

A Review of Sleep Disorders in Cancer Patients: Finding the “Dream” Treatment

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Roswell Park Cancer Institute
Oncology Symposium
11/11/17

Objectives

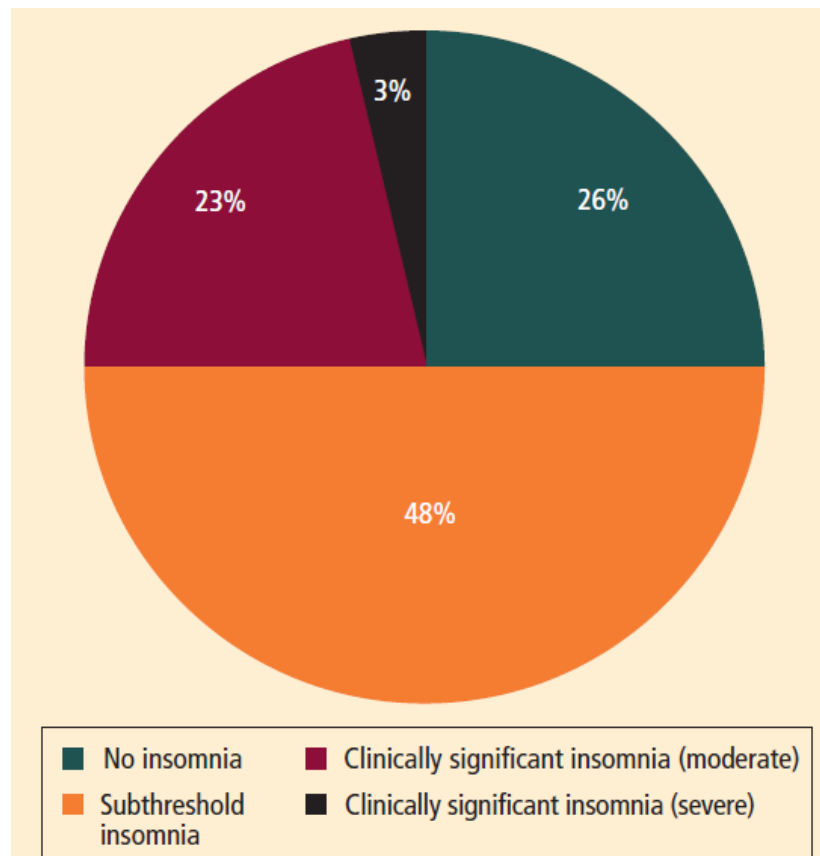
- Evaluate the issues with sleep in oncology patients
- Discuss sleep stages, architecture and neurochemistry
- Discuss positives and negatives of current treatment options
- Evaluate current guidelines as they pertain to treatment of sleep disorders

Sleep Disorders in Cancer Patients

- Sleep disturbances affect over 60% of newly diagnosed or recently treated cancer patients
- Only ~30% of patients offer information about this to their physician
- Sleep Complaints:
 - Latency (40%)
 - Length (63%)
 - Quality (72%)

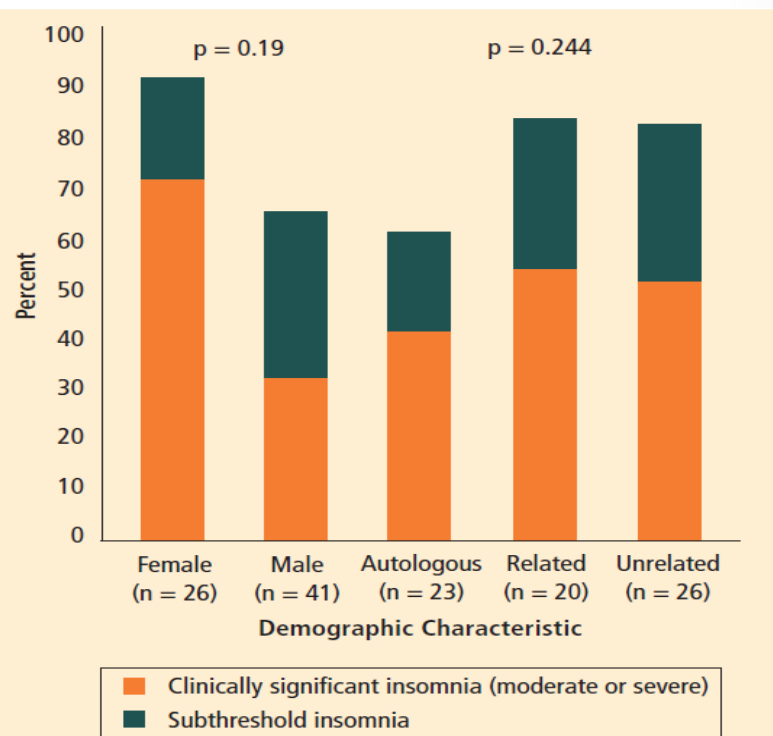


Sleep Disorders in Cancer Patients



N = 62

Figure 2. Incidence of Insomnia in Study Sample



Related—matched related donor transplantation; unrelated—matched unrelated donor transplantation

Note. Comparisons in demographics were examined using chi-square statistics.

Note. Two patients did not select their gender on the survey, so they were excluded from the demographic characteristics.

Figure 3. Frequency of Insomnia by Demographics

Sleep Disorders in Cancer Patients

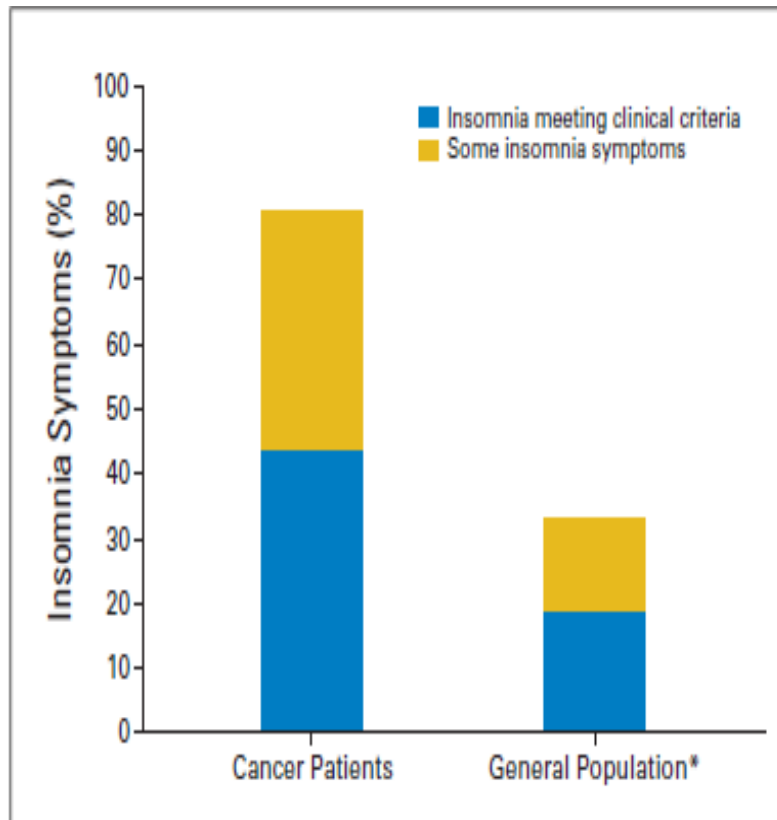


Fig 1. Insomnia symptoms in patients after first cycle of chemotherapy (N = 823) versus general population. (*) From multiple epidemiologic studies summarized in Ohayon.^{4a}

