** is a naturally occurring hormone secreted by the pineal gland, located in the center of the brain.
- The pineal gland produces melatonin (a by-product of serotonin metabolism) only during the nocturnal phase of the circadian cycle and only in the presence of relative darkness.
- Studies in adults show that melatonin has at least mild sleep-promoting properties when administered before the period of natural increase in endogenous melatonin (10 PM to midnight).

Melatonin

- It is useful when sleep disturbances are due to delayed sleep-wake phase syndrome (a circadian sleep-wake rhythm disorder) or in patients with low levels of endogenous melatonin, such as in aging.

- Doses between 0.5 and 5 mg taken close to the target bedtime in the new time zone can decrease sleep disturbances.

- It causes significantly more sleepiness when taken at 8 PM compared with 11:30 PM, theoretically because the brain's receptors are already saturated with melatonin late at night.

Melatonin

- Melatonin 0.5 t o 10 mg has been found effective for entraining the circadian rhythms in blind people, alleviating insomnia in developmentally disabled, handicapped, or autistic spectrum children and adults, and treating short-term, initial insomnia in children with attention deficit hyperactivity disorder (ADHD).

- It appears to be safe when used short-term (three months or less).

- It has NO established effectiveness for chronic insomnia.

Herbal Products

- A meta-analysis that included 14 randomized trials in over 1600 patients found NO significant difference between any herbal medicine and placebo on any of 13 clinical efficacy measures of insomnia.

- The majority of the trials (11 out of 14) studied valerian; chamomile, kava, and wuling were studied in one trial each.

- Unlike the other herbals studied, valerian was associated with a greater number of adverse events per person compared with placebo. Valerian may also produce hepatotoxic effects.

Algorithm for Treatment of Insomnia

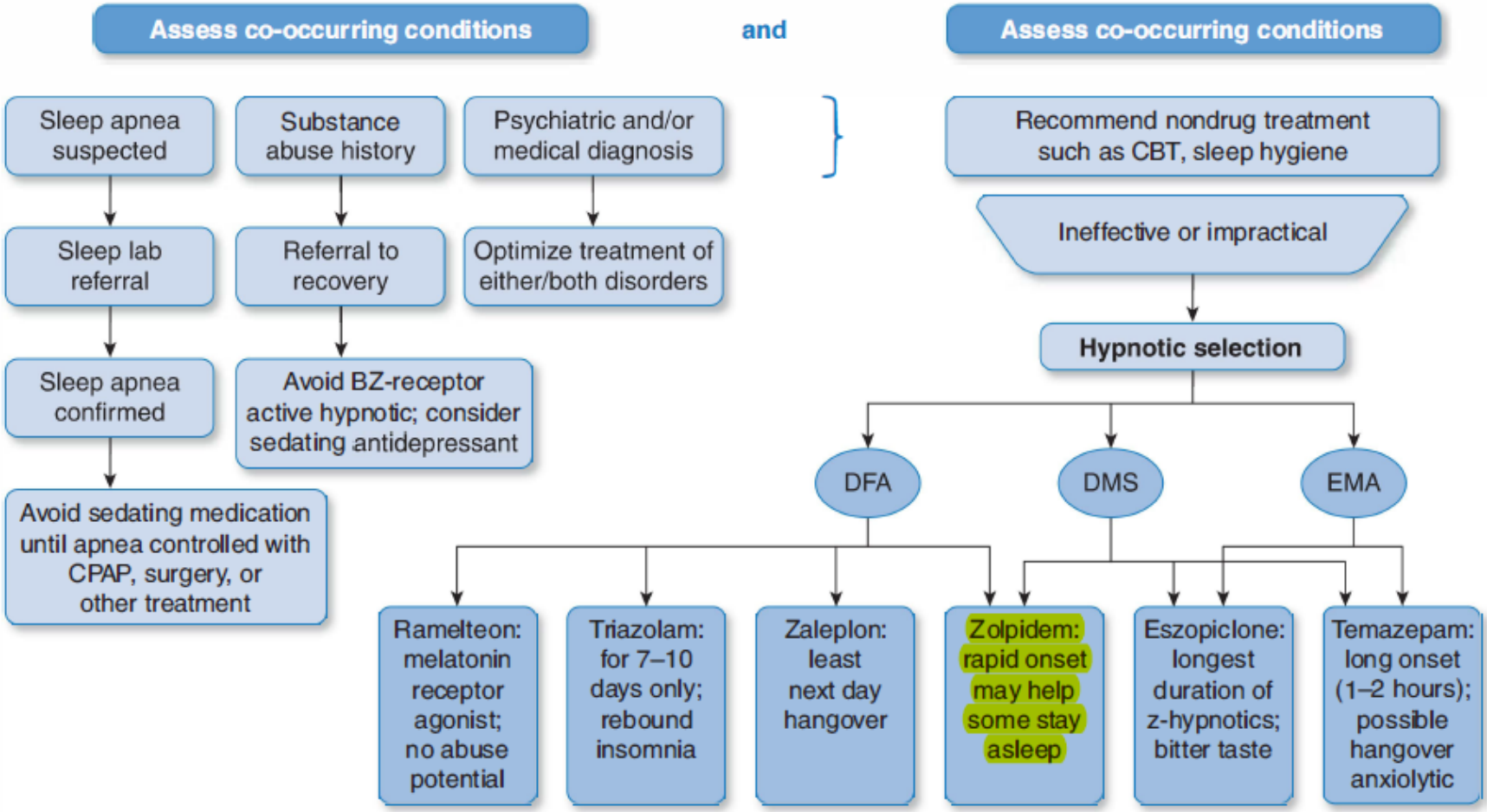


Figure 84-2 Algorithm for treatment of insomnia. DFA, difficulty falling asleep; DMS, difficulty maintaining sleep; EMA, early morning awakening.

Tips for Improving Sleep Habits

1. Avoid caffeine, alcohol and nicotine prior to bedtime

2. Keep a regular sleep schedule

3. Exercise early

4. Follow a relaxing bedtime routine

5. Go to bed only when you're sleepy

6. Use the bed to sleep, not work

7. Make your bedroom a comfortable place to rest

8. Avoid naps

9. Follow doctor's guidance on sleep medication

10. Change your electronic habits

For more sleep tips, visit dcoe.mil/blog/sleeptips

Thanks for Your Attention