

# Safe and Appropriate Use of Melatonin

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Developmental Behavioral Pediatrics



# Accreditation Statement

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of The American Academy of Sleep Medicine and the Michigan Academy of Sleep Medicine. The American Academy of Sleep Medicine is accredited by the ACCME to provide continuing medical education for physicians.

# Conflict of Interest Disclosures for Speakers

Barbara Felt, MD has no relevant financial relationships with ineligible companies to disclose.

# Learning Objectives

Upon completion of this presentation, attendees should be able to:

- Understand properties, mechanisms, location of melatonin actions.
- Apply knowledge learned to appropriately use melatonin for:
  - Jet lag
  - Shift work
  - Delayed sleep wake phase disorder
  - Non-24 sleep wake rhythm disorder
  - Insomnia
- Understand melatonin safety issues



# Melatonin History and Location

- **1958:** Lerner characterized *N*-Acetyl 5-methoxytryptamine
- **Melatonin:**
  - Present in all – bacteria/plants/animals - humans
  - Secreted by pineal gland in vertebrates
  - Synchronizes internal functions with external light/dark cycle cues
  - 80% circulating melatonin made in pineal gland
- **Other synthesis sites:**
  - Retina, bone marrow, platelets, skin, lymphocytes, GI mucosa, cerebellum.
  - Melatonin 400x greater in GI mucosa than pineal gland



# Melatonin and Development



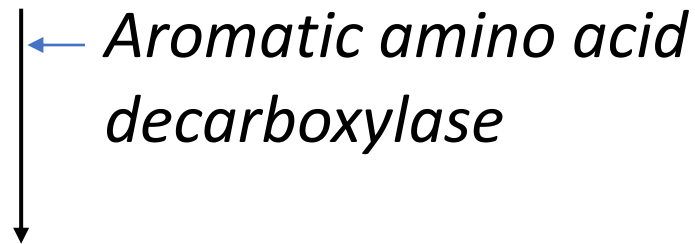
- **Fetus:** maternal melatonin via placental circulation
- **Newborn:** maternal melatonin via breast milk
  - Higher levels night; undetectable day
  - Longer sleep times
- **Infant:**
  - Melatonin production ~ 3 months
  - Circadian pattern by 3-6 months
- **Child:**
  - Highest concentrations pre-puberty (4-7 years of age)
  - Decline to adult levels by late teen years
- **Adult:**
  - Stable to 35-40 years of age then decline.
  - 20% of young adult level by 90+ years