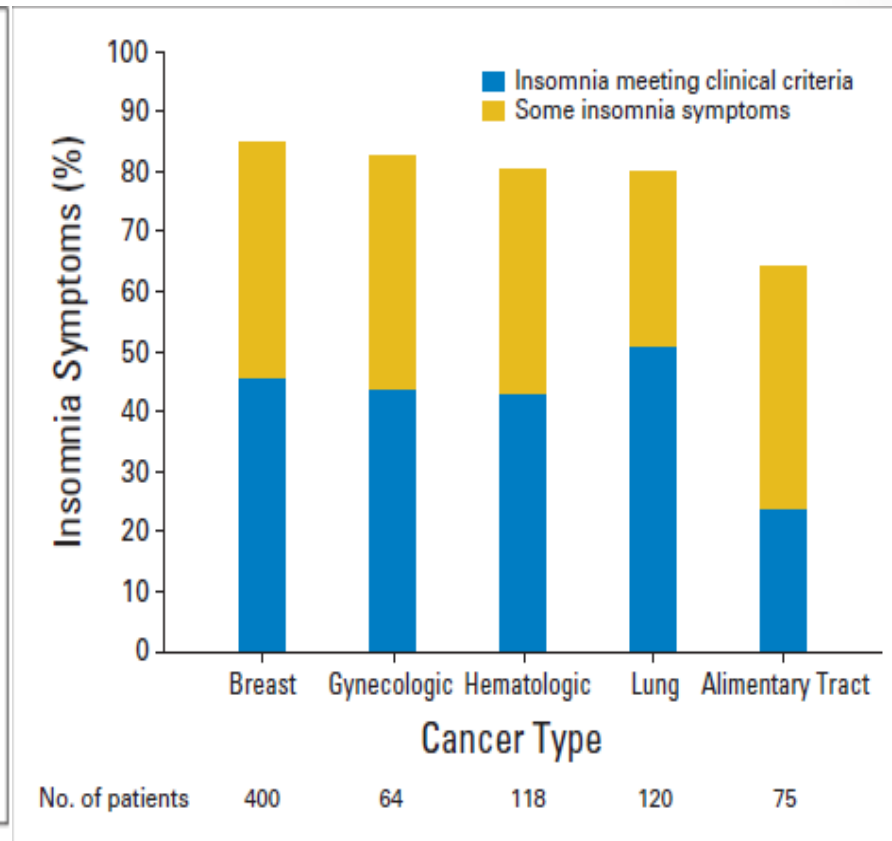


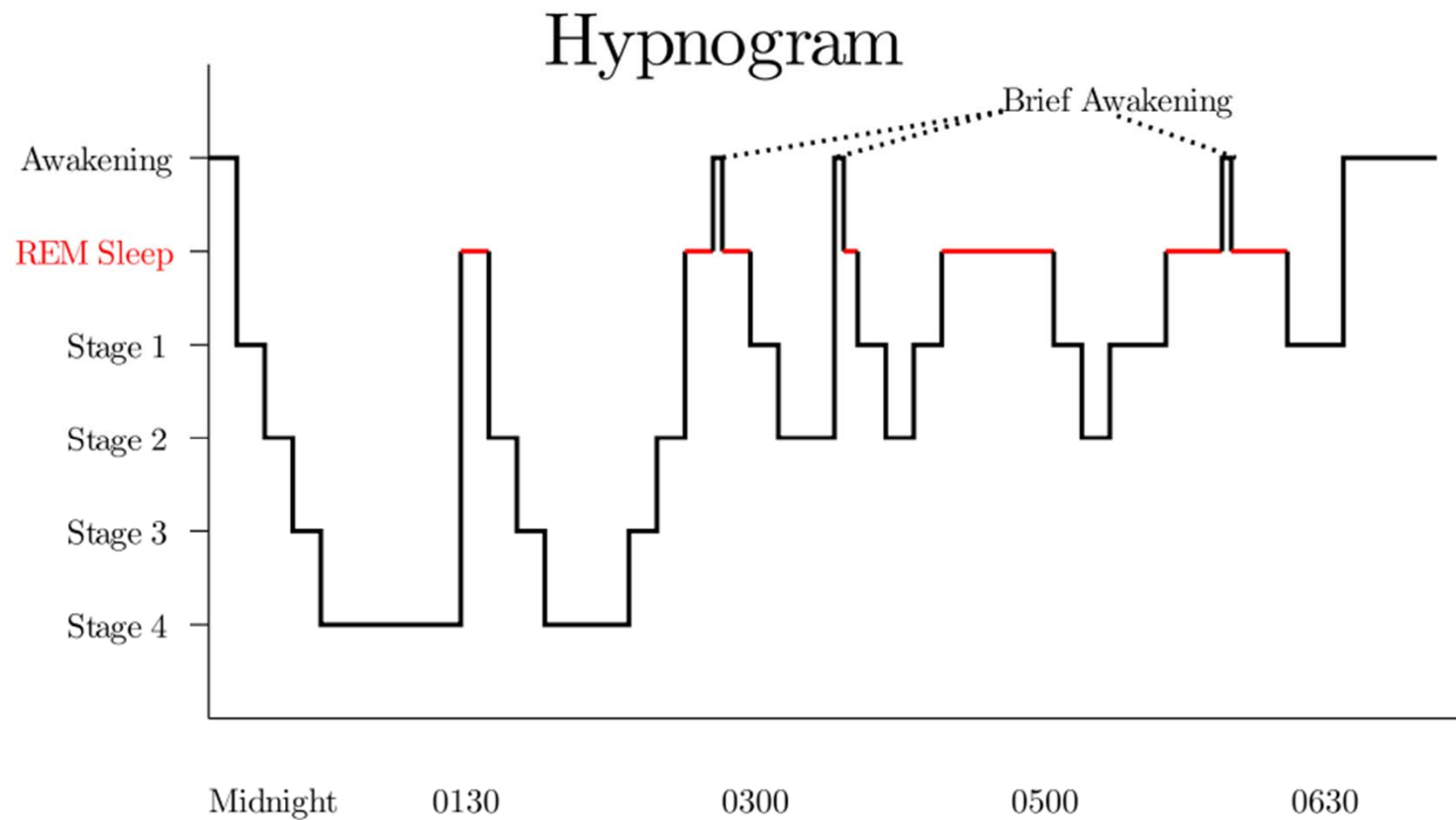
Fig 2. Prevalence of insomnia symptoms by diagnosis at cycle 1.

Three Factor Model of Sleep Disturbances in Cancer Patients

- Predisposing Factors
 - Hyperarousability
 - Gender
 - Age
- Precipitating
 - Cancer Related Treatment
 - Emotional Impact
 - Pain
- Perpetuating
 - Maladaptive Sleep Behaviors
 - Sleep Attitude



Sleep Architecture



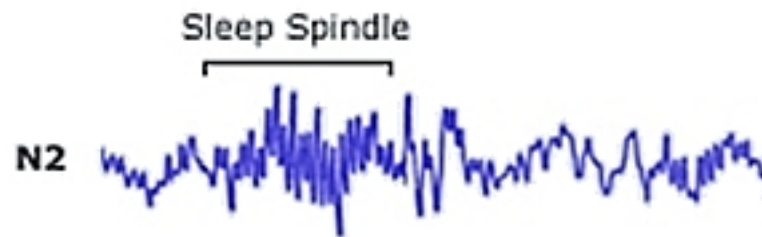
Stage 1 (NREM)

- Transitional State
 - “Twilight Phase”
- Sleep Time
 - Per Cycle: 1-7 minutes
 - Total Sleep: 2-5%
- Brain Activity
 - Low-Voltage
 - Mixed-Frequency



Stage 2 (NREM)

- Light Sleep State
 - Decreased Heart Rate/Respiration
 - Decreased Body Temperature
 - Muscle Relaxation
- Sleep Time
 - Per Cycle: 10-25 minutes
 - Total Sleep: 45-55%
- Brain Activity
 - Low-Voltage
 - Mixed-Frequency
 - Sleep Spindles and K-Complexes



Stage 3/4 (NREM)

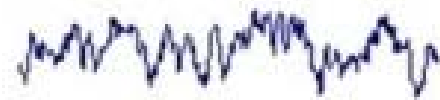
- Slow-Wave Sleep (Delta)
 - Muscle/Tissue Repair
 - Decreased Cerebral Blood Flow
 - Decreased Metabolism
- Sleep Time
 - Per Cycle: 20-40 minutes
 - Total Sleep: 15%
- Brain Activity
 - High-Voltage
 - Slow-Wave



