Describe the pharmacist’s role in identifying and treating patients with excessive sleepiness.

5% of the general population report chronic excessive daytime sleepiness (EDS).

43% of adults report missing work due to EDS at least once in the past year.

The Council for Pharmacy Education (CPA) is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Any knowledge-based program will educate pharmacists on the treatments available for excessive sleepiness.

Only 49% of adults report sleeping well most nights.

21% of adults report EDS interfering with their ability to function effectively with excessive sleepiness and offer them counseling points to communicate effectively with excessive sleepiness patients and providers in their role as a pharmacist.

• Review the etiology and epidemiology of excessive sleepiness and its effect on quality of life.

• Describe non-pharmacologic treatment options for the main sleep disorders that are causes of excessive sleepiness.

• Describe pharmacologic treatment options for the main sleep disorders that are causes of excessive sleepiness.

• Describe the pharmacist’s role in identifying and treating patients with excessive sleepiness.

How tired are we?

• 38% adults: EDS interferes with life few days/month

• 21% adults: EDS interferes with life few days/week

• Only 49% of adults sleep well most nights

• 43% missed work due to EDS at least 1X in prior 3 months

• 5% general population report chronic EDS

2005 & 2009 Sleep Foundation Polls
How Tired Are We?

- 20% Americans “too tired for sex”
- 29% Americans are sleepy at work routinely

2008 National Sleep Foundation Poll

Consequences of EDS

- Accident at Three Mile Island nuclear power plant
  - Destruction of Unit 2 reactor and release of radioactive gases and water into the environment
- Nuclear meltdown at Chernobyl
  - 300 deaths, $13 billion in economic disruption, increased cancer rates and birth defects
- Release of poisons from Union Carbide in Bhopal
  - 2,800 deaths, 20,000 cases of respiratory and eye damage, and $3 billion in immediate costs
- Grounding of the Exxon Valdez
  - 1400 miles of shoreline contaminated, over $8 billion in direct costs

Crash Stats

- 1/3 of people have fallen asleep at wheel
- 100,000 crashes/yr
- 71,000 injuries/yr
- 1500 deaths/yr
- Cost is $12.5 billion/yr
- Adolescents & young adult males most involved in sleep-related crashes

Thag Anderson becomes the first fatality as a result of falling asleep at the wheel.

Medscape Medical News, March, 2009

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**Impairment due to Sleep Deprivation**

- Sleeping 6 hr = 2-3 beers
- Sleeping 4 hr = 5 beers
- Sleeping 0 hrs = 10 beers

Study by School of Psychology, Univ. of New South Wales, Occupational and Environmental Medicine, 2007

**Sleep Deprived Health Care Providers**

Prior to 2003 resident physicians:
- Routinely worked > 80 hrs/week
- Routinely worked shifts up to 48 hrs without sleep
- Had inadequate duty-free recovery periods

**Sleep Deprived Health Care Workers**

- Nurses: 7X increase in drowsy driving behaviors after rotating shift
- Resident Physicians: Post call drive worse than when intoxicated
- Sleep deprived interns: 36% more serious medical errors and 5.6 X higher diagnostic errors
- Personal impact on their lives
- Lack of empathy, professionalism
- Negative impact on learning

**How Much Sleep Do We Need?**

- Infants: 16 hrs
- Babies/Toddlers: 10-14 hrs.
- Children: 9-12 hrs
- Teens: 9 hrs
- Adults: 7-8 hrs
- Elderly: 7-8 hrs
Causes of Excessive Daytime Sleepiness (EDS)

- Sleep deprivation
- Obstructive sleep apnea
- Narcolepsy
- Idiopathic hypersomnia
- Periodic Limb Movement Disorder
- Restless Legs Syndrome
- Circadian Rhythm Sleep Disorder
- Insomnia
- Parasomnias
- Medication side effects
- Medical conditions
- Withdrawal from stimulants
- Drug abuse/dependence

Obstructive Sleep Apnea (OSA)

- Most common cause of EDS
- 2-4% women
- 4-9% men
- During sleep, closure of upper airway causing cessation or decreased airflow despite respiratory effort. Apneic event causes brief awakening.
- Sleep is fragmented causing EDS

Risk Factors for OSA

- Overweight/obese
- Large neck circumference
- Male gender
- Advancing age
- Menopause
- Airway abnormalities
- Family history

