DISCLOSURE STATEMENT

• Dr. DeSanctis discloses that he has neither financial agreements with nor endorsement from any commercial interest in relation to the topics of this presentation.

• This presentation is designed for educational purposes only and is not intended for self-assessment or self-treatment. Any concerns related to sleep or behavior should be addressed with the appropriate health care provider. Comments by presenter in regard to audience queries regarding clinical management of clients are not meant to substitute for supervision or direct consultation.
Presentation Objectives

• 1. Describe basic circadian, homeostatic principles.
• 2. Learn practical implications of circadian knowledge for client assessments/treatments; how to screen for chronotypes.
• 3. Identify typical circadian disorders and strategies for intervention.
• 4. Discuss insufficient sleep as a behavioral risk factor related to mood, neuro-cognitive and substance use status.
• 5. Review of evidence-based solutions to remediate sleep debt and identifying the need for further consultation.

Types of Rhythms

• Natural Circadian—about 24 hours; Also involved in disease: Malaria, observed 24, 48 and 72-hour fever cycles; 24-hour cycle the deadliest
• Tides: ebb and flow: 2 high and 2 low tides q. 24 hours and 50 minutes;
• Ultradian—repeated periods throughout 24-hr day-
• respiration
• Infradian—periods >24 hours (e.g., menstrual cycle in humans)
• Circannual—seasonal—ancient way of keeping track of the days, based on light
Circadian Processes

• Intrinsic to life forms, organizing principle of life

• Circadian, Dies=day

  Kiser, K. (2005); Franz Halberg, U of MN;

• Hard-wired/DNA/clock genes/proteins

• Changes in circadian rhythms over the life span;


Specific Circadian Elements

• In humans, clock operates at a slightly greater length than a 24-hour period

• Linear time vs. circadian time


• Suprachiasmatic Nucleus-SCN-master pacemaker, connected to periphery;


  Doi: 10.1016/j.jsmc.2009.01.004;

Circadian Drivers

• Entrainment/synchronization of SCN pacemaker and peripheral clocks by external light cues, social, eating, substance use activities-zeitgebers;

• Light, dopamine promote wakefulness

• Phase Response Curve-Delays and Advances/Chronobiotics-Melatonin

• Disconnect between what we do and think and status of our inner biological clock
Creatures of Habit

• We are creatures of habit, entrained each and every day, intentionally and in a conditioned fashion; in Western culture forward propulsion;

• Deviations from our usual habits, such as eating large meals in middle of the night, traveling across many time zones puts us at cognitive and adaptive risk; insulin resistance and circadian disruption

• External and internal de-synchrony


Insomnia/Circadian Disruption

• Fall/Accident risk

• Substance use risk

• Sleepy Driving/MV Crashes

• Impact on intimacy and communication in relationships

(DeSanctis, M. J. Appl Behav Sci, 2017; e12102/https://doi.org/10.1111/jabs.12102

• Mood Disturbance
Circadian Neuro-functional Anatomy/Physiology

- Photic energy via optic nerve to SCN
- Pineal Gland/Melatonin-darkness signal; hormones signals peripheral clocks; circadian drive engaged by blue light wavelength;
- Orexin-wakefulness signal vs. adenosine

(Liu & Gao, 2007 doi:10.1112/jn.2007.133.10.115)

Circadian Inflection Points

- Wake Maintenance Zone (WMZ)
- Circadian Nadirs


- Central Clock: core body temperature, cortisol levels, behavior, hormones, metabolism; signals to and from peripheral clocks
- Cortisol peaks earlier in day, may be involved in entrainment of peripheral oscillators; external morning light amplifies signal
• Persistent
• Conscientious
• Cooperative
• Female > Male
• Better Sleep

• Addiction Risk
• Mood Disturbance
• Creativity
• Novelty seeking
• Volatility

Sharkey, 2014, Post-grad course Annual Mtg of AASM, Mpls, MN June 2014

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Homeostatic/Circadian Principles

• Homeostatic Sleep Pressure (H-drive) in a 24/7/365 business and personal culture, with less and less true darkness at night

• Homeostatic and Circadian Processes (S-drive) interact in the 24-hour period; the longer you are awake, the stronger the sleep pressure


• Rest-Activity Cycles, Light, Genes, Dopamine, Rewarding Behaviors

(Parekh et al., 2015). Alcohol 2015 Jun 49(4), 341-349.