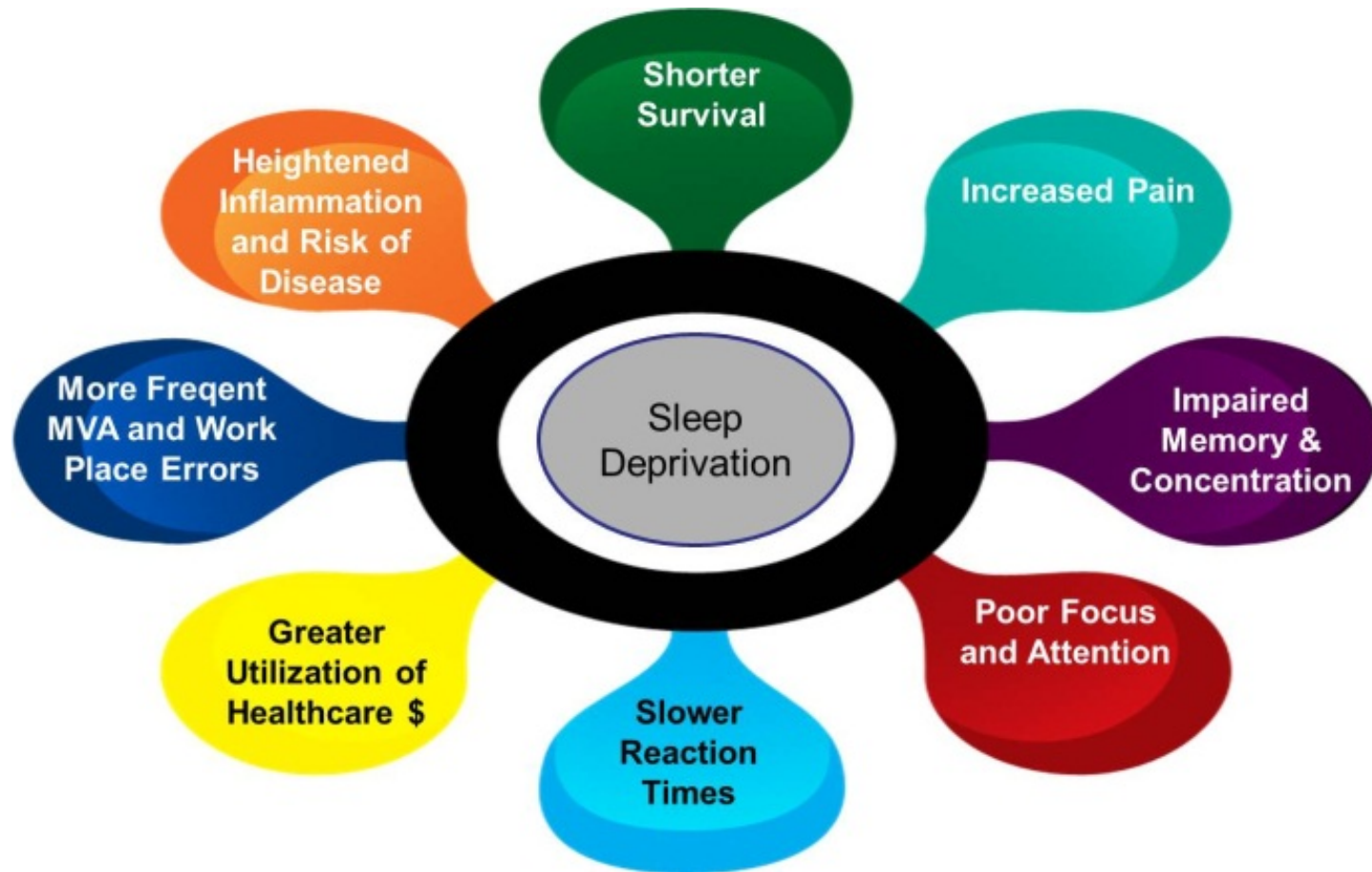
REM

- “Dream-Sleep”
 - Increased Cerebral Blood Flow
 - Increased Metabolism
 - Decreased Heart Rate/Respiration
 - Paradoxical Sleep
- Sleep Time
 - Per Cycle: 3-10 minutes
 - Total Sleep: 20-25%
- Brain Activity
 - Saw-tooth Wave Forms
 - Theta Activity

REM

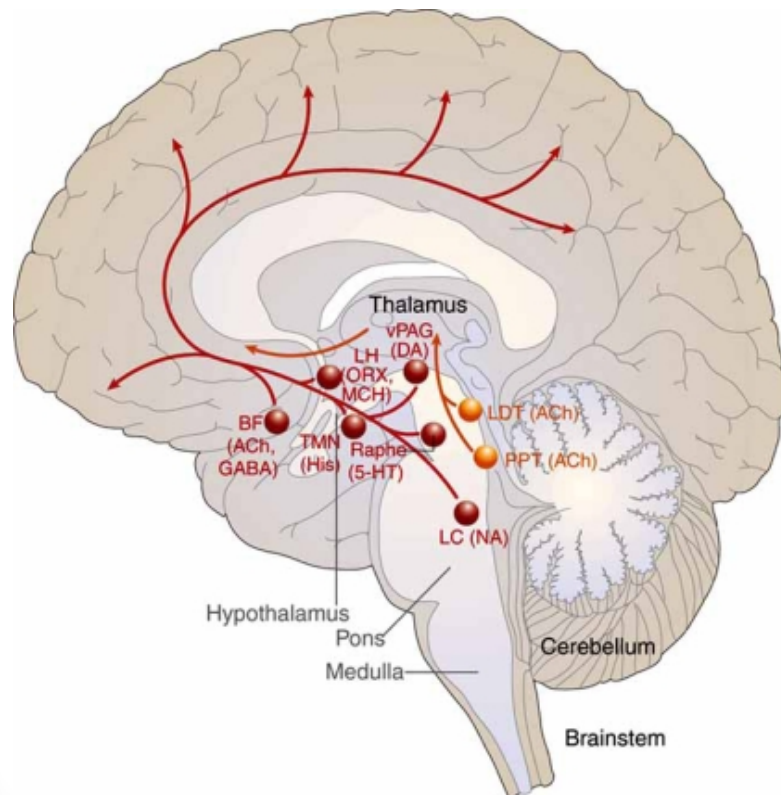


Sleep Health

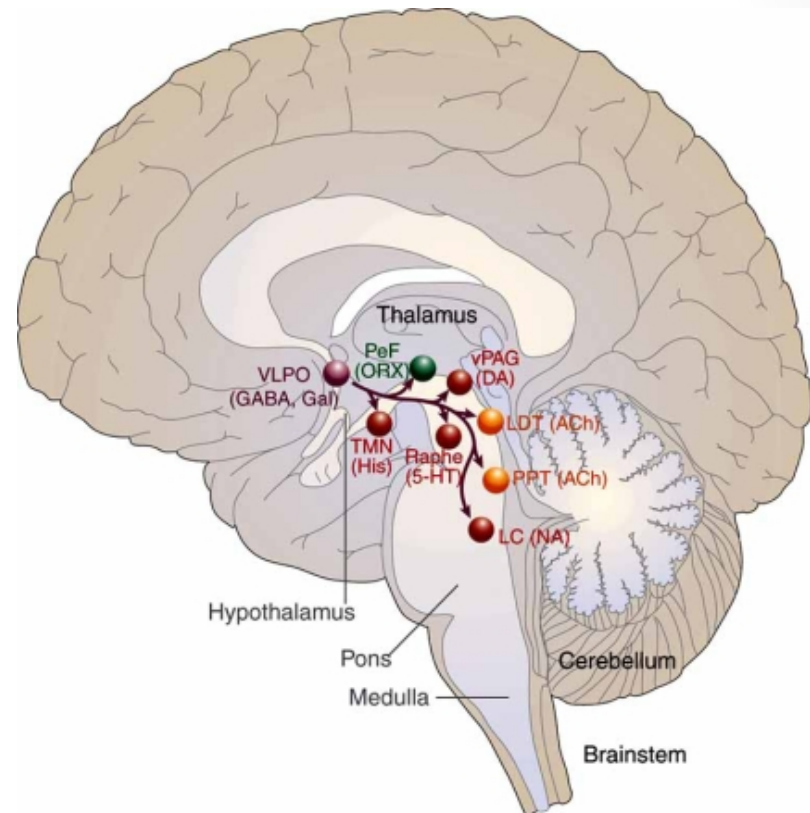


Neurotransmitters of Sleep

Wakefulness



Sedation



Neurotransmitters of Sleep

Orexin/Hypocretin



Wakefulness

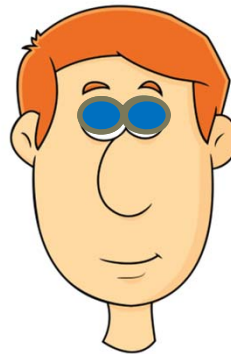
- Monoamines
 - Dopamine
 - Norepinephrine
 - Serotonin
- Acetylcholine
- Histamine



Sedation

- Adenosine
- γ -aminobutyric Acid (GABA)
- Melatonin
- Galanin

Neurotransmitters of Sleep



Adenosine
GABA
Melatonin
Galanin

Monoamines
Acetylcholine
Histamine

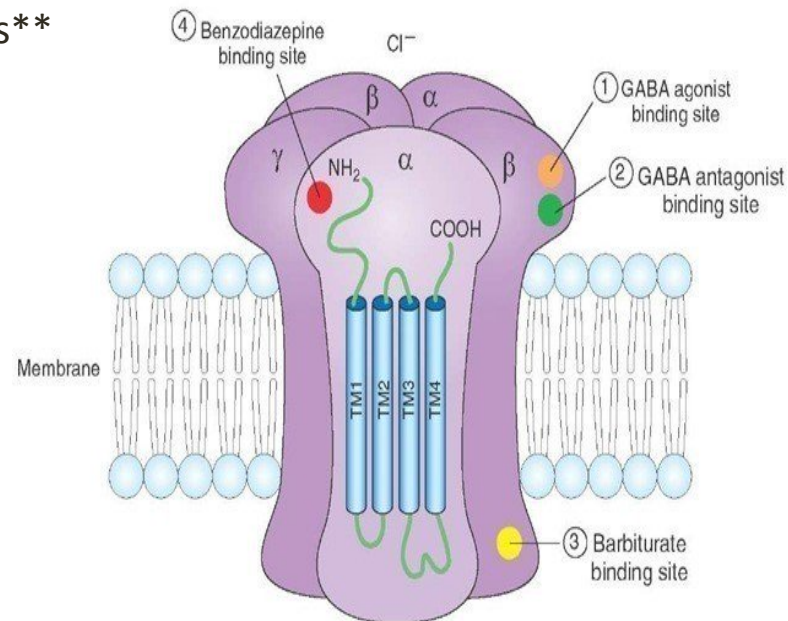
Orexin/Hypocretin

γ -aminobutyric Acid (GABA)

- Mechanism of Action
 - Inhibitory neurotransmitter of the central nervous system
 - Decreases excitability of neurons
- Role in Sleep
 - Stimulation = Sedation
 - Receptor Manipulation


GABA Agonists

- Mechanism of Action
 - Enhancement of the inhibitory effects of GABA on neuronal excitability
 - BZ₁ vs. BZ₂ Receptors
- Indication(s)
 - Short-term treatment of insomnia
 - Clinical trials= 35 days up to 6 months**
- Medication(s)
 - Benzodiazepines
 - Estazolam
 - Flurazepam
 - Triazolam
 - Temazepam
 - Z-Drugs
 - Eszopiclone**
 - Zaleplon
 - Zolpidem



