



**UW PACC**

Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

# USING MELATONIN FOR SLEEP PROBLEMS

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# GENERAL DISCLOSURES

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# SPEAKER DISCLOSURES

- ✓ I have no conflicts of interest or disclosures.

# PLANNER DISCLOSURES

The following series planners have no relevant conflicts of interest to disclose:

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# OBJECTIVES

1. Understand the role of the intrinsic hormone melatonin in our physiology
2. Learn about the appropriate uses of extrinsic melatonin for sleep problems
3. Discuss the limitations of using melatonin as a therapeutic sleep aid

# UW PACC REGISTRATION

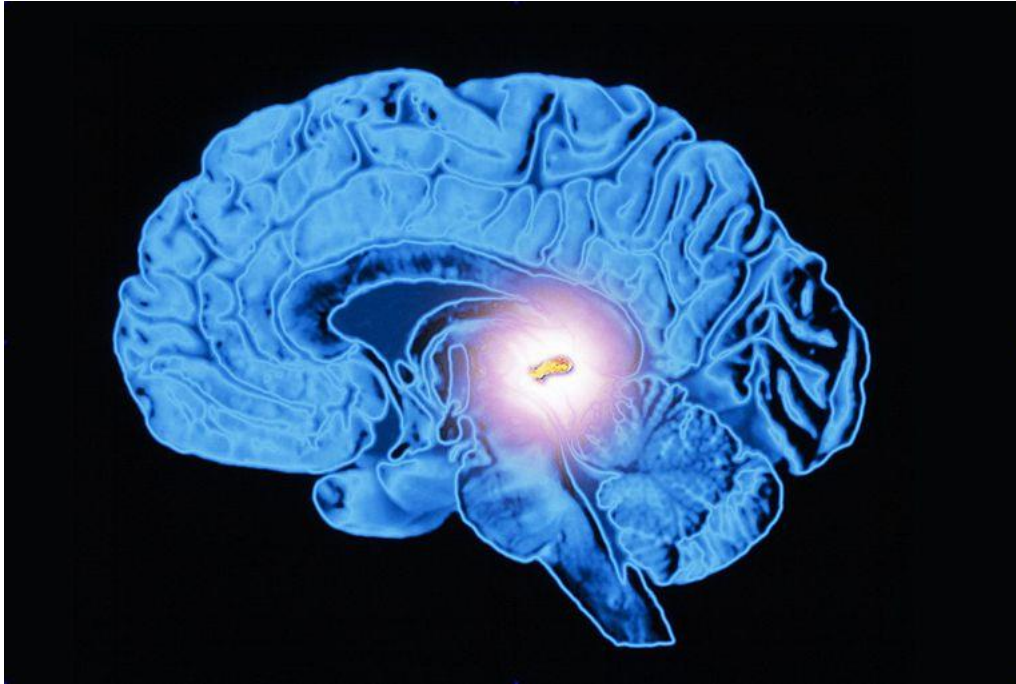
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# CASE EXAMPLE

- A 22-year-old young man comes to your clinic with a chief complaint of difficulty getting to sleep at night.
- As far back as high school, he has noticed he cannot get to sleep at a “normal” time of night. He goes to bed around 10pm and usually can’t fall asleep until after 2am. When he has to wake up in the morning before 10am, he needs two alarms. He is tired until evening, when he finally feels fully awake.
- When he can’t sleep, he uses his phone or plays video games. He has no medical problems and does not take any medications.
- He is wondering if there is a medication he can take to get to sleep at night.