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Source: Wikipedia Commons

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Clinical Assessment of Circadian/Sleep Challenges
• Sleep habits, preferences, any hx of neurologic compromise, TBI/CHI/LOC; permeable sleep-wake boundary;

• Chronotypic evaluation Morningness-Eveningness Questionnaire- (MEQ)

• Social Jet Lag

MEQ
• Scale (19 items, 4-5 forced choices)

• Scoring (range from 16-86; 41 or < =evening; 59 and >=morning; lower scores mean later morning light exposure; higher values translate to earlier morning light exposure-algorithm developed

Cf. Wirz-Justice et al, 2009, Chronotherapeutics for Affective Disorders. Basel, Switzerland: S. Karger, AG. contains copies of the MEQ, Personal Inventory for Depression and SAD (PIDS), etc.
MEQ continued

• Sample queries: what would be your preferred bedtime if you had total control over your schedule?

• Degree of alertness when first awakening

• How reliant are you on an alarm clock?

• Time interval during day for physical exercise and when you feel at peak (Breus, 2016)

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Morningness-Eveningness Questionnaire

• Morning vs. Evening Chronotypes
  Horne & Ostberg, 1976

• Self-Report, online version at www.cet.org
  Terwee et al., 2014, Center for Environmental Therapeutics

• Other versions of chronotype screening for pediatric use

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Why Do Humans Need to Sleep?

• Homeostatic: restore tissue and regulate internal body temperature; conserve energy; sleep has been millions of years in the making;

• Protect from Predation; Sleep Patterns of Grazing vs. Predatory Animals

• REM sleep - remove, prune, consolidate daily experience from neural networks; hippocampus to cortex channeling

• Sleep needs studied across all biological kingdoms

General Protocol for Sleep D/O Differential

• Diagnostic intake - include statement about sleep; R/O substance abuse, environment

• Epworth Sleepiness Scale
  Johns, 1991, Sleep, 14, 540-545

• Prospective Sleep Log

• Sleep Efficiency/Sleep Length/Quality

• Referral to primary care/BSM/sleep clinic/Actigraphy, overnight studies

Epworth Sleepiness Scale (Johns, 1991)

• 0-3 ordinal scale, with 0=no chance of dozing to 3=high chance of dozing off

• 8 items, >10 considered abnormal

• Items query one's state of sleepiness in typical situations - as passenger in a vehicle; after lunch with no ETOH, resting or watching TV, etc.,
The Challenges of Adolescence

- Delayed Sleep
- Hormone Flux
- Social Pressures
- E-Device Use
- School Start Times

Hypothetical Case Study-DSPS

- Peter, Age 16, male, referred by parents in context of truancy and academic underachievement
- PHQ-9 T=10; GAD-7 T=5
- At 9am Intake: client irritable, tired, yawning; parents primary informants; client bored, detached;
- 3-year pattern of difficulty arising in morning

Delayed Sleep-Wake Phase Disorder

American Academy of Sleep Medicine; used with permission
DSPS Case Study, continued

• MSE: no apparent neurocognitive compromise, MMSE 30/30; WNL intellect; no indication of any SLD; no CHI/LOC or seizure activity;

• Stays up late, till 2-3am every school night on his iPad, watching videos, keeps smartphone under his pillow; sleeps late on weekend mornings (11am-12noon)

• Client denies ETOH, caffeine, opioid, K2 use; Client smokes THC to take edge off school anxiety; no prescribed psychotropics

DSPS Case Study, continued

• Sleep is restorative when not awakened on school mornings; no nocturnal or sleep period awakenings; simply unable to fall asleep at 10 or 11pm on school nights; considerable friction with parents over this issue; more and more academic concerns year over year;

• Report of solid peer friendship network, no prior trauma exposure; middle-class, stable family system; no IEP or 504 IAP

DSPS Case Study Continued

• Dx Impressions? R/O Persistent Depressive Disorder, DSPS, compulsive e-device use;

  Treatment Plan:
  1. 2-week Sleep Log (BSM clinics may rely on actigraphy and log)
  2. referral to BSM clinic and to PCP; may benefit from early am bright light, evening melatonin, counseling with client and parents around DSPS
  3. Sleep Hygiene counseling;
  4. Chemical Health Screening with CAGE-AID
DSPS Case Study, continued

3. Secure ROIs, consultation with school, and/or juvenile court if truancy charges pressed by school/county attorney

4. Depression is not uncommon among adolescents with DSPS—may reflect frustration, not meeting expectations for attendance, sense of failure, circadian disruption; at risk for more self-medication;

Advanced Phase Disorder

• Seen in elderly sub-populations; Sundowning, early evening drowsiness

• Weaker circadian signaling with advancing age; Flammer, 1996, Australian New Zealand Journal of Medicine, 26, 96-104.