GABA Agonists

- Side Effects

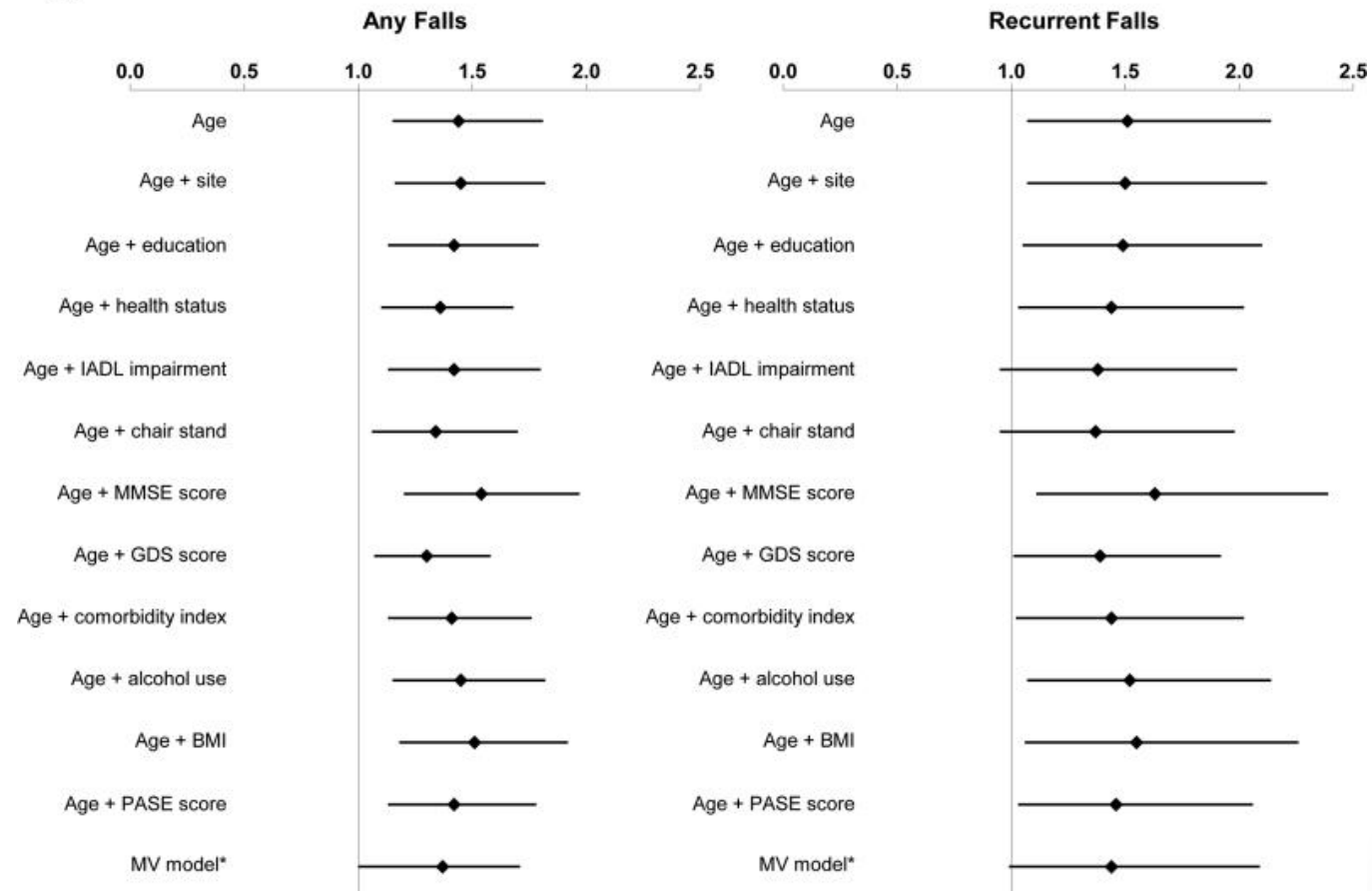
- Amnesia
 - Daytime drowsiness
 - Vertigo
 - Sleep Disturbances
 - Addiction/Abuse Potential
- 

*****FALL RISK*****






GABA Agonists

1A

Non-benzodiazepine sedative hypnotic use



GABA Agonists

Sleep Stage	Effect on Sleep Architecture
Stage 1	
Stage 2	
Stage 3	
Stage 4	
REM	

GABA Agonists

HEALTHY LIVING 01/15/2014 08:19 am ET | Updated Feb 23, 2016

The Disturbing Side Effect Of Ambien. The No. 1 Prescription Sleep Aid



01:51
The Disturbing Side Effect Of
Prescription Sleep Aid



By Allison McCabe

BAD MEDICINE More cases of adverse side effects



■ Adverse reactions to a drug do not necessarily mean it is harmful. All medicines can cause adverse reactions, but many are considered safe as the benefits outweigh the risks.

■ Some drugs are harmful as well as illegal, and more such products have been uncovered.

■ By Poon Chan Hui

When a nurse brought some black pills from her relatives earlier this year, she thought they would cure her arthritis. Instead, the pills, called Xian Ma Yu Chang Seven Leaves Ginseng, caused her to hallucinate.

Her family took her to a hospital,

■ ADVERSE DRUG REACTIONS

■ Reports received



■ Where last year's reports came from

■ Polypharmacy: 54.4%

■ Public hospitals: 39.4%

from 450 in 2000 to 24,000 last year, the Health Sciences Authority (HSA) told The Straits Times.

The spike has been particularly sharp in recent years. In 2008, 12,200 reports were filed. In 2009, the number went up to 16,000, and last year, it hit 24,000.

The reports are filed with HSA by doctors when their patients consult. More than 90 per cent of the reports are filed by doctors from polyclinics and public hospitals.

Adverse reactions to drugs vary, ranging from minor skin allergies to life-threatening heart abnormalities to hallucinations.

Such problems were the most common adverse reactions last year, including more than 8,200 reports. Mr Jonathan Tob, director of HSA's vigilance branch, said this is because they are the most visible.

The spike in reports is largely due to doctors being more aware about the harmful reactions that drugs can cause.

Technology has also made it easier for doctors to report such incidents.

In the past, doctors could only fill paper forms and mail them to HSA. Since 2004, reports can be filed through an online portal. And since 2006, public hospitals and polyclinics have also been allowed to submit reports using patients' electronic medical records.

Adverse reactions to a drug or health product do not necessarily mean it is harmful.

All medicines can cause adverse reactions, but many are considered safe as the benefits they bring outweigh the health risks.

For example, chemotherapy drugs cause undesirable side effects such as vomiting. But as the drugs can save the person's life - which is most important - than the discomfort they cause - they are still deemed for use.

Mr Tob said most of the products reported were not found to be harmful.

However, some were harmful as well as illegal, and she noted that more such products have been uncovered through the reporting system.

As of August, 15 illegal products have been detected this year, compared with

five for the whole of last year, and six in 2009.

These illegal products are usually traditional or alternative medicines that contain Western ingredients such as steroids, which are not allowed here.

Of the 15 illegal products, about 10 are not approved for sale here and were brought overseas.

In August, for example, Xian Ma Yu Chang Seven Leaves Ginseng was brought overseas.

Those were found to contain potent Western ingredients. One of them, Pao Ni Kong, had negligible, a Western anti-diabetic medication that can lead to brain damage.

In January, a Singapore General Hospital's endocrinology department revealed how the steroid-containing Xian Ma Yu Chang Seven Leaves Ginseng caused a diabetic man's blood sugar level to remain low after he had missed his lunch.

"If he had been taking normal diabetic medication, his blood sugar wouldn't have dropped so low - and if it should rebound back to normal on its own," said Dr Jonathan, who saw the patient in July.

The patient, who was dazed and confused, was later hospitalised for three days. He admitted taking Pao Ni Kong, which he had bought from Malaysia.

The hospital filed a report with HSA with a sample of the product. HSA conducted tests on it and found that it was indeed the cause of the adverse reaction in a confirmed vigilance.

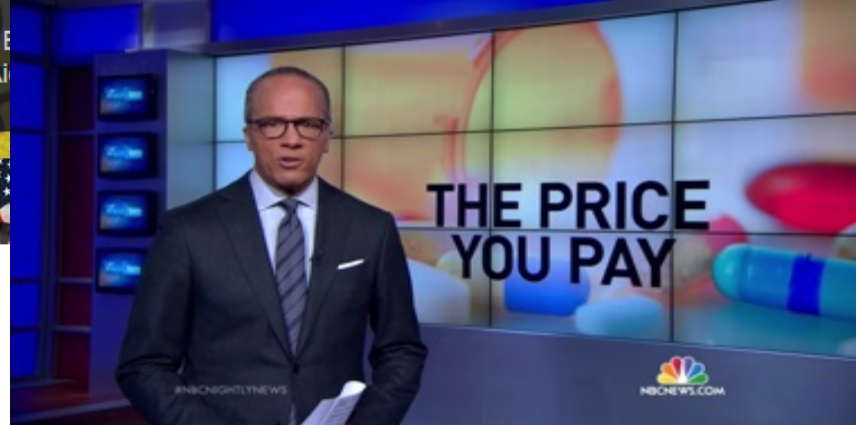
Dr Jonathan noted that the man, who is in his 50s, would have ended up in a more serious condition if he had continued taking the drug.