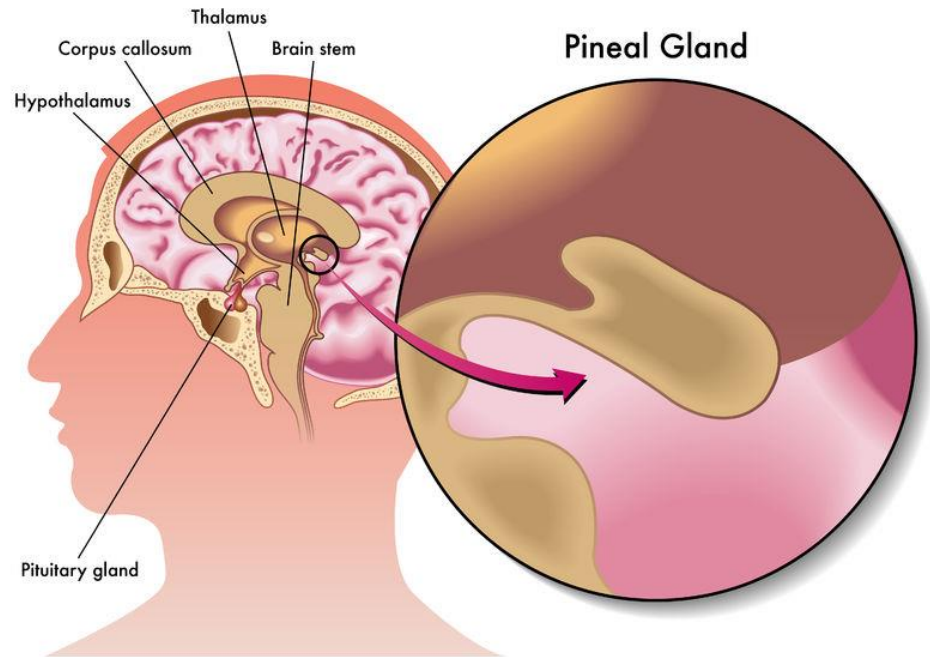




# WHAT IS MELATONIN?

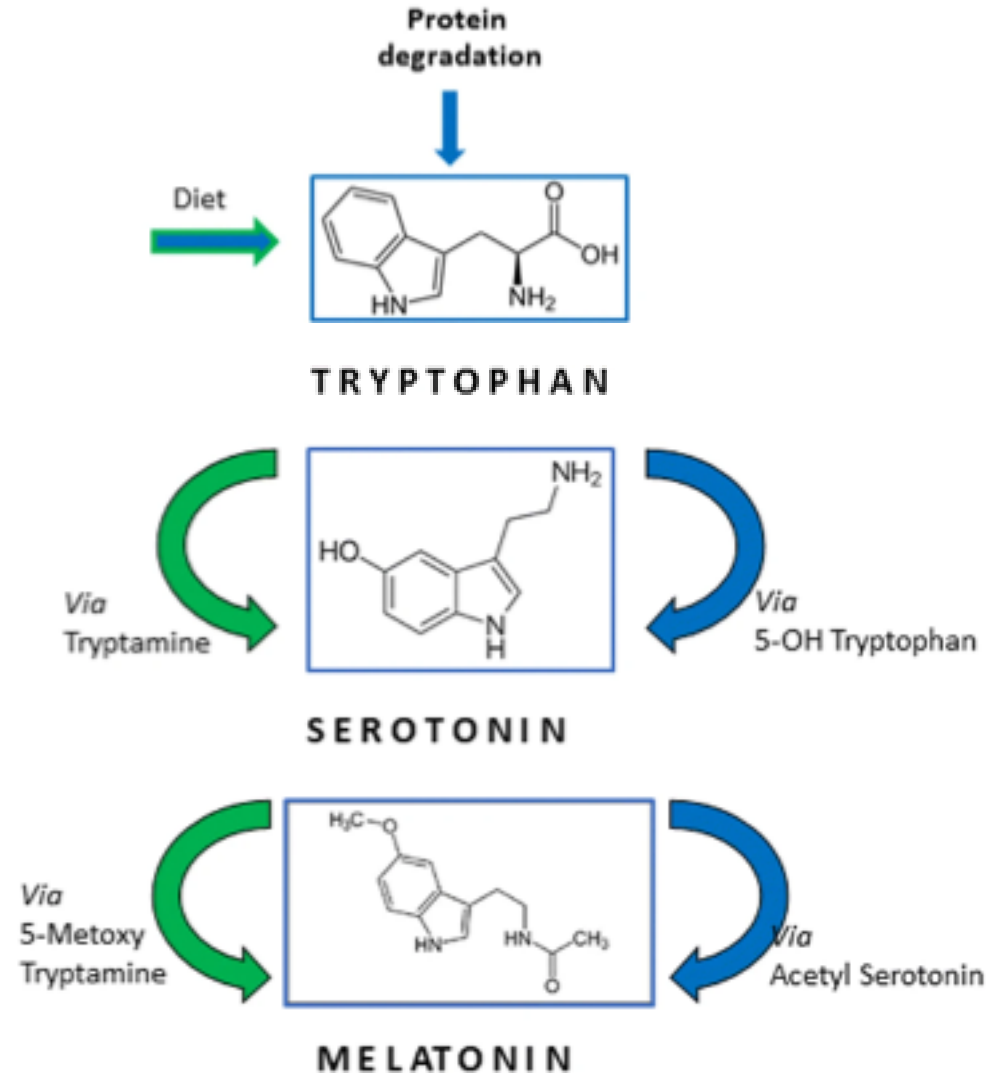
# ENDOGENOUS MELATONIN

- Melatonin is a hormone that is synthesized and released by the pineal gland into the CSF and blood circulation at night
- Discovered in 1958 in animals, but not demonstrated to have a circadian pattern until the mid-70s
- Now known to be present in almost all life forms: animals, plants, bacteria, fungi, algae



