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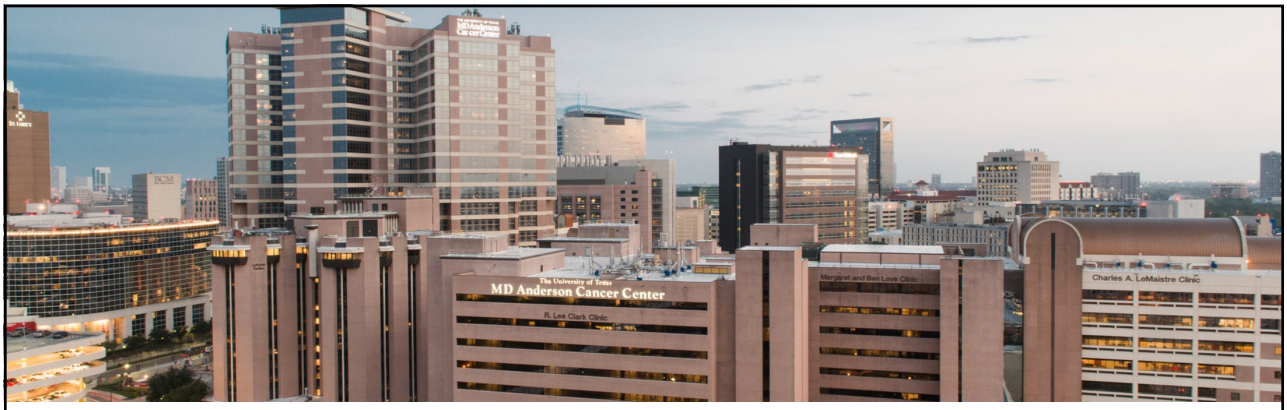
SURVIVORSHIP SYMPOSIUM

Managing Sleep Challenges after Transplant

Celebrating a Second Chance at Life
Survivorship Symposium

April 30 - May 6, 2022

Dave Balachandran MD
The University of Texas
MD Anderson Cancer Center



THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Sleep Disorders and Cancer

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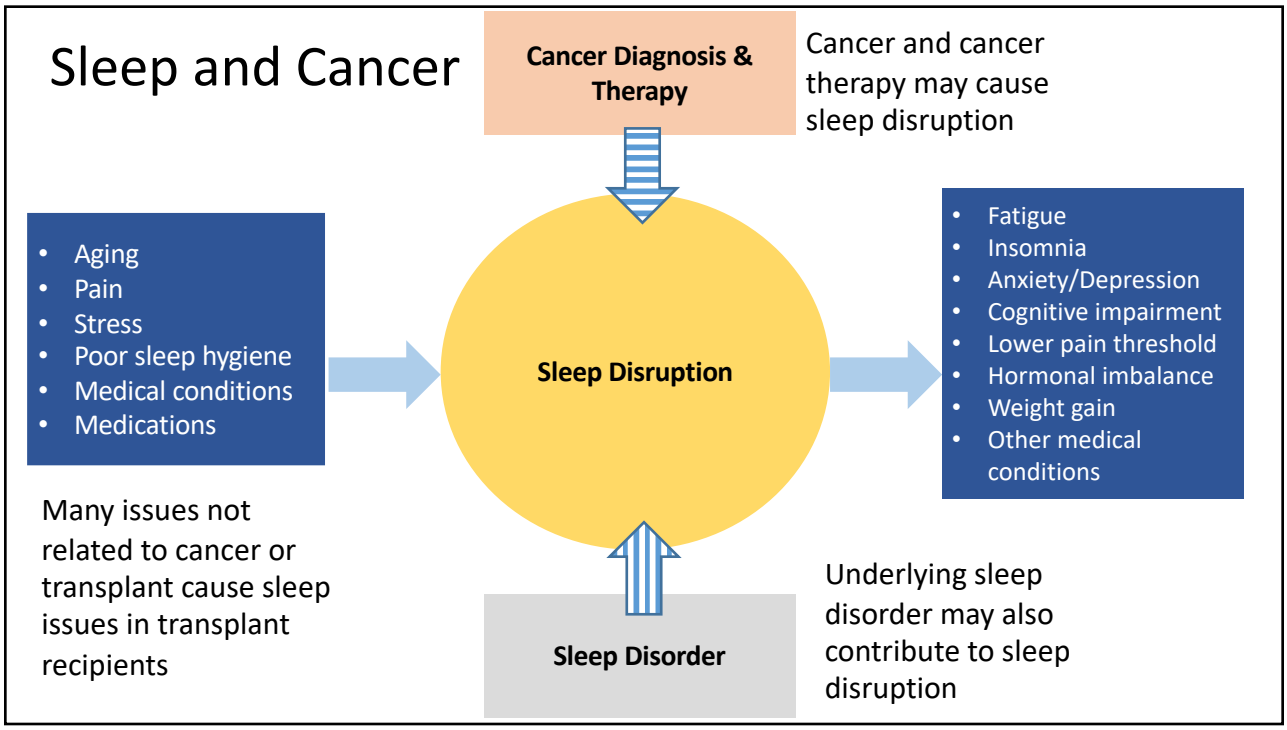