# Melatonin synthesis

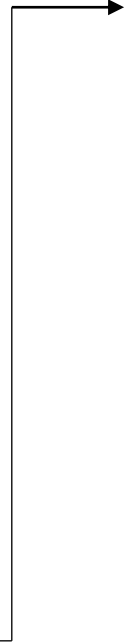
- Tryptophan



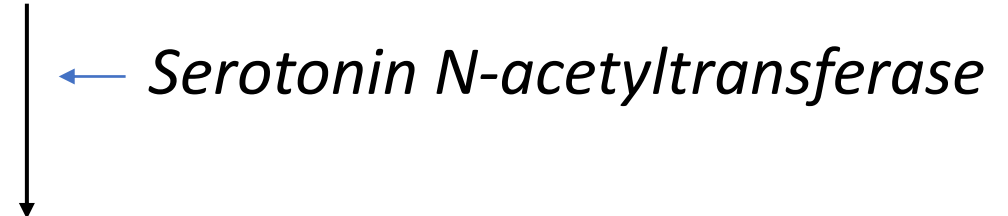
- 5-hydroxytryptophan



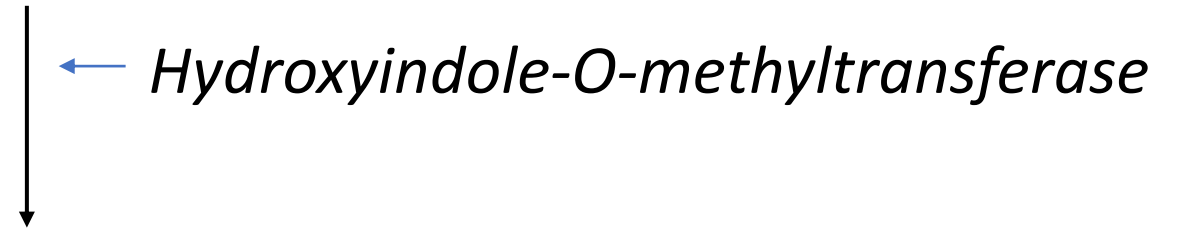
- Serotonin



- Serotonin



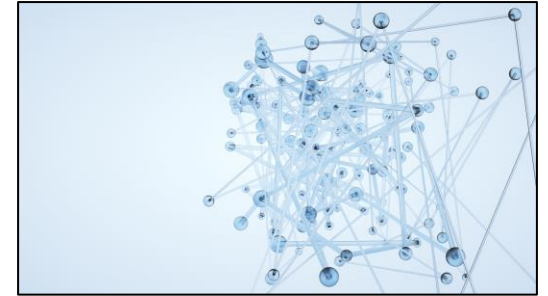
- N-Acetylserotonin



- **Melatonin**



# Melatonin Secretion, Metabolism, Action

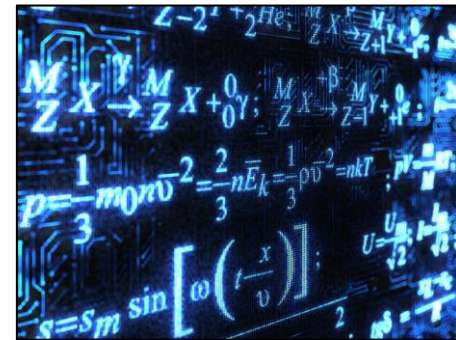


- Secretion:
  - Released to circulation and CSF
  - Not stored
  - Starts after sundown
  - Peak 2-4 AM
  - Gradual decrease 2<sup>nd</sup> half of night
- Metabolism
  - Not stored
  - Half-life ~40 minutes
  - Hydroxylation in liver
    - CYP1A2 – 6-hydroxymelatonin
    - Conjugated to 6-sulfatoxymelatonin
  - Excretion by kidney
- Action examples:
  - Non-receptor: Antioxidant properties
  - Receptor-mediated: Circadian rhythm phase shifting



# Melatonin Receptors

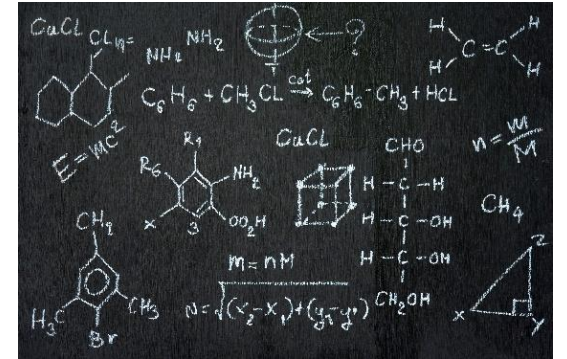
- G-protein coupled melatonin receptor expression
  - MT1: Pars tuberalis, SCN, other hypothalamic areas, hippocampus, adrenal
  - MT2: SCN, retina, pituitary, other brain areas
  - Other areas with melatonin receptors: heart, arteries, kidney, lung, liver, gallbladder, small intestine, adipocytes, ovaries, uterus, breast, prostate, skin, lymphocytes (T & B)
- Associated functions
  - MT1: Circadian and reproductive
  - MT2: Phase-shifting
- Melatonin affinity MT1 5x > MT2





# Other Conditions and Roles

- **Core body temperature:**
  - melatonin peak just before body temp nadir.
- **Energy metabolism/glucose homeostasis:**
  - ↓ melatonin → ↑ risk T2DM
- **Psychiatric disorders:** ↓
  - melatonin or phase shift → MDD, ASD, Bipolar
- **Anti-oxidant, cancer:**
  - Free radical scavenger; Oncostatic effects
    - ↓ breast and prostate cancer progression
    - Night workers have ↑ risk of cancer