# HOW IS IT MADE?

- In humans, melatonin is synthesized from serotonin
- It binds as a full agonist to G-protein-coupled MT1 and MT2 receptors throughout the body
- Involved in numerous physiologic processes

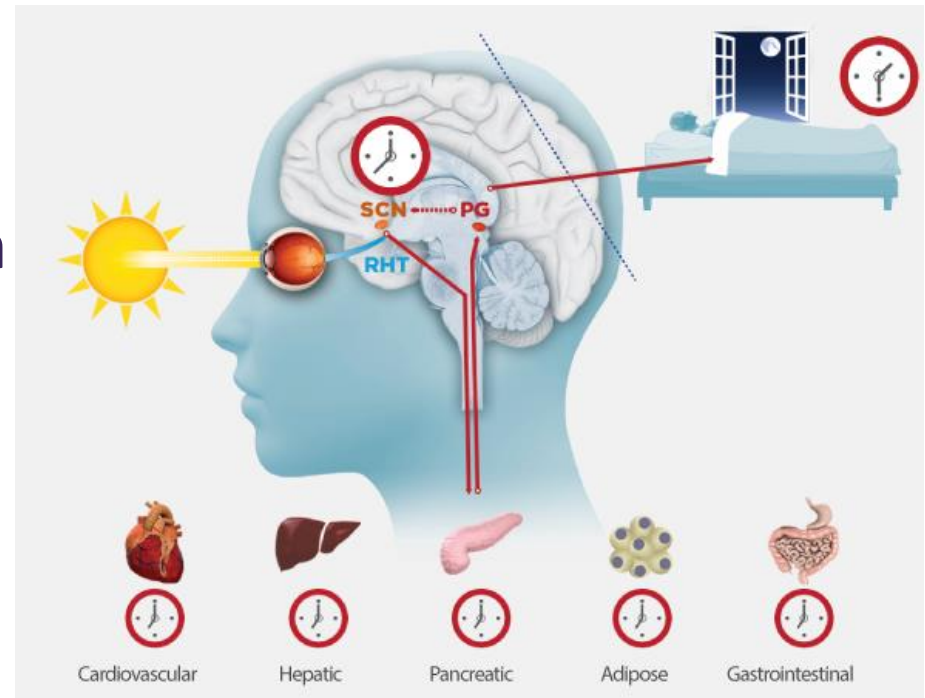


# KNOWN FUNCTIONS OF MELATONIN

- Circadian rhythm synchronizer 
- Seasonal rhythm synchronizer
- Antioxidant and free radical scavenger
- Anti-inflammatory and immune modulator
- Hormone regulator
- Glucose homeostasis modulator