• Treatable with environment/light/lifestyle modifications Ancoli-Israel et al., 2003, Behavioral Sleep Medicine, 1, 22-36.

Practical Implications of Chronotype

• Differences in chronotype among humans living together or in committed relationships; MEQ as screening tool in couples assessment/conflict resolution

• Times of day to prescribe skills training for clients such as meditation, mindfulness, Breus, 2016 - The Power of When

• Personality traits, SOL, mood, substance use correlated with morning vs. evening types
A Peek at Google Searches

• Porn searches reach maximum @ 1am

• Weather/News (5:24am/4:52am)

• Panic and loneliness searches peak at 3:24am

• Mental lapses reach maximum well after 12midnight-space out on PW at 2:44am

Source: Stephens-Davidowitz, 2015

Sleep/Circadian Issues in At-Risk Sub-populations

• Fetal Depakote Syndrome
  Garcia, 2010, Challenging and fascinating cases that arise in pediatric sleep medicine. Presentation to the MN Sleep Society, 1st Annual Meeting, St. Paul, MN

• Dementia
  (Lin et al, 2010): sleep disruption leads to increases in beta-amyloid and tau proteins

• Sundowning

• Non-24 Circadian Rhythm

• “Early to bed, early to rise, makes [one] healthy, wealthy and wise.”

Circadian/Sleep Disruption and General Health

• Shift work perils, industrial accidents, motor vehicle crashes, absenteeism

• Cardiovascular impacts; morbidity;

• Short Sleep and Diabetes risk, increase in hedonic food intake, role of endogenous cannabinoids
  Van Cauter, 2018, Annual Mtg, MN Sleep Society, October 2018

• Immune system/Chronic pain
Sleep, Circadian and Immune System Functions

- Spikes in adrenal activity correlated with presence of inflammatory cytokine (interleukin-6)
- Inflammatory cytokines and degenerative illnesses, dementia of the Alzheimer’s type, tau and amyloid deposition in central neural networks
- Relationships between circadian de-synchrony, acute sleep deprivation, cortisol levels, CRP, IL-10, TNF; Besedovsky et al, 2012, Pfluger Archiv. Jan 463(1), 123-137.

Extrinsic Circadian Disorders

- Jet Lag versus Social Jet Lag
- Misalignments
- Shift work
- Effects of Surgery, Hospitalization on circadian rhythms
  Farr et al, 1984, Nursing Research, 33, 140-146.

Facts about Sleeplessness

- Insomnia prevalent in the population; some estimates of 1 in 10 adults in US; more health care utilization, worker absences, marker for depression
- National Sleep Foundation, 2004: nocturnal awakenings typical in infants/children; impact on caregivers (primarily mothers and stepmothers)
- CDC, 2009: about 29% US adults sleep <7 hours per night; state-by-state estimates of 30 days of insufficient sleep varied from 7.4% in ND to 19.3% in WV-Hawaii actually has a problem with insufficient sleep
- Billions of prescriptions written for sleeping pills
Sleep Hygiene Basics/Rationale (HANDOUT)

- Regularity of Schedule/Strategic Light and Dark Exposures

- Stimulus Control

- Lifestyle Factors/Environmental

- Lacks efficacy as single modality tx

Sleep Hygiene and Sleep/Circadian Wisdom

- Social rhythm therapy, importance of daily routine

- Boundaries on e-device/LED exposure/Blue Wavelength
  Tosini et al, 2016

- Modifications to sleeping quarters

- Sleep Efficiency (overstaying your welcome in bed)
Still counting Sheep?