Mr Tob said it is important that people avoid buying drugs from sources that cannot be held accountable, such as over the Internet.

He urged patients to report adverse reactions to their doctors, even if they had bought the medicine overseas. Now gave the assurance that they will not be penalised even if the medicine was not found to be sold here.

"By informing us, you can help to protect your friends and family, who may also be taking the same product," she said.

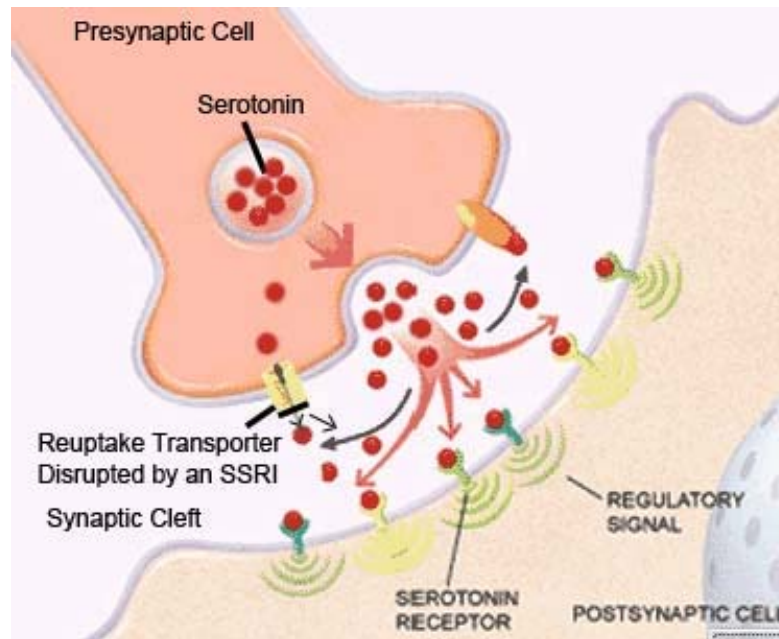
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Reference	Age, sex, and clinical state	Dose	Description of response
Harazin et al. 1999 ⁴⁴	46, male, shift work related insomnia Negative history for sleepwalking	Zolpidem 10 mg at bedtime	Within 4 days of initiation of zolpidem he would arise at night to prepare a meal and eat it. He had no memory of the events. Medication was discontinued. Unknown whether events recurred off zolpidem.
Morgenthaler, et. al. 2002 ⁴⁵	Five patients Mean age: 61.4, 3 male All 5 patients had restless legs syndrome, 3 had obstructive sleep apnea All 5 patients had a negative history for sleepwalking	Zolpidem 10-20 mg once/d	All exhibited sleepwalking and SRED 4/5 had vague memory of the events. Events ceased in all patients with zolpidem discontinuation
Sattar et al. 2003 ⁴⁶	47, male, bipolar disorder. Negative history for sleepwalking.	Citalopram 40 mg once/d, valproic acid 250 mg twice/d, Zolpidem 5 mg at bedtime	Sleepwalking started when valproic acid was added to citalopram and zolpidem. He had no memory of the events. Events ceased when valproic acid was withdrawn and returned when valproic acid was restarted.
Sharma et al. 2005 ⁴⁷	19, male, schizoaffective disorder Negative history for sleepwalking	Zolpidem 10 mg at bedtime	Within a few days of initiation of zolpidem he started to sleepwalk and talk incoherently. He had no memory of the events. Events ceased with zolpidem discontinuation.
Najjar 2007 ⁴⁸	46, female, depression, obstructive sleep apnea on continuous positive airway pressure therapy Negative history for sleepwalking or parasomnias	Zolpidem extended-release form 6.25 mg once/d	Sleepwalking and SRED began immediately after initiation of zolpidem use and ceased immediately after it was discontinued.
Chiang et al. 2008 ²⁶	Two patients: Patient 1: 75, female Patient 2: 70, female Both patients had restless legs syndrome, obstructive sleep apnea, and used continuous positive airway pressure therapy Both patients had a negative history for sleepwalking or SRED	Both patients had sleepwalking and SRED on zolpidem extended release 12.5 mg once/d. Neither patient experienced sleepwalking or SRED on the immediate release form of zolpidem.	Both patients experienced sleepwalking and SRED immediately after initiation of extended release zolpidem use and ceased immediately after it was discontinued
Sansone et al. 2008 ⁴⁹	51, female,	Zolpidem 10 mg at bedtime	Arose at night to prepare a meal and eat it. She had no memory of the events. Events stopped with cessation of zolpidem.

Serotonin

- Mechanism of Action
 - Wide family of receptors
 - 5HT₁₋₇
 - Various subtypes
 - Varying effects
 - Emotion
 - Appetite
 - Sleep
- Role in Sleep
 - Regulation of Sleep-Wake Cycle
 - Inhibitory and excitatory effects
 - NREM vs. REM
 - Melatonin production



Serotoninerbic Medications

- Mechanism of Action
 - Antagonism of 5HT_{2A/C} receptors
- Indication(s)
 - Off-Label Use
- Medication(s)
 - Doxepin
 - Dosing: 3-6 mg**
 - Mirtazapine
 - Dosing: 7.5-15 mg**
 - Trazodone
 - Dosing: 50-100 mg**
 - *Seroquel*
 - Dosing: 25-50 mg QD**

Serotoninerbic Medications

- Side Effects
 - Somnolence
 - Vertigo
 - Appetite Changes**
 - GI Disturbances
 - Suicidality
 - Serotonin Syndrome

*****FALL RISK*****

Serotonergic Medications

Table 5. Bivariate and Multivariable Association Between Antidepressant Use and Recurrent Falls Stratified by History of Falls and/or Fracture (After Age 45 Years) at Baseline.

Antidepressant Medication Use ^a	History of Falls/Fracture (n = 1092)		No History of Falls/Fracture (n = 1856)	
	Crude OR (95% CI)	Adjusted OR (95% CI) ^b	Crude OR (95% CI)	Adjusted OR (95% CI) ^b
Any use	2.02 (1.51-2.69)	1.83 (1.28-2.63)	1.83 (1.30-2.59)	0.97 (0.60-1.56)
Long duration (≥2 years)	1.61 (1.09-2.39)	1.38 (0.82-2.30)	1.84 (1.15-2.95)	1.30 (0.69-2.42)
Short duration	1.85 (1.30-2.64)	1.77 (1.17-2.68)	1.61 (1.03-2.51)	0.79 (0.42-1.48)
SDD ≥2	1.39 (0.81-2.40)	1.06 (0.57-1.97)	1.13 (0.63-2.06)	0.98 (0.48-2.01)
SDD 1-2	1.80 (1.26-2.57)	1.99 (1.31-3.01)	1.97 (1.34-2.88)	1.17 (0.71-1.93)
SDD <1	1.16 (0.41-3.31)	0.75 (0.18-3.05)	2.22 (0.99-4.93)	1.89 (0.67-5.36)
Specific class use ^c				
SSRI	2.12 (1.49-3.02)	1.92 (1.24-2.97)	2.21 (1.40-3.48)	1.11 (0.62-2.01)
TCA	1.86 (1.11-3.09)	1.47 (0.77-2.82)	1.25 (0.64-2.41)	0.86 (0.35-2.13)
Others ^d	1.90 (0.90-4.01)	2.22 (0.99-4.94)	1.65 (0.80-3.40)	0.76 (0.27-2.12)

Abbreviations: OR, odds ratio; SDD, standardized daily dose; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

^aReference group is "No Use."

^bControlling for variables forced into the model (ie, site, drugs that increase the risk of falls, self-reported depression, depressive symptoms per Center for Epidemiologic Studies Depression Scale-10, bodily pain, sleep problems, and anxiety symptoms) and those from forward selection procedures (ie, age, pulmonary disease, arthritis, urinary problems, cerebrovascular disease, diabetes, vision problems, hospitalization in previous 12 months, and private physician).

^cEach antidepressant subclass was run as a separate model and controlled for antidepressant subclass use other than the subclass being evaluated.

^dOthers: trazodone, bupropion, venlafaxine, mirtazapine, phenelzine.