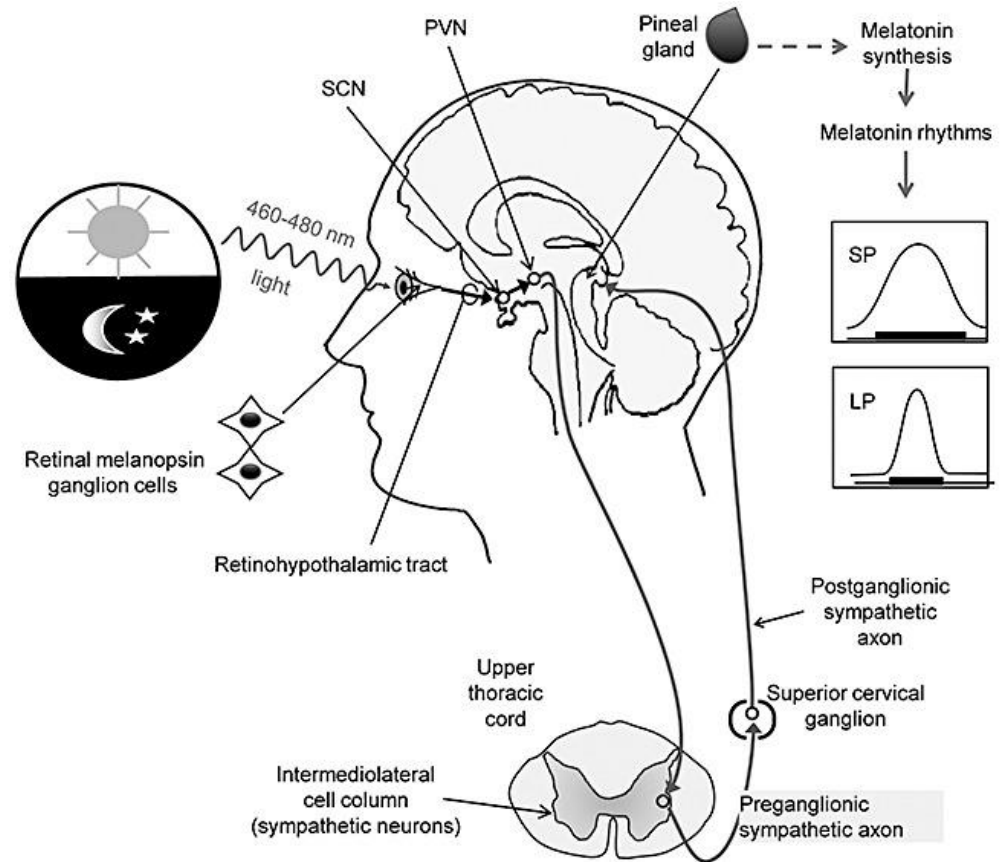
# HUMAN CIRCADIAN RHYTHM

- The source of the human circadian rhythm is in the suprachiasmatic nucleus (SCN) or “master clock” in the anterior hypothalamus
- Our endogenous rhythm is just over 24 hours, and it must be “entrained” to 24 hours by light/darkness, eating, activity, and posture (but especially light)



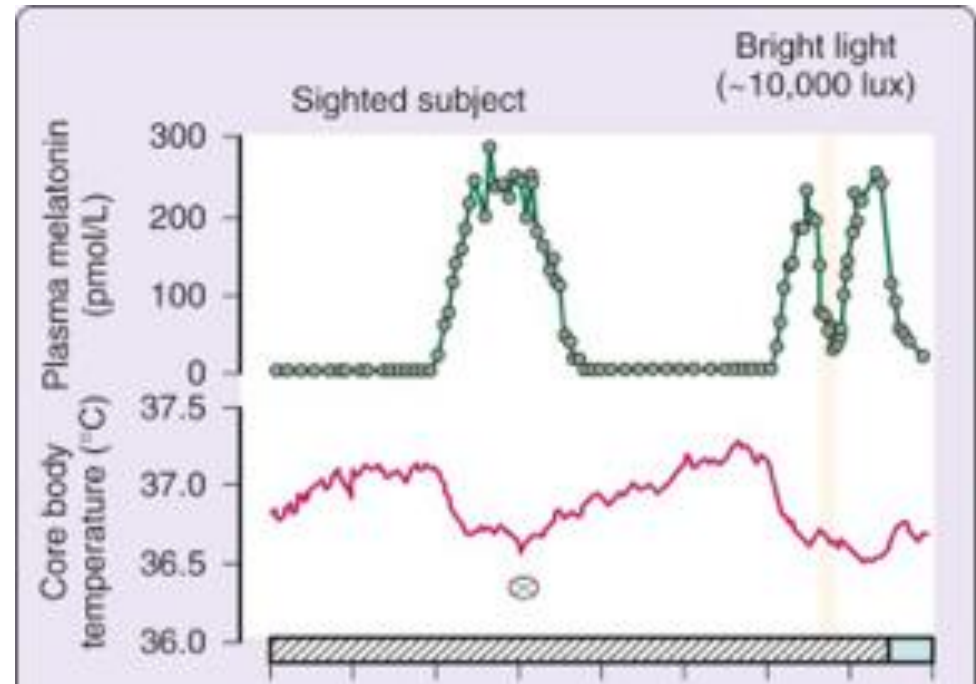
# HOW DOES MELATONIN FIT INTO THIS SYSTEM?