Risks Due to OSA

- Stroke
- Cardiovascular disease: MI, CAD
- Arrhythmias
- Hypertension
- Pulmonary hypertension
- Diabetes
- Sexual dysfunction
- Depression and anxiety
Treatment of OSA

- Weight loss
- Sleep on side
- Avoid sedative medication
- Avoid sleep deprivation
- Avoid alcohol before sleep
- Elevate head of bed
- Promptly treat colds and allergies

Narcolepsy

- Prevalence: 1/2000
- Profound EDS: “sleep attacks” - 100%
- Cataplexy: “drop attacks” - 70%
- Hallucinations: hypnopompic (awakening) and hypnogogic (falling asleep) - 66%
- Sleep paralysis - 60%
- Automatic behaviors - 60%
- Disrupted nocturnal sleep - 60%
- Adolescence is the common age of onset
- Second peak at about 40 years of age
  (5% of cases start after age 50)

Sleep Attacks

- Not instantaneous
- Profound sleepiness
- Increased propensity to fall asleep when relaxed or sedentary “microsleeps”
- Overwhelming urges to sleep
- Need extra effort to stay awake

Cataplexy

- Loss of muscle tone during strong emotions
- Partial/complete loss bilaterally
- Seconds-minutes
- Can develop years later
Biological Markers for Narcolepsy
- Low levels of hypocretin (peptide) in CSF
- Diagnostic test
- HLA subtype DQB1*0602—strong but incomplete correlation with cataplexy
- ? Autoimmune dysfunction
- Dysregulation in norepinephrine and dopamine
- Hypothalamus dysfunction

Treatment of Narcolepsy
- Sleep hygiene
- Adequate time for sleep, naps
- Wakefulness agents: stimulants, modafinil, armodafinil
- Cataplexy/hallucinations: TCAs, venlafaxine, carbamazepine, GHB or sodium oxybate (gamma-hydroxybutyrate)

Idiopathic Hypersomnia
- EDS
- Don’t meet criteria for narcolepsy (?atypical narcolepsy)
- Etiology unknown
- Long nocturnal sleep
- Sleep drunkenness, automatisms
- Sleep not refreshing
- Pharmacological treatment necessary

Periodic Limb Movement Disorder (PLMD)
- Repetitive, stereotypic dorsiflexion movements of the toes, ankles, knees and thighs that recur at regular intervals (5-90 sec)
- Most commonly in stages 1 and 2
- Patients are rarely aware of the leg movements
- Complaints are usually from bed partners
- Certain meds can exacerbate
- Associated with narcolepsy, parasomnias, Parkinson’s Disease
### Restless Leg Syndrome (RLS)
- 5-10% general population
- Abnormal, uncomfortable sensations in limbs
- Compels person to move to relieve
- Exacerbated by rest
- Occurs primarily in evening/night
- Difficulty initiating and maintaining sleep
- EDS
- Associated with depression and anxiety
- Associated with PLMD
- Familial

### Restless Legs Syndrome-Causes
- Medications: TCAs, SSRIs, Dopamine-blockers, antihistamines
- Medication withdrawal: hypnotics, barbiturates, anticonvulsants
- Stress
- Low iron
- Pregnancy
- “Growing pains”
- Diabetes, Rheumatoid Arthritis, renal disease, peripheral neuropathy

### Treatment of PLMD/RLS
- Avoid alcohol and caffeine
- Treat causative medical conditions
- Light exercise and stretching or warm baths at bedtime
- Dopamine agonists: levodopa
- Benzodiazepines
- Narcotics – severe cases
- Ropinirole (Requip)-FDA approved for RLS
- Ramipriluxole (Mirapex)-FDA approved for RLS
- Antiseizure meds: gabapentin, pregabalin

### Circadian Rhythm Sleep Disorders
- Shift work disorder, jet lag, sleep phase disorders
- Desynchronization between internal and environmental sleep-wake cadence
- EDS
- Insomnia
- 10% of shift workers
- 4X accidents, absenteeism, depression
Circadian Rhythm Sleep Disorder Treatments

- Fixed-shift work
- Rotating shifts: Day –Evening –Night
- Bright lights
- Dark room when sleeping
- White noise
- Sleep masks
- Hypnotics to sleep
- Wakefulness promoting medications when awake: modafinil, armodafinil

