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Sleep

- General
  - The circadian (daily) alerting system increases in the AM (e.g., 9 am) throughout the day, with a transient plummet around 3 pm, and a slow decrease from around 5-7 pm to the nadir in the middle of the night
  - The circadian sleep system increases throughout the day as well, peaking at 10-12 pm, reaching a nadir in the morning (e.g., 9 AM).
  - The ventrolateral preoptic (VLPO) area of the hypothalamus appears responsible for the control of deep sleep; it is an area rich in GABA receptors. It's activity is tightly coordinated with the raphe nucleus (the main center of serotonergic neurons) and the locus ceuruleus (the main center of noradrenergic neurons)
  - The suprachiasmatic nucleus (SCN) in the hypothalamus appears to be responsible for maintaining circadian rhythyms; it is rich with melatonin receptors.
  - Prevalence of persistent insomnia in adults: 9-18%
  - Hyperarousal in Clients with Insomnia
    - Overactivation of hypothalamic-pituitary axis (HPA; the cortisol stress response system) and higher cortisol levels
    - Overactivation of the sympathetic nervous system
    - Increased metabolic rate
    - Increased EEG arousal and brain metabolism
    - Evidence of increased cognitive arousal during sleep
    - Functional neuroimaging changes
    - The circadian rhythm of body temperature is often delayed so that the daily peak in adults with insomnia occurs 2-4 hours later than the peak in folks without insomnia.
- Sleep Hygeine
  - Do
    - Awaken same time every AM
    - Increase exposure to bright light during the day
    - Establish daily activity routine
    - Exercise regularly in the AM and/or afternoon
    - Set aside a worry time
    - Establish a comfortable sleep environment
    - Maintain regular bedtime and wake time
    - Do something relaxing prior to bedtime
    - Use bed for sleep and intimacy only (or possibly reading)
    - Try a warm bath
    - No media within 1 hour or more of sleep time, including phones, iPads, etc
    - Cognitive behavioral therapy
      - Stimulus control
        - If unable to fall asleep within 20", get out of bed and repeat as needed
      - Sleep restriction therapy
        - Decrease time in bed to equal time actually asleep and increase as sleep efficiency improves
      - Sleep education and hygiene
        - Promote habits that help sleep
          - Awaken same time every morning
          - Increase exposure to bright light during the day
          - Establish daily activity routine
          - Exercise regularly in the AM and/or afternoon
          - Set aside a worry time
          - Establish a comfortable sleep environment
          - Do something relaxing prior to bedtime
          - Try a warm bath
        - Eliminate habits that interfere with sleep; avoid
          - Alcohol
          - Caffeine, nicotine, other stimulants
          - Exposure to bright light/blue light during the night (plus or minus blue light filter glasses)
          - Browsing internet, doing emails/work in bed
          - Exercise within 3 hours of sleep
          - Heave meals or drinking within 3 hours of bedtime
          - Using your bed for things other than sleep (or sex)
          - Napping (unless a shift worker)
          - Watching the clock
          - Noise
          - Excessive heat/cold in room
      - Cognitive therapy
        - Talk therapy to dispel unrealistic and exaggerated notions about sleep
      - Arousal reduction/relaxation training
        - Biofeedback
        - Progressive muscle relaxation
        - Guided imagery
        - Breathing techniques
      - Paradoxical intention
        - Try to stay awake (without substances)
      - CBT
        - Combine all the above
    - With kids, above and:
      - Graduated extinction
      - Positive bedtime routines

- Scheduled awakenings
- Bedtime fading
- Bedtime pass
- Monster spray
- Reinforcement/sleep fairy