Sleep and Cancer

(n=1012)

	All Cancer	Breast	GI	GU	Gyn	Lung	Skin
Overly Fatigued	44.3%	48%	38.9%	40.0%	46.1%	56.1%	31.7%
Restless leg syndrome	40.8%	42.7%	37.0%	37.4%	42.8%	46.5%	35.8%
Insomnia	30.5%	37.8%	32.4%	18.1%	29.4%	36.8%	22.8%
Daytime sleepiness	28.0%	26.5%	21.3%	30.3%	31.7%	39.5%	18.7%
Sleep medications	21.5%	20.5%	19.4%	14.8%	22.8%	40.4%	14.6%
Increased time in bed	18.3%	13.6%	15.7%	15.5%	20.0%	34.2%	18.7%
Periodic Limb movement disorder	16.5%	13.9%	15.7%	18.1%	12.8%	28.1%	16.3%
Sleep apnea	11.1%	9.6%	7.4%	11%	8.3%	14.9%	18.7%

Davidson, 2002

Sleep Disorders

- Insomnia is the most common sleep disorder in cancer patients
- Sleep-related breathing issues include obstructive sleep apnea (OSA), central sleep apnea and sleep-related hypoventilation
- Large epidemiologic studies link both insomnia and obstructive sleep apnea to cancer

Insomnia is 3 times higher in cancer patients

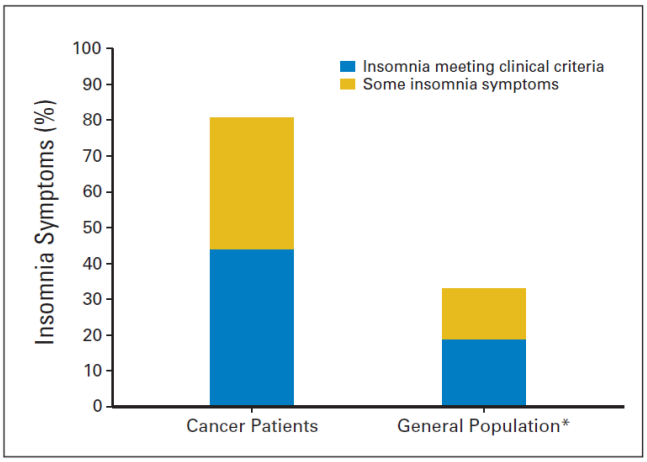


Fig 1. Insomnia symptoms in patients after first cycle of chemotherapy (N = 823) versus general population. (*) From multiple epidemiologic studies summarized in Ohayon.[4a]

Sleep Disorders and Cancer

J Savard, *Journal of Clinical Oncology* 2001
OG Palesh, *Journal of Clinical Oncology* 2010