Insomnia

- Hyperarousal and weakened H-drive (primary); Intersection of Circadian and Homeostatic; overrides GABA

- Association with Anxiety/Trauma/Physical Environment, insomnia is most common PTSD symptom

- Insomnia common in abstinence, early recovery, creates relapse risk

Tips for Zeroing in on Insomnia

- Bed partner/parent/caregiver input, possible delayed circadian phase

- Predisposing factors: cognitive ruminative styles; circadian desynchrony, lifestyle, personality traits

- Precipitating: acute grief or loss, trauma;

- Perpetuating: anxiety/mood/substances/e-device overuse
  Spielman et al, 1987, Sleep, 10, 45-56.
SLEEP PROBLEMS ARE ENDEMIC

- Nearly everyone experiences some transient sleeplessness
- People with insomnia have perfected the art of not sleeping
- Mechanical view of sleep (viewed as a necessary evil by some)
- Family sleep attitudes/Insomnia is a cross-cultural issue


Sleep Hygiene-Learning How to Sleep

- Behavioral (clock watching, regularity of sleep-wake schedule, scheduling of heavy meals, social activity, cell-phone/laptop use in or just before bedtime)
- Environmental: temperature, ambient light in bedroom, noise levels, air circulation, humidity, allergens, mattresses, etc.
- Avoid caffeine, nicotine, ETOH anywhere near late evening/bedtime
More about insomnia as a learned problem

- People copy others and use caffeine to stay awake, ETOH or Cannabis/THC, but do not learn enough about the dose-response relationships
- People try hard to sleep, very hard!
- Learning to live without distractions
- Positive and Negative Sleep Thoughts


New & Existing Sleep Tracking Technologies

- Growing consumer awareness/interest, part of the digital universe
- Pillows/Mattresses; Apps
- Motion/Movement Detectors/Actigraphy
- Search for holy grail of technology to improve sleep
- Limitations in understanding sleep quality/impact of measurement

Insomnia and Primary Care

- Insomnia still not snuffed out in primary care to the extent needed;
- Insomnia may be missed or not reported in the record even though surveyed providers may view it as an important issue, perhaps equal to other non-behavioral sleep issues (e.g., apnea)
- Reliance on Rx as expedient; not behavioral health interventions especially for transient and acute insomnia;
Medications/Substances that cause Insomnia

- Steroids, theophylline, decongestants, pseudoephedrine, stimulants
- Beta blockers (impact melatonin), diuretics
- Antidepressants, such as Prozac, Effexor, Zoloft
- Alcohol, Nicotine, Caffeine, Thyroid meds
- Opioid withdrawal

CBT-I

- Evidence-based practice for managing insomnia
  (Pigeon, 2010)
- Online programs/manuals
  Blom et al., 2016, Sleep, June 39(6), 1267-1274, need for external coaching/support;
  Readily adapted from standard CBT
  Imagery Rehearsal Training (IRT) for nightmares

Co-morbid Medical Issues Impacting Sleep

- Respiratory illnesses, Apnea, Snoring
- Nocturia/GI problems; indigestion, heartburn
- Chronic pain, fibromyalgia/Obesity/RLS/PLM (one indication for PSG)
- Dementia; mild TBI, decreased REM sleep

Mento et al., 2017, Sleep, Jun 1, 40(6), Doi 10.1093/sleep/zdx162.
Periodic Limb Movement Disorder

- Unlike RLS, these are involuntary movements that occur while asleep; Hauri & Linde, 1996, No More Sleepless Nights. New York: John Wiley & Sons, Inc.
- Baffling to person affected, as they awaken in morning tired despite “sleeping all night”
- Similar pharmacologic remedies as with RLS—elevate dopamine

Melatonin Facts

- Neuro-hormone produced by pineal gland, not a sleeping pill!
- Responsive to circadian clock, light and ambient temperature; internal melatonin levels decline with age;
- Dietary supplement (US Dietary Supplement Health and Education Act, 1994; Rx not required; most people are dosing too high, >3mg
- Mixed findings re: efficacy in insomnia (National Sleep Foundation, 2004), be aware of potential interactions with other meds

Pharmacologic Interventions for Insomnia

- Sedating Tricyclics (Trazodone)
- Benzodiazepine Receptor Agonists (e.g., Lunesta, Ambien)
- Over-the-Counter Remedies (anti-histaminic)-Unisom
- Melatonin Agonists (e.g., Ramelteon)
- Orexin Antagonists (Suvorexant)
Caveats with Rx