- Melatonergic agents
  - General
    - Trials up to 6 months have not shown significant changes in safety parameters
    - Side effects:
      - Next day sedation
      - Vivid dreams/nightmares
      - Rise in prolactin
      - Decrease in FSH
      - No weight gain
  - Rozerem (ramelteon, TAK-375)
    - May not regulate other non-sleep circadian rhythms like melatonin does
    - Mechanism
      - Selective melatonin-1 and 2 receptor agonist (which are located only in the suprachiasmatic nucleus (SCN) in the brain which serves as the brain's clock)
      - Ramelteon is more specific to melatonin-1 and 2 receptors than the natural hormone melatonin; no measurable affinity to other receptors
      - By activating the melatonin-1 and 2 receptors in the SCN, ramelteon dampens the alerting signal generated by the SCN as an individual's need for sleep increases
    - Discovered in Japan in 1996
    - > 100 pre-clinical studies; 43 clinical studies involving > 4,200 patients.
    - FDA-approved 2005 for insomnia characterized by difficulty with sleep onset; approved for long-term use; available 8/05
    - Recommended dose is 8 mg taken 30 min prior to bedtime; range
    - Half-life of 1-2.6 hours
    - Tmax 0.3-0.75 hours
    - High fat foods will delay absorption, 1A2 metabolism
    - 8 mg tabs
    - Not directly sedating
    - Side effects and risks
      - no adverse effects on alertness or ability to concentrate in the morning
      - minimal side effects (rates of headache same as placebo, more likely to cause sleepiness than placebo)
      - dizziness
      - fatigue
      - ?increased prolactin/decreased testosterone?
      - was safe and effective in geriatric clients (with no more likelihood of side effects than with younger adults)
      - safe and effective in clients with COPD and sleep apnea
      - associated with decreased testosterone levels and increased prolactin levels in adults (which could affect menstrual cycles, sexual functioning, lactation)
      - avoid with fluvoxamine (due to decreased metabolism of ramelteon)
  - Melatonin
    - 19 studies involving 1683 subjects
      - Efficacy in
        - Reducing sleep latency (average ~7 minutes)
        - Increasing total sleep time (average ~8 minutes)
        - Improved sleep quality
    - Recent short-term study in children with ADHD positive
    - Take roughly 2-3 hours before sleep when possible
    - Plasma peak level about 1 hour post-dosage
    - Minimal effects on sleep architecture
    - Half-life is about 45 minutes
    - Dose range 0.2 -10 mg/pm (more common range 3-10 mg/pm, 2-3 hours before desired sleep time)
    - Pediatric studies
      - Hollander et al, 2011; 13 controlled studies in kids with neurodevelopmental disorders (424 subjects), 1-10 mg/d
        - Melatonin > placebo in all 13 studies
        - Adverse events mild and similar to placebo
      - Van Gailswick, 2010
        - Advanced sleep onset by about 1 hour
        - Increased sleep onset latency by about 35 minutes
      - Melatonin in ADHD plus autism spectrum disorder (Smits, 2001, 2003; Van der Heljden, et al, 2006, 2007; Weiss, 2006; Nir, et al, 1996; Kulman, et al, 2000; Pasivronan, 2003, 2004; Gerstang, 2006; Giannotti, et al, 2006; Andersen, 2008; Wasdell, 2006; Bream, 2009; Wright 2011
        - Shortens sleep onset latency
        - 1-6 mg/day
    - Side effects
      - Headache
      - Abdominal cramps
      - Headache
      - Dizziness
      - Irritability
      - Vasoconstriction
      - Low heart rate/hypotension
      - Pruritis
      - No weight gain (may protect against "metabolic syndrome")
    - Risks (which are not fully studied so not certain)
      - Inhibits secretion of GnRH/LH/FSH
      - May suppress the hypothalamic/pituitary/gonadal axis and could trigger precocious puberty upon d/c
      - May cause gonadal suppression
      - May cause infertility