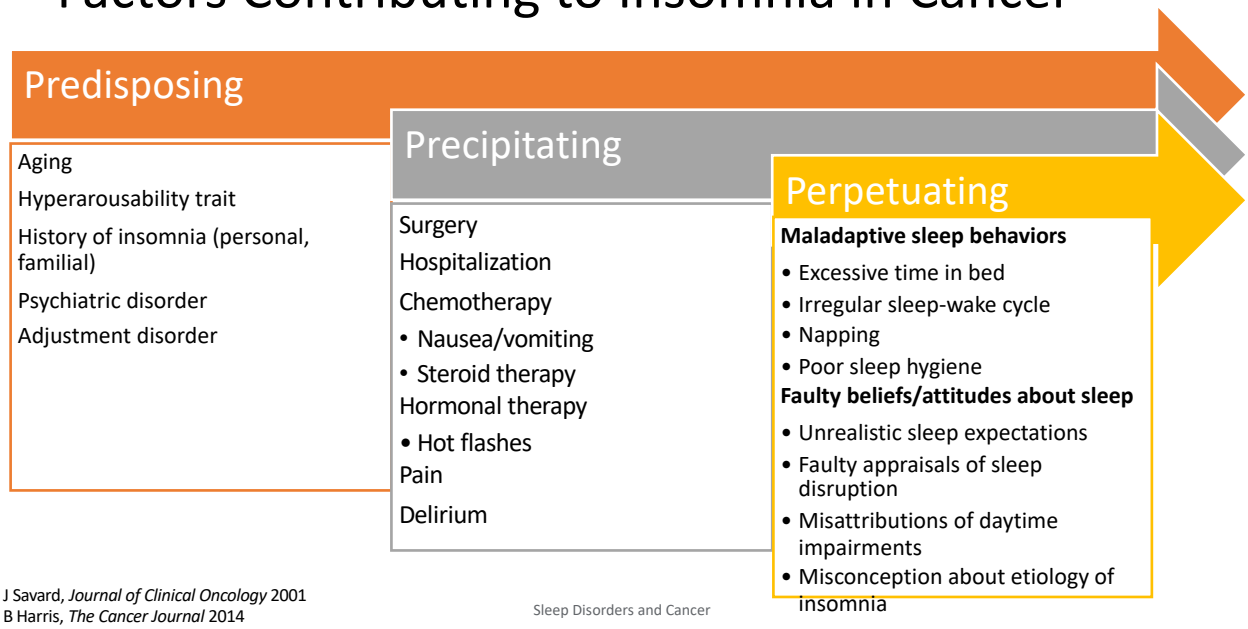
Insomnia: Symptoms

- Patient-reported symptoms:
  - difficulty falling asleep
  - difficulty staying asleep
  - sleep does not restore energy, refresh
- Can cause distress or significant daytime impairment
- Pharmacology therapy (sedatives, hypnotics) often prescribed
- Cognitive behavioral therapy ideal

Sleep Disorders and Cancer

J Savard, *Journal of Clinical Oncology* 2001
OG Palesh, *Journal of Clinical Oncology* 2010

Factors Contributing to Insomnia in Cancer



J Savard, *Journal of Clinical Oncology* 2001
B Harris, *The Cancer Journal* 2014

Sleep Disorders and Cancer

Treatment Options for Insomnia

- Non pharmacologic therapy
  - Sleep hygiene
  - Cognitive and behavioral therapy (CBT-I)
  - Light/ Melatonin
  - Exercise/ Yoga
- Pharmacologic therapy
  - Sedatives hypnotics
  - Anti depressants
  - Stimulants

Sleep Hygiene: Bedroom

- Pain-free mattress and pillow
- Comfortable sheets and blankets
- Cool temperature (around 65 degrees) during sleep time
- Block sources of light
- Drown out sources of noise
  - Earplugs
  - Noise machine
- Aroma therapy

sleepfoundation.org/sleep-hygiene

Sleep Hygiene: Bedtime Routine

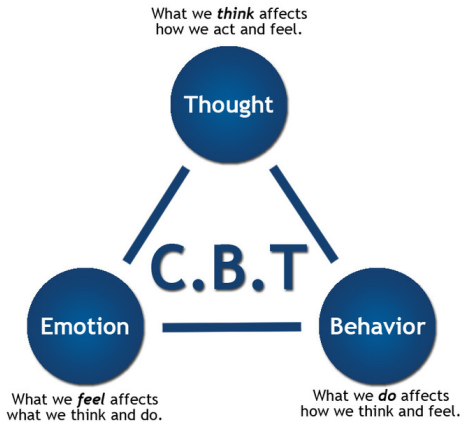
- Go to bed at the same time each night
- Have a consistent bedtime routine
- Unplug electronics 30-60 minutes before bedtime
- Wind down and relax 30 minutes before sleep
  - Soft music, stretching, reading, relaxation exercises
- Dim lights that hinder production of sleep-promoting melatonin
- Create a mental connection between being in bed and sleep
  - If unable to sleep after 20 minutes, get up and do something calming before trying again

Sleep Hygiene: Healthy Daily Habits

- Get daylight exposure, especially sunlight, to drive circadian rhythm
- Be physically active
- Avoid naps, or keep them short, and limit to early afternoon
- Avoid smoking: nicotine is a stimulant that can disrupt sleep
- Avoid alcohol consumption later in the evening
  - Alcohol makes it easier to fall asleep BUT the effect wears off, disrupting sleep later in the night
- Reduce caffeine in afternoon and evening
- Avoid heavy meals late at night
- Use your bed only for sleep and sex

Cognitive Behavioral Therapy for Insomnia (CBT-I)