- Light enters the retina and activates the SCN
- SCN activity suppresses melatonin release during the day
- In darkness, this inhibition is released and the pineal gland releases melatonin



# MELATONIN IS THE “HORMONE OF DARKNESS”

- Melatonin release starts in low light conditions 1-2 hours before sleep and lasts through the sleep period
- Typical physiologic “dose” released is ~0.3 mg
- It is a key marker of circadian function
- Melatonin secretion can be suppressed by light – particularly blue light



# ENDOGENOUS MELATONIN AND SLEEP

- The exact mechanism by which melatonin helps facilitate sleep is unclear– it seems to reduce the SCN wake-promoting effects rather than actively promoting sleep
  - Induces a behavioral state that resembles quiet wakefulness, predisposing to normal sleep initiation
  - Does not appear to cause a rapid increase in subjective sleepiness
- Low melatonin levels have been associated with difficulty with sleep onset and restless sleep





# EXOGENOUS MELATONIN

# MELATONIN AS A SUPPLEMENT

- Melatonin is available as an over-the-counter supplement in the US
- It is not monitored or regulated by the FDA
- Usage of melatonin has dramatically increased in recent years
  - Between 2007 and 2012, sales increased by more than 500%
  - 3.1 million people were taking the drug in 2012
  - Fourth most popular “natural” product in the US
  - Second most popular “natural” product for children

# MELATONIN AS A SUPPLEMENT

- Melatonin is available as traditional solid and liquid gel tablets, rapid-dissolve tablets and strips, chewable tablets, flavored liquids, in capsules with other compounds (such as vitamins, minerals, whole plant extracts), and even vape/diffuser formulations
- Marketing focuses on the supplement being a “natural” and “healthy” product – does not typically advertise it as being a hormone
- Melatonin supplements are almost never available at physiologic doses (~0.3mg)



# WHAT ARE YOU REALLY GETTING?

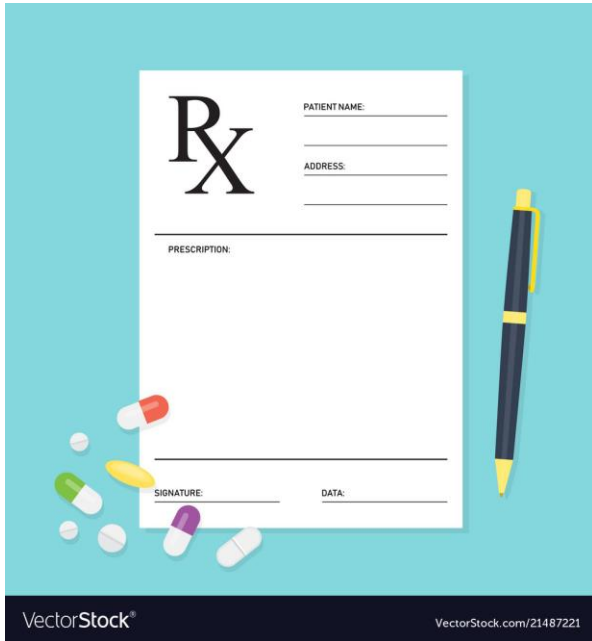
- A study in 2017 analyzed the actual contents of 31 different melatonin supplements from 16 different brands
  - Actual content ranged from 83% less to 478% more than advertised (one chewable tablet was labeled as having 1.5mg but contained almost 9mg)
  - Even within a product, variability between lots ranged between 0.37% and 465%
  - 26% of these products also contained serotonin



# WHAT YOU (AND THE PATIENT) SHOULD KNOW IF USING IT

- Oral melatonin is rapidly absorbed with peak levels 20-30 minutes after ingestion
- Short half-life of 40-60 minutes
- Mostly well-tolerated with minimal side effect profile: headaches, next-day somnolence, BP changes, GI upset, abnormal dreams, mood swings, rash
- Avoid during pregnancy, breastfeeding, or with liver disease
- May reduce efficacy of BP and diabetes medications
- Look for a brand that is verified by USP, NSF International, or consumerlab.org





# WHEN SHOULD I PRESCRIBE MELATONIN?

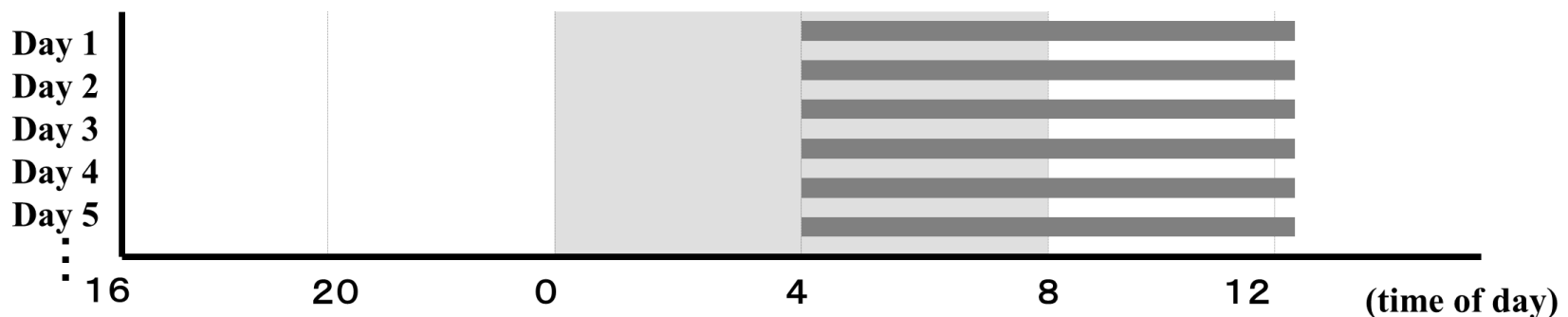
# RECOMMENDED USES FOR MELATONIN RELATED TO SLEEP