• Benzodiazepines such as Ativan should be used for short-term anxiety reduction, up to 8 weeks duration but less than a fortnight when treating insomnia

• Long-term use of sedative-hypnotics creates risk of falls, dependence, drowsiness, erosion of coping skills, amnestic periods, complex sleep behaviors; need to emphasize non-pharmacologic approaches

Potential Complementary Approaches

• B-vitamins: Deficiencies in thiamine (B1), folic acid, riboflavin (B2), Niacin and Pyridoxine (B6)  Hauri & Linde, 1996;

• Aromatherapy for depression, anxiety and pain relief;

• CBD oil legal status in flux; lack of high quality human research

• Yoga


Bright Light/Dawn Simulation

• Dawn Simulation studies  Avery et al, 2002, Biological Psychiatry 50(3), 205-216.

• Bright Light Interventions for winter SAD  Avery et al. 2008 Winter Blues, New York: The Guilford Press.

• Bright Light for Re-setting circadian rhythm  (Czeisler et al, 1984)

• Chronotherapeutics for depression  (Nico-Aldana, Terman & Benedetti, 2006)

• Chronotherapy using behavioral scheduling
Sleep Requirements for Adults

- Young Adults lose deep sleep in their 20s
- Middle-agers lose sleep consolidation
- Adults and Seniors: average 7-8 hours of sleep requirement; less stage 1 and REM in aging males and females
- SWS declines more in males as opposed to females over time


- N1: from wakefulness to sleep: 5 minute period; alpha to theta at 4-7Hz; tonic muscle activity decreases
- N2: first stage of true sleep; irregular brain wave activity; sleep spindles (.5 sec epochs); beta, alpha, theta; K-complexes; high amplitude, eye movements rare
- N3: Delta, large, slow brain waves .5 to 3Hz; 50% Delta; blood pressure falls/muscle repair
- REM: longer intervals toward end of night’s sleep
- SWS and sleep spindles move info from hippocampus to prefrontal cortex for LT storage


E-Devices

- Blue wavelength
  Tosini et al, 2016
- f.lux software for changing screen illumination; “night light” option on device
- Social media utilization among adolescents and sleep disruption
Sleep Deprivation

- Working memory and attention; pre-frontal impacts
  Alhola & Kantola, 2007, Neuropsychiatric Disease and Treatment, 3(10), 563-567.

- Cumulative effects, drowsy driving, accident rates

- “Nothing good happens after midnight” suicide rates in 24-hour period
  Perlis et al, 2011

- Health consequences of chronic, partial sleep debt

More on sleep deficit

- Medication errors/critical thinking of interns on call, extended duty hours
- Impaired learning of new tasks (loss of REM on first night after learning impacts memory of cognitive procedural tasks but not declarative or fact retrieval; loss of stage 2 sleep impairs learning of motor procedural tasks;
  Dotto, 1996, Canadian Medical Association Journal, Apr 15 154(8), 1193-1196.

- “SLEEP ON IT” - retrieval better when sleep period intervenes before recall as opposed to learning early in day and recall later that day;

Sleep Deficit-General Points

Factors to consider:
- type of task-visual-motor vs. auditory vs decision
- time of day (circadian), chronotype
- acute sleep deprivation (SD) vs. partial SD vs. chronic
- effects of situational fatigue, boredom, motivation
- simple reaction time vs. complex tasks
- impact of age and gender (little data on latter variable)
- total SD in research paradigm studied more but does not mimic life

**Pregnancy, Gender and Sleep**

- Females at slightly greater risk of insomnia than males, across geographic regions, progressive with age

- Pregnancy and clearly post-partum period are risk factors for sleep initiation and maintenance
  - >2x greater risk of insomnia in 3rd as opposed to the 1st and 2nd trimesters; 52.2% prevalence of insomnia in random sample N=486

**Psychological Disorders and Sleep**

- Bipolar Disorder: evening chronotype

- Generalized Anxiety, Trauma and Stress (nightmares, flashbacks)

- Sleep Disordered Breathing

- Insomnia can raise risk of Major Depression; depression and sleep problems bi-directional impact;

**Depression and Sleep, (Riemann et al, 2001)**

- Interval from sleep onset to first REM period is abbreviated; Less time in N3 deep sleep (SWS)