- Rationale for CBT-I
- What is involved in doing CBT-I?
- How effective is CBT-I vs pharma interventions?
- Where to find a CBT-I practitioner



Light and Melatonin

- Melatonin is a hormone that regulates your sleep cycle
- Sunlight **reduces** production of melatonin, darkness **increases** it
- Artificial light, particularly blue light from fluorescent and LED lights, as well as electronic screens, can reduce production of melatonin at night and delay sleep
- Melatonin
  - Effectiveness
  - Side effects

Yoga and Exercise

- Yoga during the day can improve quality of sleep at night
- Regular moderate to vigorous exercise can
  - reduce the time it takes to fall asleep at night
  - reduce daytime sleepiness
  - reduce weight and risk of obstructive sleep apnea

Pharmacologic (drug) Therapy for Insomnia

- Sedatives hypnotics
  - Zolpidem, exzopiclone, suvorexant
- Anti depressants
  - Trazadone, amitriptyline
- Pros and cons of each
  - Side effects
  - Duration of effectiveness

Other Sleep-Related Disorders

Movement Disorders – Restless Leg Syndrome

- Neurological disorder; causes uncontrolled movement of legs when asleep or inactive
- Affects > 12 million people in the U.S.
- Can lead to poor quality sleep
- Potential causes
  - metabolic problems (electrolyte imbalances, thyroid, diabetes)
  - excessive caffeine consumption
  - hematologic (blood) abnormalities (iron, B12 deficiency)
  - neuropathy from chemotherapy

Sleep Disorder and Cancer

Ferri, *European J Neurology* 2007

Movement Disorders - Diagnosis

Movement Disorder	Definition	Diagnosis
Restless Legs Syndrome (RLS)	• Unpleasant, tingling, creeping feelings or nervousness in legs during inactivity and sleep with an irresistible urge to move • Improves with movement	• Clinical • When you try to relax in the evening or sleep at night, do you have unpleasant, restless feelings in your legs that can be relieved by walking or movement?
Periodic Limb Movement Disorder (PLMD)	Based on clinical history of sleep disturbance or fatigue combined with sleep study data showing excessive limb movements	• Sleep study • Significant if PLMD Index > 15/hour of sleep • Exclude movement with respiratory events

Sleep Disorder and Cancer

Ferri, *European J Neurology* 2007

Movement Disorders - Treatment

- Treat medical issue causing the problem
- Eliminate caffeine
- Dopamine agonists
  - Pramipexole and ropinirole
  - Augmentation

Sleep Disorder and Cancer

Ferri, *European J Neurology* 2007

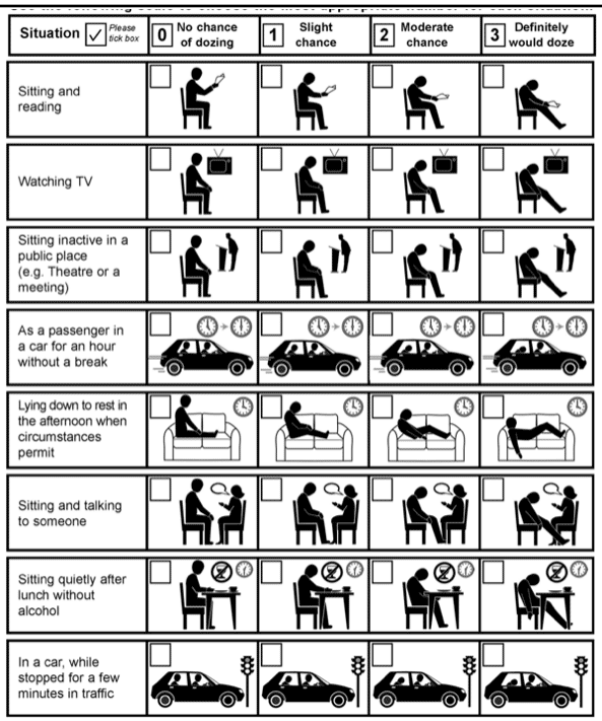
Hypersomnia: Excessive Daytime Sleepiness

- Caused by insufficient or disturbed sleep
- Affects 1/3 of sleep-deprived individuals in the U.S.
- Interferes with daytime activities