- Melatonin is not FDA-approved for any indication
- Recommended (“weak for” evidence) by the American Academy of Sleep Medicine for treatment of specific circadian rhythm disorders
- It is also recommended for the treatment of REM behavior disorder



# DELAYED SLEEP-WAKE PHASE DISORDER

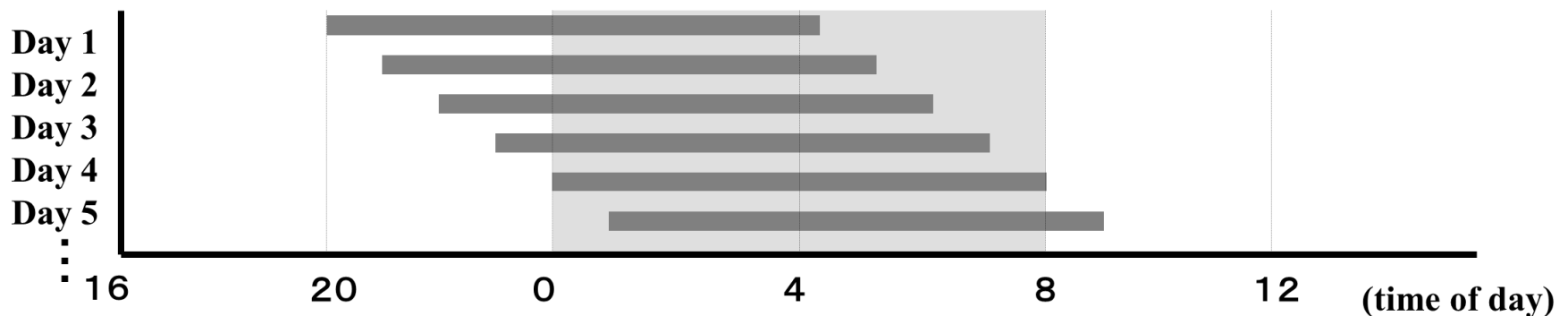
- An intrinsic circadian rhythm disorder characterized by a delay in sleep and wake times by >2 hours relative to societal averages
- Often misdiagnosed as sleep onset insomnia
- The sleep time often cannot be advanced by sedative-hypnotics
- Recommended treatment is:
  - Phase advancement with **physiologic** doses of melatonin up to 5-6 hours before the current DMLO
  - Strategically timed bright light exposure