- More fragmentation, arousals, Stage 1

- Reduced latency to first REM, increased REM density

- Early am insomnia (terminal insomnia)
Generalized Anxiety Disorder and Sleep
• Decreased efficiency of sleep: more time awake in bed
• More awakenings during the night, sleep architecture disrupted
• Nocturnal Panic episodes


Schizophrenic Spectrum and Sleep Kaskie et al, 2017
• Significant delays in sleep onset
• Less SWS, rapid entry into REM phase; more fractionated sleep, possible marker for relapse
• Nocturnal VH/AH alone do not = psychosis
• Impact of Medications for Psychosis: diurnal sedation, movement disorders

Sleep and ASD (Cf. Williams et al, 2004)
• Adult ASD-frequent complaints of insomnia; sensory sensitivities/poor insight/perseveration; intolerant of transitions/change in environments
• ASD have indicated shorter periods of sleep and decreased TST, possibly related to e-device use, obsessional anxiety, sensory disruptions
• ASD with co-morbid Social or Generalized Anxiety
Sleep and ADHD (Owens, 2009)
- ADHD, hyperactive, delayed sleep onset, RLS, OSA; circularity of causation, impact on diurnal functioning in school setting
- Evening chronotypic preference
- Sleep hygiene problematic in ADHD compared to normal developing children
- Psychostimulants and insomnia

Sleep and Alcohol
- 2-3 drinks before bed can promote sleep, but less impact after 3 days of same behavior
- REM inhibition at high doses within 1 hour of sleep, but chronic ETOH leads to less REM suppression; with cessation, REM rebound occurs
- SWS increases following moderate use at bedtime but effects diminish with chronic use
- Dose dependent stimulating or sedating effect, and interval from use to bedtime

Sleep and Alcohol, Part 2
- Partial sleep deprivation (insomnia) leads to more sedation with ETOH than those without sleep deficiency
- Moderate ETOH in chronically sleep deprived individuals increases risk of accidents-drowsy driving impact & BAC comparisons
- Persistent sleep disturbance in recovery

Sleep and Illicit/Recreational Substances


- THC chronic use can reduce REM and increase SWS sleep; sleep problems raise risk of relapse into use;

- Opioid use: cravings, sleep disruption, parasomnias, diurnal sleepiness; chronic use with withdrawal leads to REM rebound, more nocturnal arousals, respiratory depression, apneas.

Sleep and Aging

- Sleep architectural changes/sleep debt

- Older drivers, reaction time, accidents and sleepiness

- Advanced Circadian Phase / Co-morbid Anxiety/Depression

- Cardiovascular stress for even healthy seniors, less than 5 hours per night

Sleep Wellness Resources

- National Sleep Foundation [www.sleepfoundation.org](http://www.sleepfoundation.org)

- Lighting Science [www.lsgc.com](http://www.lsgc.com)

- American Academy of Sleep Medicine [www.aasmnet.org](http://www.aasmnet.org)

- Sweet Dreamzzz, Inc. [www.SweetDreamzzz.org](http://www.SweetDreamzzz.org)

- iSideSleep [www.iSideSleep.com](http://www.iSideSleep.com); [www.justgetflux.com](http://www.justgetflux.com)
Professional Training/Research Resources

• CBT-I Training - Michael Perlis, PhD, U of Penn Behavior Sleep Medicine
  • www.apa.org/monitor/2016/10/insomnia.aspx

• Society for Behavior Sleep Medicine www.behavioralsleep.org
  • www.sleepresearchsociety.org

• Society for Light Treatment and Biological Rhythms www.sltbr.org

Clinician Resources


• Behavioral Sleep Medicine; International Journal of Chronobiology; Sleep; Journal of Clinical Sleep Medicine;

Insomnia/Circadian Aids Online

• David Ackerman podcasts
  • www.sleepwithme.com

• Online CBT-I

• Meditation apps

• American Academy of Sleep Medicine—sleep calculators, info kits for school start times, etc; www.aasmnet.org
New Horizons for Clinical Practice

- Integrated Health Care/Sleep Behaviors/Blending of Western/Eastern

- Transferability of skills (Acceptance/Commitment, CBT, CT, PMR, exposure therapies, IRT, systematic desensitization, hypnotherapy, etc)

- Public Awareness/Safety/Athletic Performance

- Future Healing: genomic, environmental, specialized, more precision around circadian rhythm biomarkers (Mullington, et al, 2016)