Sleep Disorder and Cancer

www.sleepfoundation.org/hypersomnia

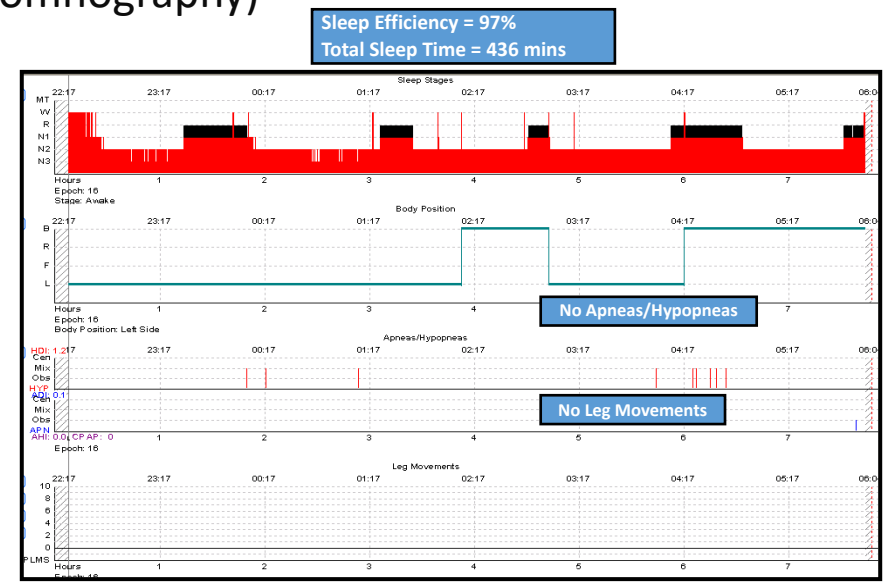
Diagnosis:
Epworth Sleepiness Scale



Situation (Please tick box)	0 No chance of dozing	1 Slight chance	2 Moderate chance	3 Definitely would doze
Sitting and reading				
Watching TV				
Sitting inactive in a public place (e.g. Theatre or a meeting)				
As a passenger in a car for an hour without a break				
Lying down to rest in the afternoon when circumstances permit				
Sitting and talking to someone				
Sitting quietly after lunch without alcohol				
In a car, while stopped for a few minutes in traffic				

Johns. *Sleep* 1991

Hypersomnia Diagnosis: Sleep Study (Polysomnography)

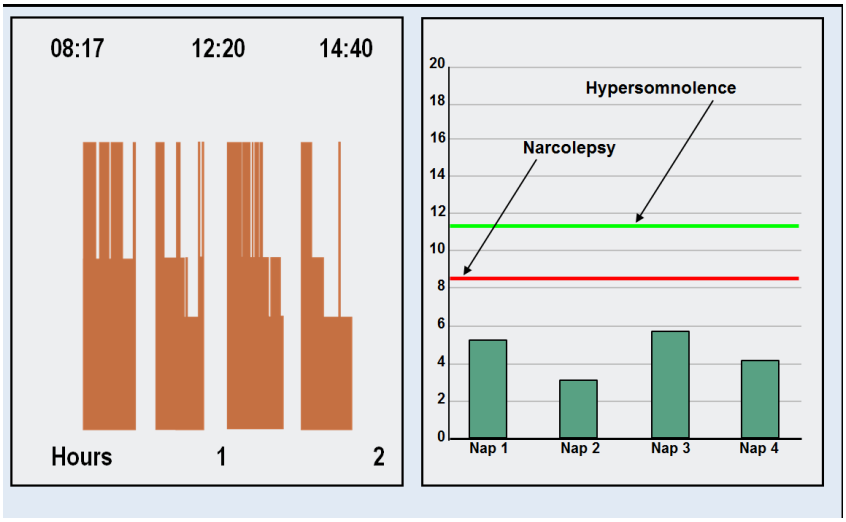


Hypersomnia Diagnosis: Multiple Sleep Latency Test (MSLT)

- Measures latency to sleep onset (how long it takes to fall asleep after lights out)
  - Provides information about daytime sleep and sleepiness
- Polysomnographic (sleep study) recording that follows an overnight sleep study
  - Darkened room, comfortable bed, quiet setting
- 4 or 5 naps (15-20 min), 2 hours apart
  - Unit of measure
    - Minutes to sleep onset (stage 1)
    - Minutes to REM sleep onset (beginning with stage 1)
- Increased sleep latency = increased alertness
- Decreased sleep latency = increased sleepiness

Carskadon et al. Sleep. 1986;9:519

Daytime sleepiness and the MSLT



Balachandran *Med Case Reports* 2017

Excessive Daytime Sleepiness: Treatment with Stimulants

Stimulant Medications

- Amphetamines
  - Methylphenidate
- Provigil (modafinil)
- Nuvigil (armodafinil)