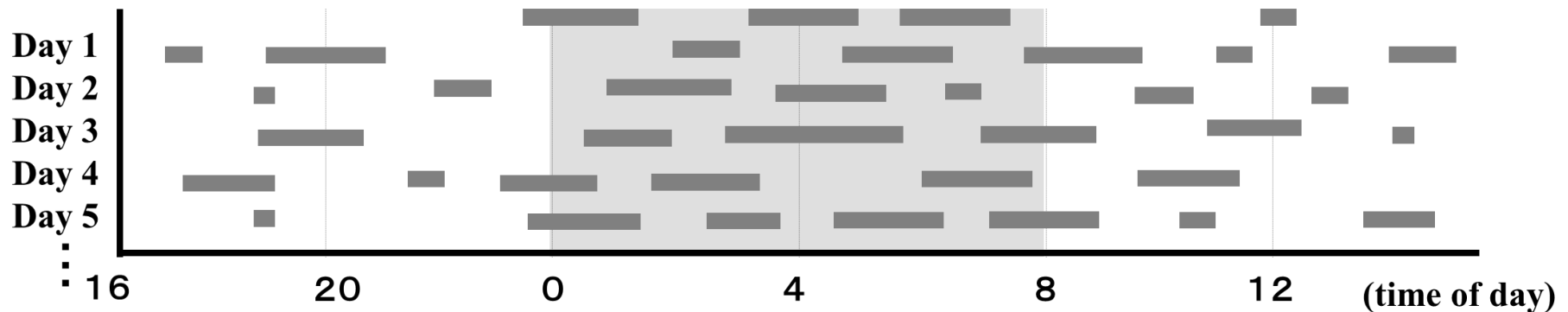
# NON-24-HOUR SLEEP-WAKE DISORDER

- A pattern of progressively delayed sleep and wake times
- Seen most often in blind individuals
- When sleepiness is occurring at the optimal bedtime, physiologic melatonin doses can help prevent further delay
- Tasimelteon (a melatonin agonist) is also approved for treating this disorder



# IRREGULAR SLEEP-WAKE RHYTHM DISORDER (ISWRD)

- Characterized by the absence of a defined sleep-wake cycle, with three or more irregular sleep periods/24 hours
- Total sleep time/24 hours is usually normal for age
- AASM recommends strategically timed melatonin (2-10mg) for children with ISWRD and neurologic disorders



# SHIFT WORK DISORDER AND JET LAG DISORDER

- These are considered *extrinsic* circadian rhythm disorders because the desynchrony arises from external factors (working night shifts or traveling)
- Melatonin (1.8-3mg in studies showing best effect) taken prior to daytime sleep in shift workers is indicated to promote sleep
- Melatonin (0.5-5mg) at bedtime before and after travel may improve symptoms of jet lag
- Strategically timed bright light exposure and planned sleep-wake schedules are also helpful



# RAPID EYE MOVEMENT BEHAVIOR DISORDER (RBD)

- RBD is a parasomnia associated with violent dream enactment during rapid eye movement (REM) sleep
- Associated with the later development of alpha-synucleinopathies such as Parkinson's disease
- Evidence now favors using melatonin over clonazepam (the prior first-line treatment) due to the reduced risk profile
- Effective doses range from 3mg to 18mg at bedtime
- Some studies have also found benefit with ramelteon



# WHAT ABOUT INSOMNIA?

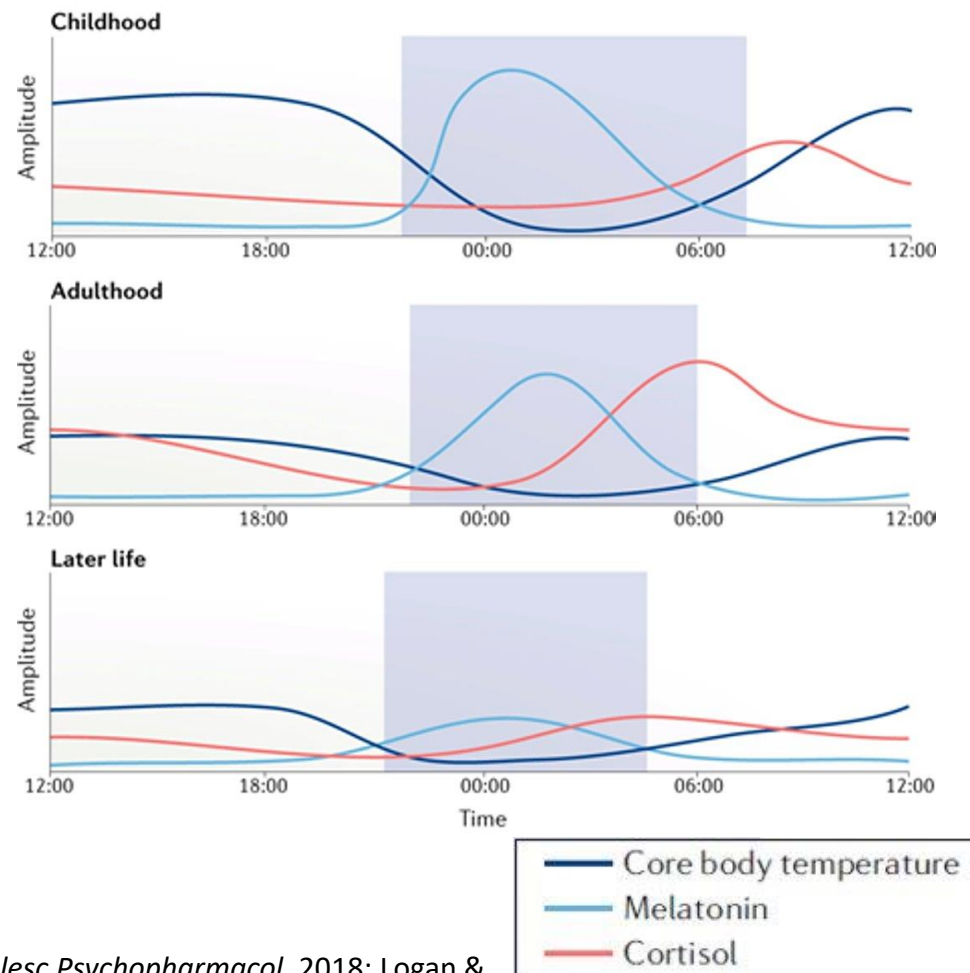
- Insomnia (difficulty getting to sleep or staying asleep) is a growing issue throughout the world
- Melatonin has gained a reputation as a safe, “natural” remedy, especially compared with prescribed drugs such as Ambien
- Even safer than “natural” supplements is the recommended first-line treatment for insomnia: cognitive-behavioral therapy for insomnia (CBT-I)