Serotoninerbic Medications

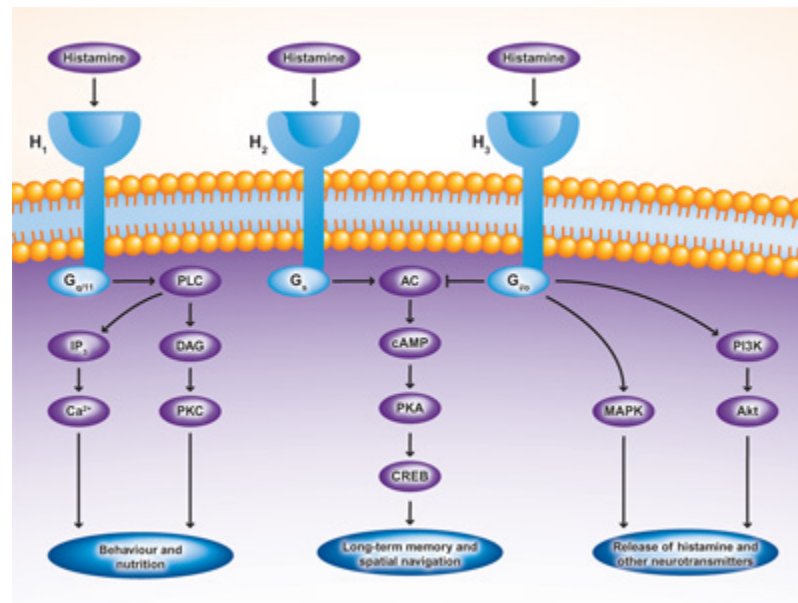
Sleep Stage	Effect on Sleep Architecture
Stage 1	↓
Stage 2	⊘
Stage 3	⊘
Stage 4	⊘
REM	↑

Histamine

- Mechanism of Action
 - Four Subtype Receptors
 - H₁: Sleep-Wake, Body Homeostasis
 - H₂: Gastric Acid Secretion
 - H₃: Histamine Regulation, Appetite
 - H₄: Immune Response
- Role in Sleep
 - Regulation of Sleep-Wake Cycle
 - Inhibitory effects of lead to sedation
 - Increase in NREM
 - Decrease REM

Anti-Histamines

- Mechanism of Action
 - Inverse agonists that stabilize the inactive conformation of H₁ receptors interfering with histamine
 - Poor receptor selectivity
- Indication(s)
 - OTC Temporary Sleep Aid
 - Off-Label Use
- Medication(s)
 - Diphenhydramine
 - Doxylamine
 - Hydroxyzine
 - *Seroquel*
 - Dosing: 25-50 mg QD**



Anti-Histamines

- Side Effects

- Anticholinergic Properties

- TSLUD

- Daytime drowsiness

- Vertigo






- Sleep Disturbances

- Dependence/Tolerance???



*****FALL RISK*****

Anti-Histamines

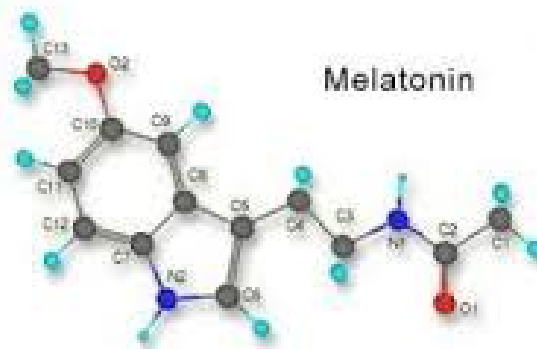
Sleep Stage	Effect on Sleep Architecture
Stage 1	
Stage 2	
Stage 3	
Stage 4	
REM	

Melatonin

- Mechanism of Action
 - Secreted from the pineal gland and is the main regulator of sleep/darkness
- Role in Sleep
 - Regulation of Circadian Rhythms
 - Sleep-Wake Syndromes

Melatonin Receptor Agonists

- Mechanism of Action
 - Selective Melatonin Type-1 and Type-2 receptor agonist
- Indication
 - Insomnia
 - Circadian Rhythm Disorders
- Medication(s)
 - Ramelteon
 - Tasimelteon
 - Melatonin**
- Side Effects
 - Dizziness
 - Somnolence



Melatonin Receptor Agonists

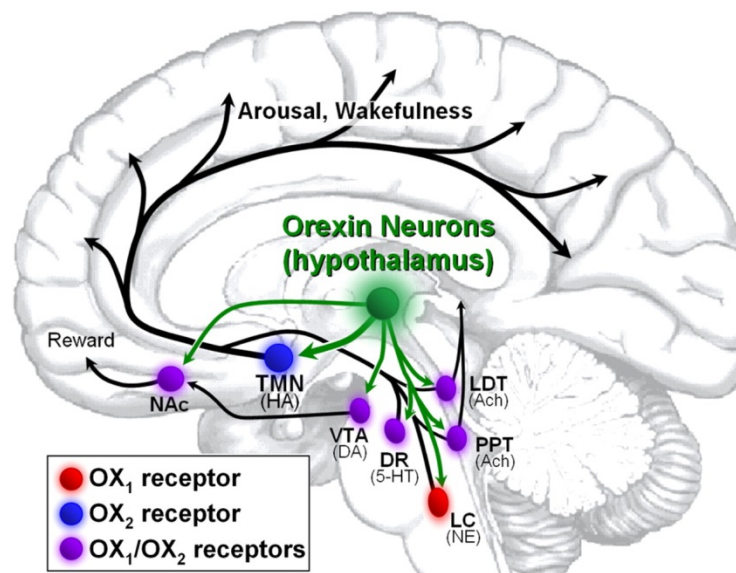
Sleep Stage	Effect on Sleep Architecture
Stage 1	↓
Stage 2	⊘
Stage 3	⊘
Stage 4	⊘
REM	↑

Hypocretin/Orexin






- Mechanism of Action
 - Peptide associated with arousal stability
- Role in Sleep
 - Conductor of neuromodulation network
 - Coordinator of sleep-wake cycles

Orexin Receptor Agonist

- Mechanism of Action
 - Selective antagonism of ORX1 and ORX2 receptors
- Indication
 - Insomnia
 - Narcolepsy
- Medication(s)
 - Suvorexant
- Side Effects
 - Somnolence



Orexin Receptor Agonist

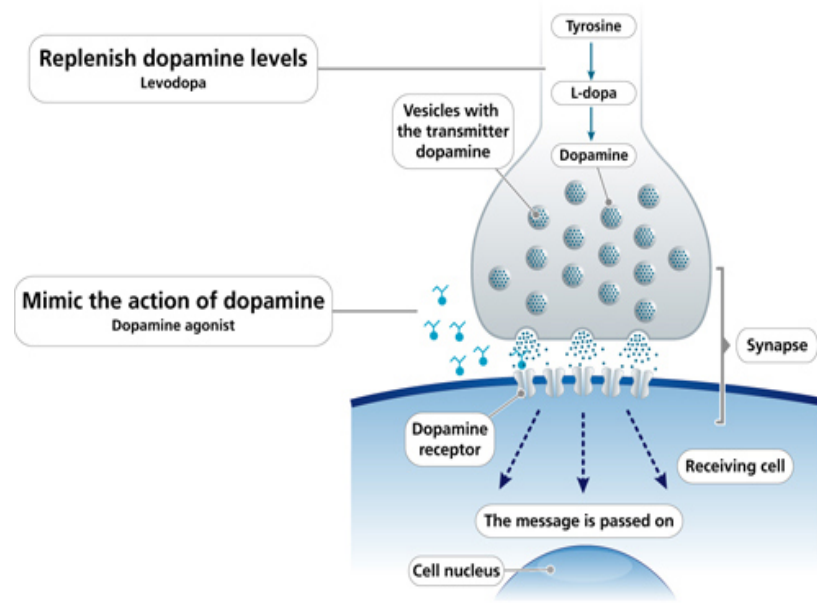
Sleep Stage	Effect on Sleep Architecture
Stage 1	
Stage 2	
Stage 3	
Stage 4	
REM	

Dopamine

- Mechanism of Action
 - Movement Control
 - Reward System
 - Sleep-wake Cycles
- Role in Sleep
 - REM modulation
 - Movement Disorders

Dopamine Agonists

- Mechanism of Action
 - Affinity for D2 receptors associated with rhythmic movement in caudate nucleus
- Indication
 - Restless Leg Syndrome
- Medications
 - Ropinrole
- Side Effects
 - Orthostatic Hypotension
 - Vertigo
 - Somnolence



Alternative Therapies

- L-Tryptophan
 - Precursor to serotonin
 - No improvement in sleep latency
- Valerian Root
 - Inhibits GABA uptake, adenosine/serotonin agonist
 - Minimal sleep latency effects
 - CYP 450, P-GP interactions
- Medicinal Marijuana
 - Mild Stimulant
 - Dose Variability
 - REM Suppression



Sleep Hygiene

GENERAL TIPS FOR HAVING HEALTHY SLEEP HYGIENE¹⁴²



Go to bed and wake up at the same time every day (even on the weekends!)