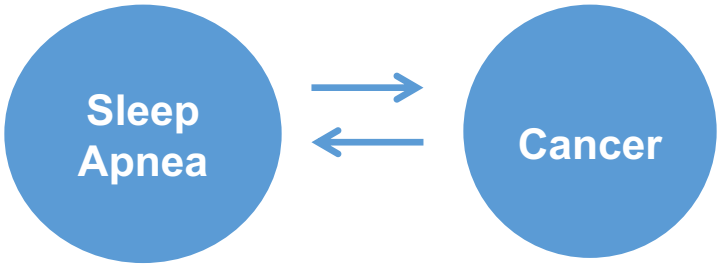
Author	Cancer related Fatigue RCTs	Intervention	Result compared with placebo
Spathis 2014	Adv. Lung Ca	Modafanil	No difference
Escalante 2014	Solid Tumors	Methylphenidate	No difference
Bruera 2013	Solid Tumors	Methylphenidate + phone intrv.	No difference
Kerr 2012	Solid Tumors	Methylphenidate	Improved fatigue scores
Moraska 2010	Solid Tumors	Methylphenidate	No difference
Jean-Pierre 2010	Solid Tumors	Modafanil	Severe fatigue improved

Excessive Daytime Sleepiness: Other Treatments

- Change medications that may be causing excessive drowsiness
- CPAP if cause is sleep apnea
- Eliminating alcohol or caffeine
- Increasing amount of sleep

Sleep Apnea (sleep disordered breathing)

Sleep Apnea and Cancer



- Patients with sleep apnea have a 5-fold increase in cancer-related mortality[1]
- Intermittent lack of oxygen (hypoxia) stimulates tumor growth[2]

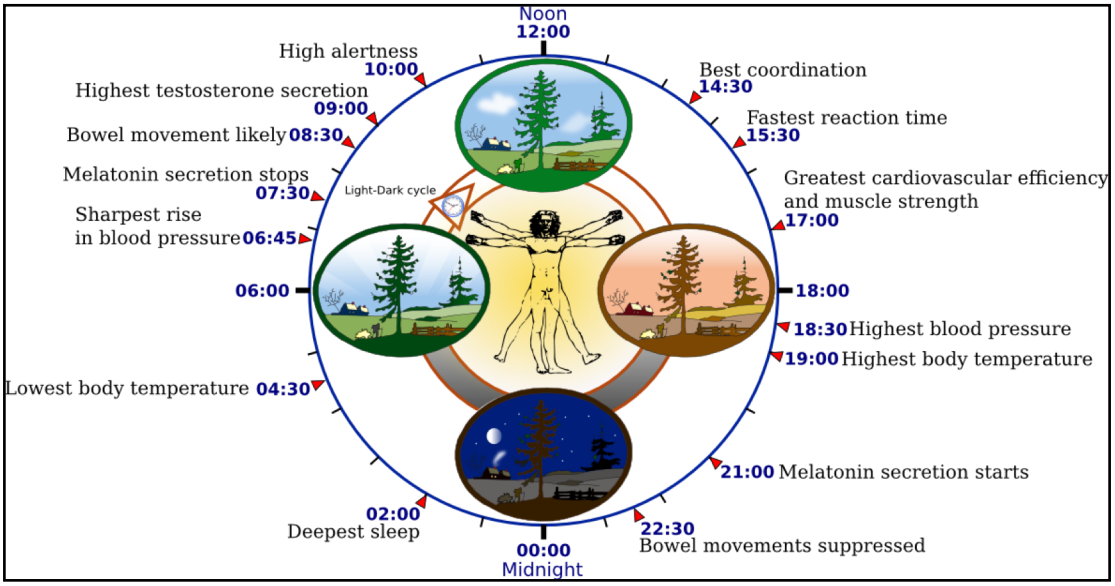
1. Nieto. AJRCCM July 2012
2. Almendros. Eu Resp Journal 2012

Obstructive Sleep Apnea (0SA) and Cancer

- Higher incidence of cancer among patients with sleep apnea who were:
  - less than 65 years old
  - male
  - did not experience daytime sleepiness
  - not obese patients
  - were not being treated for their obstructive sleep apnea