# DOES MELATONIN HELP INSOMNIA?

- One meta-analysis of 19 studies found efficacy in reducing sleep onset latency by ~7 minutes and increasing total sleep time by about 8.3 minutes – modest improvement
- AASM clinical practice guidelines suggest not using melatonin, mostly due to low quality of evidence
- There are populations which have reduced intrinsic levels of melatonin in whom studies have found benefit

# POPULATIONS WHO MAY BENEFIT FROM MELATONIN FROM INSOMNIA

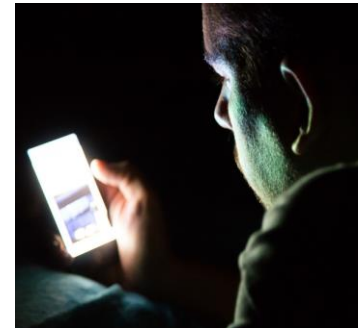
- Children with neurodevelopmental disorders
- Older adults (due to declining peak levels of melatonin)
- Older adults with neurodegenerative disorders
- Patients on beta blockers



Rossignol & Frye, *Dev Med Child Neurol*, 2011; Maras et al, *J Child Adolesc Psychopharmacol*, 2018; Logan & McClung, *Nature Neurosci Rev* 2019; Scholtens et al, *J Psychosom Res*, 2016; Pierce et al, *Sr Care Pharm*, 2019; Vural et al, *Drugs Aging*, 2014; Chen et al, *Mol Neurobiol*, 2016; Cardinali et al, *Curr Neuropharmacol*, 2010; Scheer et al, *Sleep*, 2012

# LIGHT/DARK EXPOSURE AND MELATONIN

- Bright light – from the sun and from electronics – inhibits melatonin release and can delay the sleep-wake phase
- Advise patients that avoiding light in the evening allows their own melatonin release to occur, which can increase readiness to sleep
- Blue-blocking glasses in the evening may help as well





# WHAT ABOUT MELATONIN AGONISTS?

- Ramelteon (Rozerem) is a melatonin (MT1 and MT2) agonist approved by the FDA for sleep onset insomnia
- Effectiveness of ramelteon is modest (mean sleep latency reduction of 4-9 minutes and improved subjective sleep quality), but has few adverse effects and is not habit-forming
- May decrease risk of delirium in older adults
- AASM recommends ramelteon for sleep onset insomnia with weak evidence

# TAKEAWAYS

- Melatonin is the “hormone of darkness” that your body produces in very small amounts (~0.3mg) at night
- It has many functions in the body, including synchronization of the circadian clock
- As a supplement, it is commonly believed to be a “natural” sleep aid, but is not regulated, not always sold in the amount advertised, and the lowest typically available dose is ~10x physiologic amounts
- Melatonin can help treat circadian rhythm disorders and parasomnias
- It may help people with low endogenous melatonin - but start at physiologic doses if possible
- Ramelteon is an FDA-approved melatonin agonist that may be preferable in older adults for sleep and delirium prevention

# PATIENT CASE FOLLOW-UP

- You suspect your patient has delayed sleep-wake phase disorder. You also suspect his habit of using his phone and playing video games at night may worsen the problem.
- He fills out a sleep diary for 2 weeks and it confirms a pattern consistent with this disorder.
- You advise that he avoid sources of bright light starting around 10pm, and that he could take a small dose of melatonin (cutting a 1mg pill in half) around that time. You recommend that he get bright light exposure when he wakes up, and that he can then (slowly) advance his wake time over time.

# QUESTIONS?