Don't go to bed feeling hungry, but also don't eat a heavy meal right before bed



Avoid caffeine consumption (e.g., coffee, soft drinks, chocolate) starting in the late afternoon



Develop a relaxing routine before bedtime – ideas include bathing, music, and reading



Expose yourself to bright light in the morning – sunlight helps the biological clock to reset itself each day



Reserve your bedroom for sleeping only – keep cell phones, computers, televisions and video games out of your bedroom



Make sure your bedroom is conducive to sleep – it should be dark, quiet, comfortable, and cool



Exercise regularly during the day



Sleep on a comfortable mattress and pillow



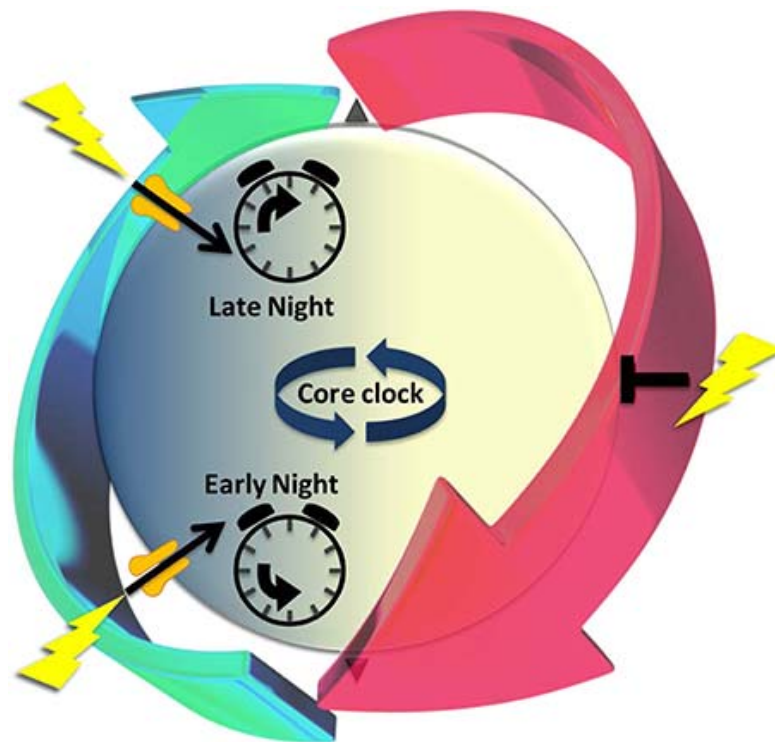
Don't have pets in your bedroom

Sleep Disorders (DSM-V Categories)

- Sleep-Wake Disorders
 - Disrupted sleep
 - Altered daytime function
- Circadian Rhythm Disorders
 - Altered internal clock
- Parasomnias
 - Abnormal movements/behaviors

Circadian Rhythm Disorders

- Non 24-hour Disorder
- Shift Worker Disorders
 - Jet-Lag
 - Overnight Schedules
- Sleep Phase Disorders
 - Advanced
 - Delayed



Parasomnias

- Chemical Induced Disorders
- NREM/REM Sleep Arousal Disorders
 - Sleepwalking
 - Sleep Terror
 - Sleep Paralysis
- Restless Leg Syndrome
- Unspecified Sleep Disorders



Sleep-Wake Disorders

- Hypersomnolence Disorders
 - Idiopathic
- Insomnia
 - Transient
 - Acute
 - Chronic
- Narcolepsy
 - Orexin Deficiency
 - Secondary to another medical condition
- Sleep-Related Breathing Disorders
 - Obstructive Sleep Apnea



American Academy of Sleep Medicine Guidelines: Circadian Rhythm Sleep-Wake Disorders

Table 5—Overview of AASM recommendation status for Intrinsic CRSWD treatments

Treatment	ASWPD	DSWPD	N24SWD	ISWRD
Prescribed sleep-wake scheduling	No Recommendation	No Recommendation	No Recommendation	No Recommendation
Timed physical activity/exercise	No Recommendation	No Recommendation	No Recommendation	No Recommendation
Strategic avoidance of light	No Recommendation	No Recommendation	No Recommendation	No Recommendation
Light therapy	5.1.4a WEAK FOR (adults)	No Recommendation	No Recommendation	5.4.4a WEAK FOR (elderly with dementia)
Sleep-promoting medications	No Recommendation	No Recommendation	No Recommendation	5.4.5a STRONG AGAINST (elderly with dementia)
Timed oral administration of melatonin or agonists	No Recommendation	5.2.6.1a WEAK FOR (adults with and without depression) 5.2.6.2.1a WEAK FOR (children/adolescents without comorbidities) 5.2.6.2.2a WEAK FOR (children/adolescents with psychiatric comorbidities)	5.3.6.1a WEAK FOR (blind adults) No Recommendation (sighted)	5.4.6.1a WEAK AGAINST (elderly with dementia) 5.4.6.2a WEAK FOR (children/adolescents with neurologic disorders)
Wakefulness-promoting medications	No Recommendation	No Recommendation	No Recommendation	No Recommendation
Other somatic interventions	No Recommendation	No Recommendation	No Recommendation	No Recommendation
Combination treatments	No Recommendation	No Recommendation (adults) 5.2.9.2a WEAK FOR (light therapy + multicomponent behavioral interventions for children/adolescents)	No Recommendation	5.4.9.1a WEAK AGAINST (combination treatment of light and melatonin for demented, elderly patients)

American Academy of Sleep Medicine Guidelines: Circadian Rhythm Sleep-Wake Disorders

Figure 2—Meta-analysis of data for PSG determined TST in response to melatonin treatment of adult patients with DSWPD and comorbid depression.

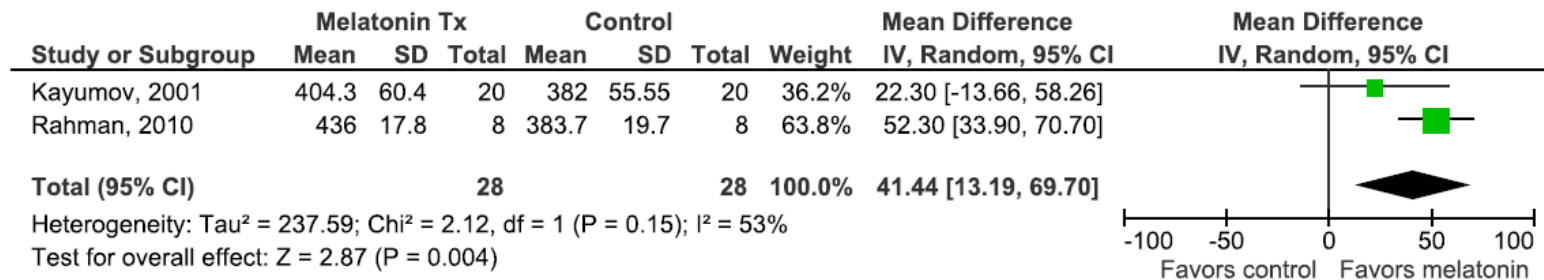
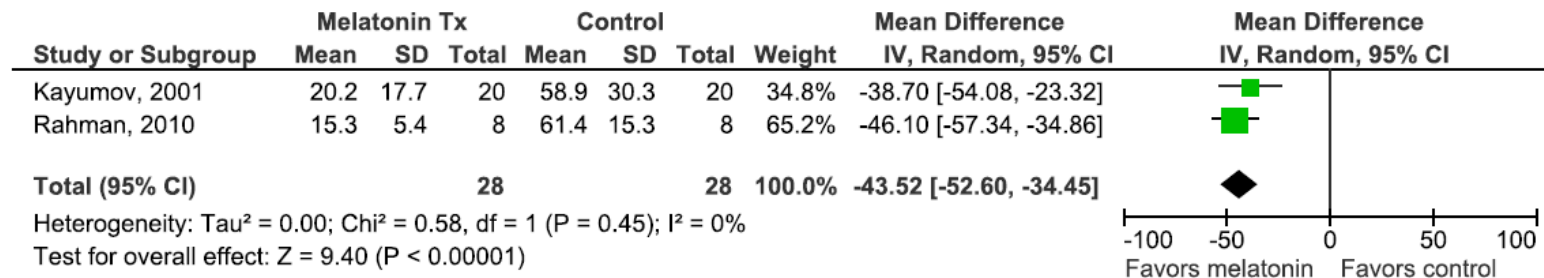
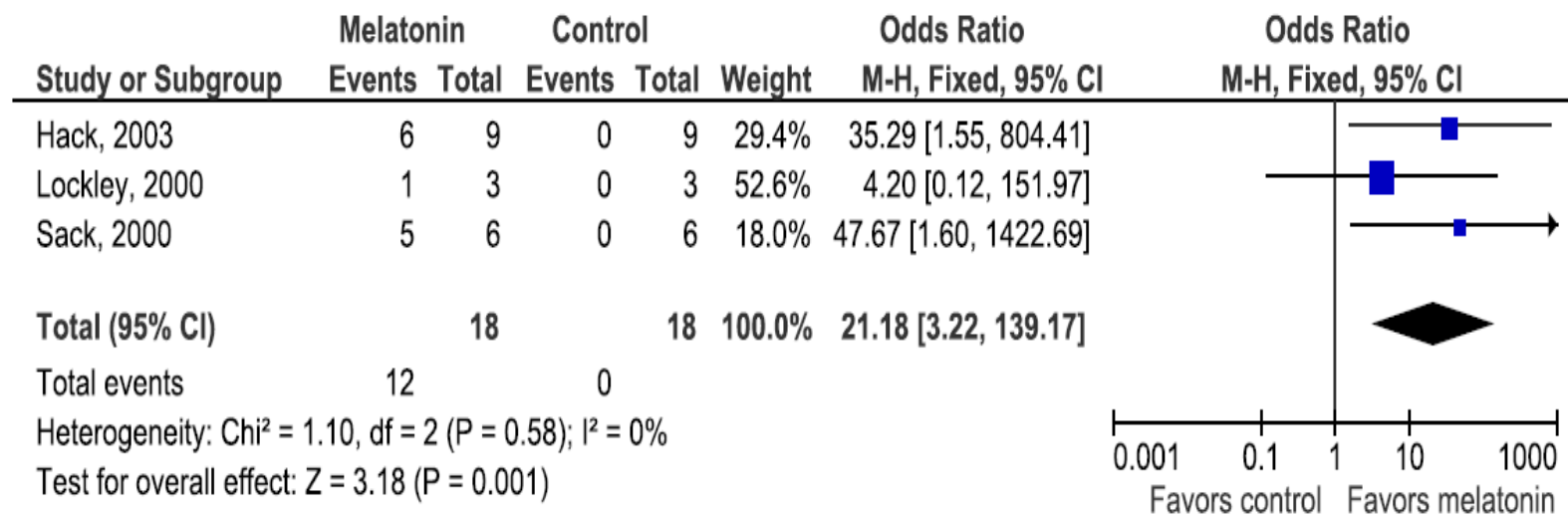


Figure 3—Meta-analysis of data for PSG determined ISL in response to melatonin treatment of adult patients with DSWPD and comorbid depression.