Sleep Disorders and Cancer
M Martinez-Garcia et al, *Chest* 2016

Circadian Rhythms



Circadian Gene Alterations in Human Cancers

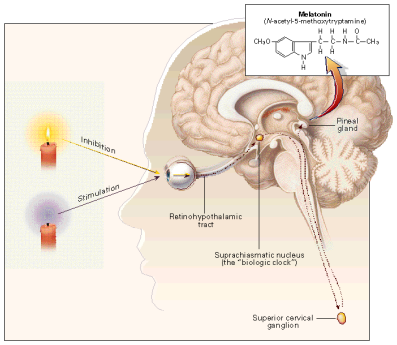
- Breast Cancer
- Stomach Cancer
- Neuroblastoma
- Acute Lymphocytic Leukemia (ALL)
- Prostate Cancer
- Ovarian Cancer
- Salivary Cancer
- Breast Cancer
- Chronic Myeloid Leukemia
- Glioma
- Pancreatic Cancer
- Endometrial Cancer
- Non-Small Cell Lung Cancer

Circadian Rhythms are disrupted while tumors form

Sleep Disorders and Cancer

Melatonin and Cancer

- Oncostatic Properties
  - In vitro studies: Melatonin reduces growth in malignant cells
  - Pinealectomy boosts tumor growth in rats
  - Anti-mitotic and antioxidant
  - Modulates cell cycle
  - Increases p53 (tumor suppressor) expression
  - Blind woman have lower rates of breast cancer



Hormone under circadian control

Schernhammer, 2009

Can Chronotherapy Improve Response to Cancer Treatment?

- Studies show some medicines provide a better response, depending on time of day given
- Chronotherapy tailors the time therapy is given to maximize its effect on human cells
- Small studies done, involving a number of different cancers, including acute lymphoblastic leukemia, have shown benefit of timing treatment to optimize effect

Cancer chronotherapy

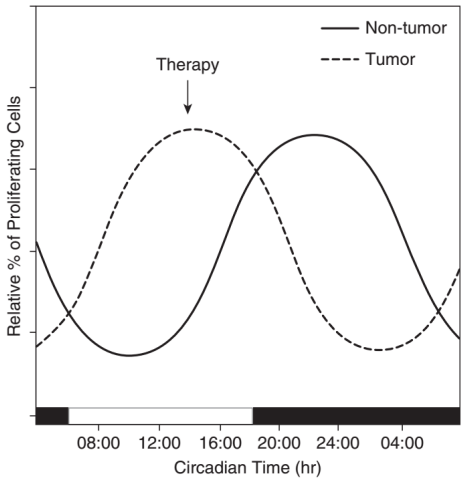
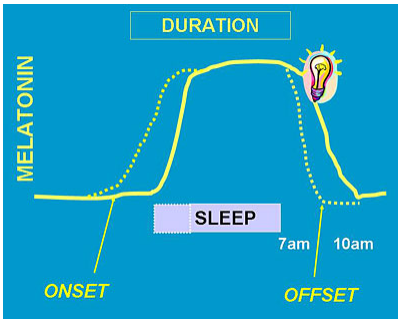
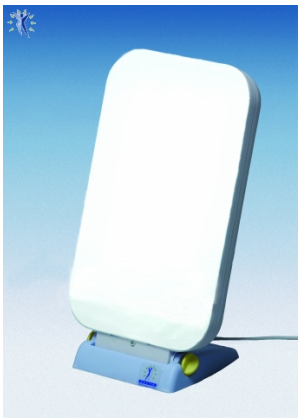


Figure 4. Concept of chronotherapy in cancer therapy. The timing of proliferation is different between tumor and nontumor cells (95). Chemotherapy with time-specific delivery (*arrow*) maximizes therapeutic potential while minimizing effect on normal cells.

K. Truong *Chest* 2016

Circadian therapy

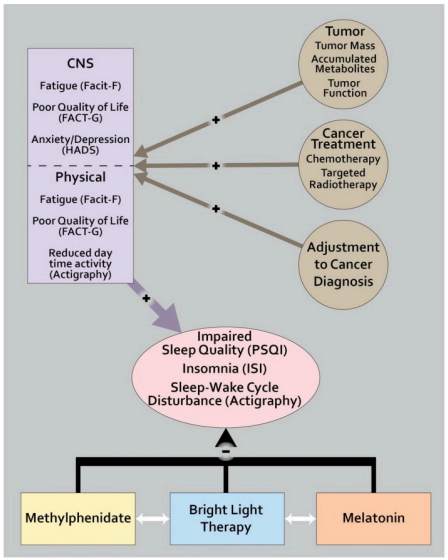




Chrono-rehabilitation

Behavioral

- Light therapy
- Interpersonal social rhythm therapy
- Scheduled meals
- Scheduled exercise
- Cognitive and behavioral therapy for insomnia



Pharmacological

- Melatonin and melatonin agonists
- Sleep aides
- Stimulants
  - methylphenidate
  - modafanil, armodafanil