        - ?reduced seizure threshold
        - Suspected risks of myocardial infarction, or stroke
        - Evidence of protecting against and possibly increasing risk of cancer
        - May impair glucose tolerance
        - May have beneficial effects on thrombus growth, cholesterol levels, and blood pressure
    - Tasimelteon
        - MT1 and MT2 agonist
    - Piromelatine
        - MT 1 and MT2 agonist
        - 5HT1a and 5HT1D agonist
        - 5HT2B antagonist
    - Agomelatine
        - MT1 and MT2 agonist
        - 5HT2C antagonist
        - Also treats major depression
        - Pecenak et al, 2013
            - Open label, 8 week, multicenter, 111 patients with moderate to severe depression
            - 25-50 mg/day
            - Safe and effective (with no hepatotoxicity (though this risk is reported elsewhere)
                - 14.1% responded in first 233k
                - 74.5% responded by study completion
    - Enol-3-IPA
        - melatonin agonist/lipocortins synthesis antagonist
    - PD66735 (LY-156735)
        - synthetic melatonin
- Non-benzodiazepine GABA-receptor agonists
    - General
        - Side effects: drowsiness, dizziness; rare withdrawal symptoms: insomnia, muscle cramps, seizures
        - Take on empty stomach for faster onset
        - Dose about 50% lower in women
    - Ambien (zolpidem)
        - 2.5-10 mg/PM
        - Half-life 2-4 hours (elsewhere: 2.5 hours (2.9 hours in elderly))
        - Tmax 1.6 hours
        - Physiologically dependency forming at doses above 10 mg; 36 cases in world 1966-2002 (Hajak)
        - Tabs: 5 mg and 10 mg; now comes generic
        - 2011: Sublimox, orally dissolving tablet of zolpidem, approved in Canada
    - Ambien CR
        - 6.25-12.5 mg/PM
        - Half-life 2.8-2.9 hours
        - Tmax 1.5 hours
        - modified-release formulation that incorporates both immediate- and controlled-release preparations to improve sleep maintenance while maintaining the same elimination half-life as the standard preparation
        - with higher blood level 3-6 hours postdose to maximize middle of the night coverage while minimizing morning sedation)
        - 6.25 and 12.5 mg tablets
    - Sonata (zaleplon)
        - 5-20 mg/night
        - Half-life 1-2 hours (elsewhere: 1 hour)
        - Tmax 1 hour
        - Short half-life allows middle of the night dosing
        - Extended release form in progress
    - Lunesta (eszoplicone)
        - 1-2 mg/pm for falling asleep, 2-3 mg for staying asleep
        - Half-life 6 hours (9 in elderly)
        - Tmax 1 hour
        - Enantiomer of zoplicone which is available in Europe
        - Studied for up to 6 months in 788 patients. A total of 24 clinical studies involving more than 2,700 adult patients; more than 60 pre-clinical studies; some research up to 12 months use.
        - No evidence of tolerance, generally (though 22 cases of dependence 1966-2002 (Hajak))
        - Adverse effects include unpleasant taste and headache
        - Available in 1-, 2-, and 3-mg tablets
    - Indiplon
        - under investigation
        - 20 mg/pm
        - IR form (1-1.5 hour elimination half-life allowing middle of the night dosing)
        - MR form: 30 mg/pm. GABA-A receptor modulator
        - No evidence of next-day residual effects
        - No evidence of withdrawal or rebound upon abrupt discontinuation.
- Other GABAergic agents
    - Gaboxadol
    - Gabatril (tiagabine)
    - Neurontin (gabapentin)
    - Depakote
    - Vigabatrin—inhibits GABA transaminase
    - Topamax—acts on GABA at ion-gated channels
    - Pregabilin (Lyrica)
    - Ocinaplon , GABAa receptor modulator
    - Theanine
        - Amino acid
        - Lyon, et al, 2011
            - 93 boys with ADHD (some treated with stimulants, some not)

- 200 mg twice-a-day
- Sleep efficiency significantly improved
- Somewhat improved likelihood of awakening after sleep onset
- No change in sleep onset latency or total sleep time

- Valerian
  - Extract of Valeriana officinalis
  - Several potentially active components, including valerinic acid, other sesquiterpenes, valepotriates
  - May reduce sleep latency and improve total sleep time
  - Extracts of 2-3 mg taken 1-3 times-a-day in a tincture or tea
  - Side effects
    - Restless sleep
    - Gastrointestinal distress
    - Headache
    - Contact allergy
    - Pupillary dilation
    - Sedation, drowsiness
    - Unsteadiness
    - Dizziness
    - Possible carcinogen
    - Possible liver toxicity
    - Overdoses: cramping, tremor, unsteadiness, confusion
  - Mechanisms of action of valerenic acid (derived from valerian root):
    - inhibition of GABA catabolism
    - binds to GABA receptors
    - 5HT1a receptor activity
    - actions on adenosine receptors