American Academy of Sleep Medicine Guidelines: Circadian Rhythm Sleep-Wake Disorders

Figure 6—Meta-analysis of evidence for entrainment as a result of melatonin treatment of blind adult patients with N24SWD.



Insomnia (DSM-V Criteria)

- Dissatisfaction with sleep quantity or quality associated with ≥ 1 of the following:
 - Sleep Initiation
 - Sleep Latency
 - Sleep Maintenance
- Clinically Significant
 - Distress
 - Impairment in daily function
 - Behavioral changes

Insomnia Variability

- Transient
 - Symptoms for ≤ 1 week
- Acute
 - Symptoms for >1 week up to 3 months*
- Chronic
 - Symptoms for ≥ 3 months*

**Disturbances occurring ≥ 3 nights per week*

American Academy of Sleep Medicine Guidelines: Chronic Insomnia in Adults

Recommended for Treating Sleep Onset Insomnia	
Eszopiclone	Sleep latency: Mean reduction was 14 min greater, compared to placebo (95% CI: 3 to 24 min reduction); Quality of sleep*: Moderate-to-Large ^a improvement in quality of sleep, compared to placebo; Side effects: See Recommendation 2, "Harms" <i>This recommendation is based on trials of 2 mg and 3 mg doses of eszopiclone.</i>
Ramelteon	Sleep latency: Mean reduction was 9 min greater, compared to placebo (95% CI: 6 to 12 min reduction); Quality of sleep*: No improvement ^b in quality of sleep, compared to placebo; Side effects: See Recommendation 7, "Harms" <i>This recommendation is based on trials of 8 mg doses of ramelteon.</i>
Temazepam	Sleep latency: Mean reduction was 37 min greater, compared to placebo (95% CI: 21 to 53 min reduction); Quality of sleep*: Small ^a improvement in quality of sleep, compared to placebo; Side effects: See Recommendation 6, "Harms" <i>This recommendation is based on trials of 15 mg doses of temazepam.</i>
Triazolam	Sleep latency*: Mean reduction was 9 min greater, compared to placebo (95% CI: 4 to 22 min reduction); Quality of sleep*: Moderate ^c improvement in quality of sleep, compared to placebo; Side effects: See Recommendation 5, "Harms" <i>This recommendation is based on trials of 0.25 mg doses of triazolam.</i>
Zaleplon	Sleep latency: Mean reduction was 10 min greater, compared to placebo (95% CI: 0 to 19 min reduction); Quality of sleep*: No improvement ^b in quality of sleep, compared to placebo; Side effects: See Recommendation 3, "Harms" <i>This recommendation is based on trials of 5 mg and 10 mg doses of zaleplon.</i>
Zolpidem	Sleep latency: Mean reduction was 5–12 min greater, compared to placebo (95% CI: 0 to 19 min reduction); Quality of sleep*: Moderate ^a improvement in quality of sleep, compared to placebo; Side effects: See Recommendation 4, "Harms" <i>This recommendation is based on trials of 10 mg doses of zolpidem.</i>

American Academy of Sleep Medicine Guidelines: Chronic Insomnia in Adults

Recommended for Treating Sleep Maintenance Insomnia	
Doxepin	<p>Total sleep time: Mean improvement was 26–32 min longer, compared to placebo (95% CI: 18 to 40 min improvement); Wake after sleep onset: Mean reduction was 22–23 min greater, compared to placebo (95% CI: 14 to 30 min reduction); Quality of sleep*: Small-to-moderate^a improvement in quality of sleep, compared to placebo; Side effects: See Recommendation 8, "Harms"</p> <p><i>This recommendation is based on trials of 3 mg and 6 mg doses of doxepin.</i></p>
Eszopiclone	<p>Total sleep time: Mean improvement was 28–57 min longer, compared to placebo (95% CI: 18 to 76 min improvement); Wake after sleep onset: Mean reduction was 10–14 min greater, compared to placebo (95% CI: 2 to 18 min reduction); Quality of sleep*: Moderate-to-Large^a improvement in quality of sleep, compared to placebo; Side effects: See Recommendation 2, "Harms"</p> <p><i>This recommendation is based on trials of 2 mg and 3 mg doses of eszopiclone.</i></p>
Temazepam	<p>Total sleep time: Mean improvement was 99 min longer, compared to placebo (95% CI: 63 to 135 min improvement); Wake after sleep onset: Not reported; Quality of sleep*: Small^a improvement in quality of sleep, compared to placebo; Side effects: See Recommendation 6, "Harms"</p> <p><i>This recommendation is based on trials of 15 mg doses of temazepam.</i></p>
Suvorexant	<p>Total sleep time: Mean improvement was 10 min longer, compared to placebo (95% CI: 2 to 19 min improvement); Wake after sleep onset: Mean reduction was 16–28 min greater, compared to placebo (95% CI: 7 to 43 min reduction); Quality of sleep*: Not reported; Side effects: See Recommendation 1, "Harms"</p> <p><i>This recommendation is based on trials of 10, 15/20, and 20 mg doses of suvorexant.</i></p>
Zolpidem	<p>Total sleep time: Mean improvement was 29 min. longer, compared to placebo (95% CI: 11 to 47 min. improvement); Wake after sleep onset: Mean reduction was 25 min greater, compared to placebo (95% CI: 18 to 33 min reduction); Quality of sleep*: Moderate^a improvement in quality of sleep, compared to placebo; Side effects: See Recommendation 4, "Harms"</p> <p><i>This recommendation is based on trials of 10 mg doses of zolpidem.</i></p>

American Academy of Sleep Medicine Guidelines: Chronic Insomnia in Adults

- Strength of Recommendations: WEAK
 - Head to Head Studies
- Limited information on adverse effects
 - Limited evaluation
- Co-morbid conditions not evaluated
 - Anxiety/Depression
 - Psychosis
- American Geriatric Society BEER's Criteria
 - Recommendation to avoid use
 - First-Generation Antihistamines
 - Anti-Psychotics
 - Benzodiazepines
 - Recommendation to caution and avoid chronic use
 - Z-Drugs

Clinical Analysis: Efficacy

Medication Class	Sleep Latency (Avg. Decrease in Minutes)
Benzodiazepines	9-37
Z-Drugs	5-14
Anti-depressants	8-10
Orexin Agonists	2-10
Anti-psychotics	9
Melatonin	9
Melatonin Agonists	9
Anti-histamines	8

Clinical Analysis: Efficacy

Medication Class	Total Sleep Time (Avg. Increase in Minutes)
Benzodiazepines	99
Z-Drugs	29-57
Anti-depressants	26-32
Anti-psychotics	24
Melatonin	13
Anti-histamines	12
Melatonin Agonists	2-12
Orexin Agonists	10

Clinical Analysis: Sleep Quality

Medication Class	Quality of Sleep	Sleep Architecture
Anti-depressants	+	+
Melatonin	+	+
Melatonin Agonists	+	+
Anti-psychotics	+	+
Benzodiazepines	+	-
Z-Drugs	+	-
Orexin Agonists	N/A	+
Anti-histamines	N/A	-

Clinical Analysis: Safety

Medication Class	Addiction/ Abuse Potential	Beer's Criteria	Daytime Sedation	Fall Risk
Melatonin	-	-	-	-
Melatonin Agonists	-	-	-	-
Orexin Agonists	+	-	-	--
Anti-depressants	-	-	+	+
Anti-psychotics	-	+	+	+
Anti-histamines	+/-	+	+	+
Benzodiazepines	+	+	+	+
Z-Drugs	+	+	+	+

Discussion

- Evaluate your patient
 - Circadian Rhythm vs. Insomnia
 - Transient vs. Chronic
 - Risk Factors
- Concerns of current guidelines
 - Elderly Patients
 - Length of treatment
- Understand your treatment options
 - Safety vs. Efficacy

A Review of Sleep Disorders in Cancer Patients: Finding the “Dream” Treatment

Jordan Pleskow, PharmD
Roswell Park Cancer Institute
Oncology Symposium
11/11/17