S. Yennu, D. Balachandran *BJM Supp Pall Care* 2020

Table 2 Clinical algorithm for work up of sleep disorders in a cancer center (78-82)

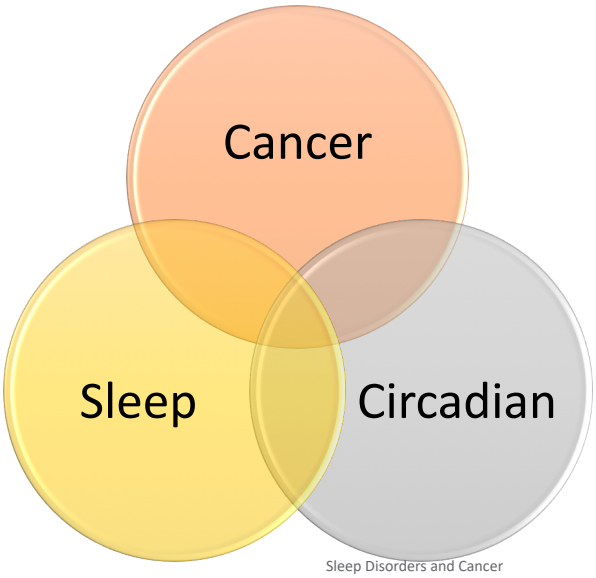
Tools to detect sleep disorders	Significance
Surveys	• **STOP-BANG.** An 8 question tool, incorporates symptoms (snoring, fatigue), medical history (hypertension), and anthropometric data (age, gender, body mass index, neck circumference). Successfully validated for the peri-operative assessment of OSA with a high sensitivity. With a maximum score of 8, total signifies the following: a score of <3 low risk for OSA; ≥3 and <5 intermediate risk for OSA; ≥5 high risk for OSA • **Epworth Sleepiness Scale.** An 8 question survey which measures daytime sleepiness. With a maximum score of 24, a score ≥ 10 represents increased daytime sleepiness. • **Pittsburgh Sleep Quality Index Questionnaire.** A survey that measures sleep quality over the last 1 month. With a maximum score of 24, a score ≥ 5 or 8 represents disturbed sleep • **Brief Fatigue Inventory.** The Brief Fatigue Inventory (BFI) is a 6-item, 10-question, uni-dimensional outcome measure used to assess the severity and impact of fatigue on daily functioning of an individual.
Physical exam	• **BMI (kg/m2).** BMI ≥ 30 kg/m2 is considered obese and correlates with severity of OSA • **Upper airway**. Evaluate oral aperture with a Mallampati I-IV (higher number is more prevalent in OSA). Identify macroglossia and enlarged tonsils. Find signs of vocal cord dysfunction including hoarseness or reports of dysphagia. • **Neck.** Neck circumference ≥41 cm correlates with risk of OSA. Also evaluate for firmness on the neck in sites of previous radiation. Inspect neck for thyromegaly and goiter. • **Chest.** Evaluate for wheezing (obstruction, tracheobronchial disease) or dullness to percussion (mass, pleural effusion, consolidation) • **Abdomen.** Look for hepatosplenomegaly, abdominal masses, ascites, or central obesity
Imaging	• **Chest.** Parenchymal infiltrates or masses, elevated diaphragms, cardiomegaly, pleural effusion • **Neurologic**. Brain mass or lesion, stroke, and brainstem abnormalities
Pulmonary studies	• Flow volume loop may reveal fixed inspiratory or expiratory processes suggesting vocal cord disease, or extrinsic or intrinsic lesions • Evaluate for obstructive or restrictive defects
Echocardiography	• Look for systolic or diastolic dysfunction, and valvular abnormalities • May also detect pulmonary hypertension and/or infiltrative disorders
Laboratory studies	• Anemia, hypothyroidism, electrolyte abnormalities • Ferritin Level <40ng/mL associated with symptoms of RLS

Clinical algorithm for evaluation of sleep disorders in cancer

Balachandran, Bashoura, Faiz. Sleep-related breathing and cancer. *Current Pulmonary Reports* 2017

Conclusions

- Sleep is essential for life
- Sleep disruption is common in cancer
- Symptoms of fatigue, insomnia and sleepiness may be related CRF or underlying sleep disorders
- Identify underlying sleep disorders and treat accordingly
- Sleep may impact tumor behavior and mortality, but further study is needed



Sleep Disorders and Cancer

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Questions?


Dave Balachandran MD

Celebrating a Second Chance at Life Survivorship Symposium 2022

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