- Serotonin 2a blockers
  - Trazodone
    - Inhibits serotonin reuptake
    - Decreases adrenergic sensitivity
    - Antihistamine side effects → sedative properties
    - Onset of action 30-120 minutes
    - 25-100 mg 30-120 minutes before bedtime; up to 300 mg/pm
    - Peak level reached within 2 hours
    - Metabolized by 2D6
    - Half-life of 7-8 hours (biphasic: 3-6 hours and 5-9 hours)
    - →
      - improved sleep continuity
      - increases slow wave sleep
      - decreased REM sleep
    - No controlled studies in youth
    - Side effects
      - Sedation
      - Orthostatic hypotension
      - Fast heart rate
      - Dry mouth
      - Constipation
      - Blurred vision
      - Priapism in 1/6000 men
      - Worse anxiety if combined with a 2D6 inhibitor (due to build-up of mCPP)
  - Remeron
    - Alpha-2agonist
    - 5HT2 antagonist
    - Sedating at 3.75-15 mg/day; dose up to 45 mg/pm
    - Improved sleep onset latency and less waking up after sleep onset
    - Increase sleep duration
  - Esmirtazepine maleate (Org-50081)
  - Doxepin
    - Histamine-1 antagonist
    - Tmax 3.5 hours
    - Half-lie 15 hours (31 hours for metabolite)
    - Dose: 3-6 mg
    - Side effects: somnolence, nausea
    - Contraindicated in severe urinary retention, narrow angle glaucoma, MAOI within previous 2 weeks
  - Amitriptyline
  - Seroquel
    - 25-100 mg improves sleep induction and continuity and increases total sleep time, sleep efficiency, % stage 2 sleep, and subjective sleep quality
  - Eplivanserin (SR 46349): increases slow wave sleep
  - M-100907
  - Clonidine (especially for PTSD-related sleep problems)
    - Rapid absorption
    - Onset within 1 hour
    - Peak effects 2-4 hours
    - →
      - increase in slow wave sleep
      - decrease in REM sleep
    - begin with 0.05-0.1 mg and titrate weekly to 0.2-0.3 mg/pm
    - Pediatric studies (data not high quality)
      - Prince, et al, 1996
        - improvement
        - adverse effects in 31%

        - Wilens, et al, 1995
            - rapid onset (30 minutes)
            - all night duration
            - improvement
            - no adverse effects
        - Ming, et al, 2008
            - parent reported improvements
    - Side effects
        - hypotension (rebound hypertension)
        - anticholinergic
        - irritability
        - dysphoria
        - tolerance
        - parasomnias
        - risk of overdose
- Prazosin (especially for PTSD-related sleep problems)

- Other agents
    - Antihistamines (e.g., Benadryl)
        - Side effects
            - **Oversedation** (next day)
            - Dry mouth
            - Urinary retention
            - Restless legs
            - Increased intraocular pressure
            - Nausea
            - Depression
            - Malaise
            - Weakness
            - Gastrointestinal distress
            - Headache
            - Impotence
    - Tricyclic antidepressants
    - ?Buspar
    - Prazosin
        - Helps reduce PTSD-related nightmares
        - Raskind et al, 2013: 15 week, RCT, up to maximum dose of 5 mg/midmorning and 20 mg/pm; average dose 15.6 mg; effective; blood pressure did not change
    - Belsomra (Suvorexant)
        - Targets orexin system
        - 10-20 mg
        - Half-life 12 hours
        - Tmax 2 hours
        - Side effects
            - Somnolence
            - Headache
            - Impaired alertness
            - Motor coordination/impaired driving
            - Contraindicated in narcolepsy