Primary Insomnia

- Difficulty initiating, maintaining sleep, distress, impaired daytime functioning
- 5-10% of general population
- 1.5-2X greater in women
- Increased reporting with age (controversial)
- May not necessarily complain of EDS
- Associated with depression, anxiety, suicide
- More likely to abuse drugs, alcohol, nicotine dependent
- Misperception of nocturnal sleep
- Phobic insomnia
- Polysomnography not helpful, sleep diary may help

Parašomnias

- Somnambulism
- Sleep terrors
- Nightmare disorder
- REM sleep behavior disorder
- Sleep paralysis
- Nocturnal seizures
- Psychogenic dissociative states
- Malingering

Comorbíd Insomnia

- Schizophrenia
- Substance abuse disorders
- Depression/anxiety
- Hypothyroidism
- Fibromyalgia/chronic pain syndromes
- COPD/respiratory disease
- Cerebrovascular event
- Dementia
- Reflux
Medication-Induced EDS… a few culprits

- α & β blockers
- Antiepileptics
- Antiemetics
- Antihistamines
- Antipsychotics
- Muscle relaxers
- Opioid agonists
- TCAs
- SSRIs
- Benzodiazepines

Diagnosing Sleep Disorders

- History—lots and lots of questions
- Self-rating scales
- Sleep/wake diary
- Polysomnography
- Drug Screen—some cases
- Multiple sleep latency test (MSLT)
- Maintenance of wakefulness test (MWT)

Normal Sleep Cycle

- 25% REM
- 75% Non-REM
- Stages 1&2: light sleep
- Stages 3&4: deep sleep

Polysomnography

- ECG: electrocardiogram
- EEG: electroencephalogram
- EOG: electro-oculogram
- EMG: electromyogram
- Pulsoximetry: Oxygen saturation
- Respirations: chest movement, airflow, snore sensor
Polysomnography Parameters

- Sleep stages (percentage)
- Sleep efficiency: #min sleep/#min in bed
- Apnea Hypopnea index (AHI): 5-15 mild, 15-30 moderate, >30 severe
- Respiratory Disturbance Index (RDI)
- Paradoxical respiration, desaturations and cardiac arrhythmias

### Sleep Disorder | Polysomnography Findings
--- | ---
OSA | Sleep fragmentation, Apnea/Hypopnea Index >5, reduced stage 3, 4 and REM sleep, increased respiratory arousals, cyclical variation in heart rate, oxygen desaturation
Narcolepsy | Short REM latency, short sleep latency, low sleep efficiency, sleep fragmentation, reduced sleep wave sleep, +/- PLMs
PLMD/RLS | Increased sleep latency, sleep fragmentation, PLMs
Parasomnias | AV, EEG recordings of events in various stages of sleep

### 24-hour hypnograms in control and untreated narcoleptic patients

### PSG with OSA

Adapted from Rogers et al. Sleep. 1994;17:7-36.
Multiple Sleep Latency Test

- Standard way to measure daytime sleepiness
- Lab test with EEG, EMG, EOG
- 4-5 20 min. nap opportunities with 2 hr breaks in between
- Sleep latency < 5 minutes is abnormal
- 2 or more sleep-onset REM sleep: narcolepsy
- Performed in environment conducive to sleep
- Measures sleep latency and type of sleep
- Normal mean latency ~10 min

Maintenance of Wakefulness Test (MWT)

- Assesses function of wakefulness system
- May be used as a means assessing therapeutic response or safety issues
- Performed after an adequate time of sleep
- Four 40 min sessions with 2 hrs in between
- Room is conducive to sleep
- Individual is seated in bed, comfortable
- EEG, EMG, ECG measured
- Sleep latency, stages of sleep, total sleep time measured
- Mean sleep latency < 8 min: abnormal
- Paucity of normative data

Epworth Sleepiness Scale

Never (0) Slight (1) Moderate (2) High (3)
Chance of dozing when:
- Sitting and reading
- Watching TV
- Sitting inactive in public place (theater, mtg)
- Passenger in car 1 hr without break
- Lying down in afternoon
- Sitting talking to someone
- Sitting quietly after a lunch without alcohol
- Sitting in car stopped for few minutes in traffic
- Normal is < 10
- 0-24 scale
- Quick, in-office assessment

Sleep Hygiene

- Consistent sleep schedule 7 days/week
- Regular, relaxing bedtime routine
- Bedroom for sleep, sex only
- Slightly cool room
- Comfortable, quiet, dark bedroom
- No TV, phone, computers in bedroom
**Sleep Hygiene**

- Turn clock around
- Only go to bed when tired
- Not asleep in 20 min-get up and do something relaxing/boring until drowsy
- Light snack at bedtime-banana
- No caffeine in pm
- Limit alcohol
- Something relaxing prior to bed
- Eat right
- Exercise regularly: not w/i 4 hrs of bedtime

**Sleep Promoting Agents- Benzodiazepines**

- Target GABA receptors
- Short, medium and long-acting
- Dependence, abuse
- Withdrawal, tolerance and rebound insomnia
- Don’t combine with other sedatives, alcohol

**Sleep-Promoting Agents-OTC**

- Antihistamines
- Next day drowsiness
- Usually not restful sleep
- Paradoxical insomnia in some

**Sleep-Promoting Agents: Nonbenzodiazepine Hypnotics**

- Zolpidem (Ambien, Ambien CR)-long acting, need to sleep 7-8 hrs, good for initiation and maintaining sleep
- Zaleplon (Sonata)-shorter acting, need at least 4 hrs, good for initiation of sleep
- Eszopiclone (Lunesta) sleep initiation and daytime alertness
- Ramelteon (Rozerem) targets melatonin receptors
- Don’t take with other sedatives, alcohol
- Dependency, tolerance, withdrawal, rebound insomnia
Sleep-Promoting Agents: Antidepressants
- Trazodone: 50-250mg nightly, priapism
- Doxepin: 10-150mg nightly
- Amitriptyline: 10-50mg nightly
- Mirtazapine: 15-45 mg nightly, lower dose may be better

Sleep-Promoting Agents: Herbal Agents
- Limited scientific evidence
- Don’t need FDA approval—not regulated
- Melatonin
- Valerian Root
- Kava
- 5HTP
- Can have severe side effects

RLS Treatment: Ropinirole (Requip)
- Dopamine agonist
- Available 0.25mg-5mg tabs
- FDA approved for Parkinson’s Disease and RLS
- Dosing for RLS: 0.25 mg-4 mg/day 1-3° before bed
- Side effects: nausea, dizziness, sleep disturbance, headache, dry mouth, hypotension, sleep attacks, compulsive behaviors (sex, gambling)
- Drug interactions: Ciprofloxacin, estrogens, neuroleptics

RLS Treatment: Pramipexole (Mirapex)
- Dopamine agonist
- Available 0.125-1.5mg
- FDA approved for Parkinson’s Disease and RLS
- Dosing for RLS: 0.125-0.5mg/day 2-3° prior to bed
- Side effects and drug interactions similar to Requip
Wakefulness Agents: Modafinil

- Modafinil (Provigil) - approved for OSA, Narcolepsy, SWD
- Dosing 200mg-600mg per day (once or twice daily)
- Side effects: rashes, nausea, headache, diarrhea, insomnia, GI distress, mood changes

Wakefulness Agents: Armodafinil

- Armodafinil (Nuvigil): approved for OSA, narcolepsy, SWD
- Longer lasting than modafinil
- Once day dosing: 150mg or 250mg in am or prior to shift
- R-isomer of modafinil
- Side effects: rashes, headache, nausea, dizziness, mood changes

Wakefulness Agents: Stimulants

- Methylphenidates and amphetamines (short and long acting)
- Dosed from 5-60mg/day, divided doses
- Side effects: insomnia, nausea, headache, nervousness, tremors, appetite suppression, BP increase, palpitations, irritability
- Tolerance can develop
- Rebound hypersomnia

Anticataplectic Agents

- GHB (gamma-hydroxybutyrate, sodium oxybate or Xyrem) - a central nervous system depressant
  - Can help with hallucinations, sleep paralysis
  - Mechanism of action unknown
  - Dosing from 2.25mg-9mg in one or two night time doses
  - Can be withdrawn
  - Alcohol and sedative effects additive
  - Side effects: nausea, bedwetting, sleep walking
- TCAs and SSRIs can help
- Venlafaxine and Atomoxetine can help
- Carbamazepine can help
Key Points For Sleep Disorders

- Occur commonly
- Occur more in patients with acute and chronic medical conditions, mental health problems
- Underdiagnosed and undertreated
- Impair quality of life for individual (physically and mentally)
- Many negative consequences for society

References