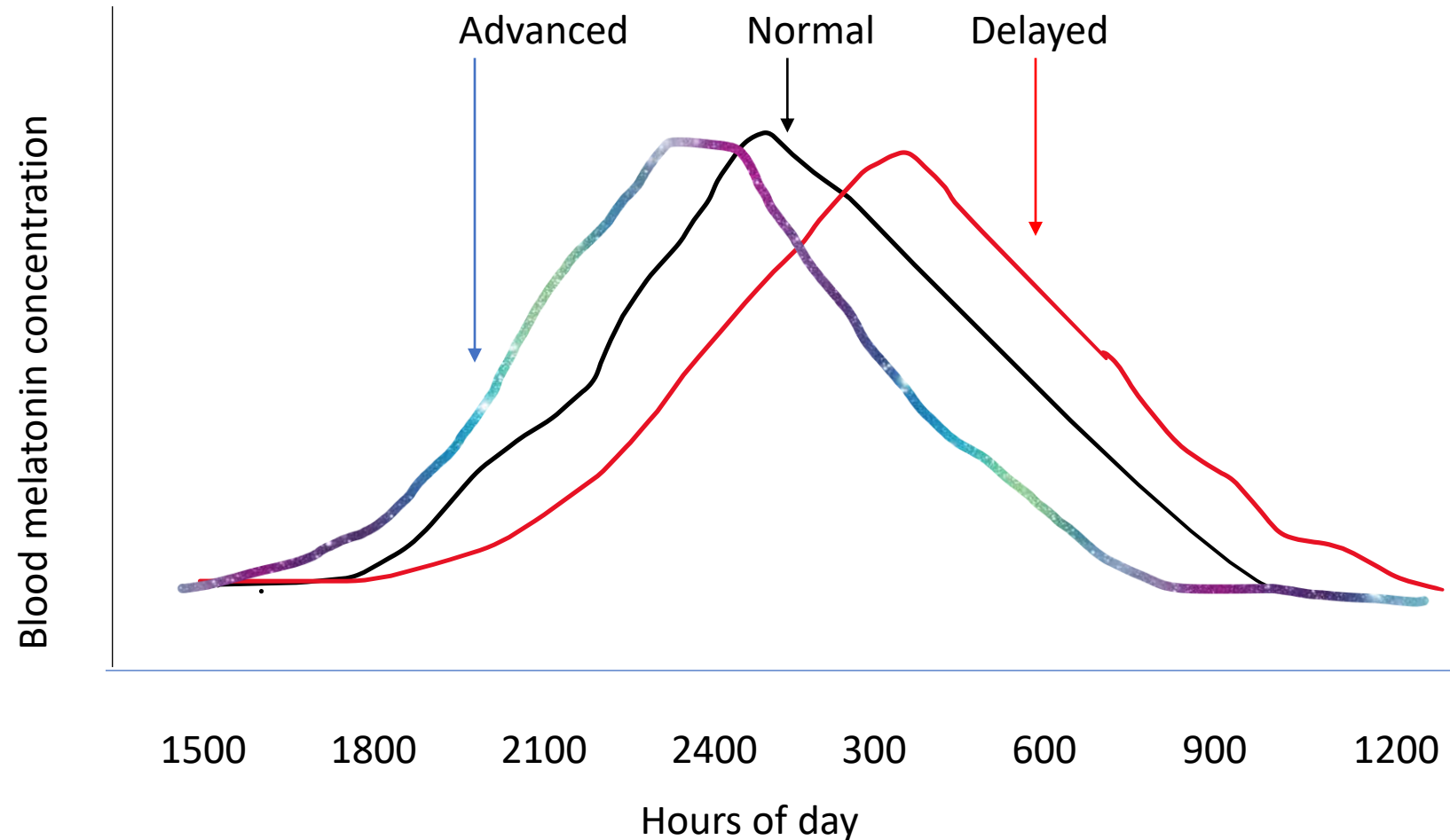
# Sleep and Endogenous Melatonin

- Primarily pineal origin
- Dim Light Melatonin Onset (DLMO):
  - ↑s 90-120 min prior to habitual bedtime
- Provides for quiet wakefulness
- One factor in the regulation of sleep onset timing
- Circadian rhythm disturbances
  - External factors
  - Internal factors



# Melatonin, Sleep Phase and Biological Night

---Biological night---



# Exogenous Melatonin: Use and Considerations

- Efficacy for circadian disorders:
  - Jet lag
  - Delayed sleep-phase syndrome
  - Non-24 sleep wake disorder.
- Benefit less clear: Insomnia
- Circulation peak ~-50-60 minutes
- 1-5 mg - 10-100x > than endogenous concentration; start at low doses.
- Biphasic decline
- Basal concentration in 4-8 hours.

## • **General Rules:**

- Evaluate for and manage primary sleep and medical problems
- Attend to behavioral, mental health and psychosocial issues
- Provide general education about sleep and sleep hygiene
  - Light exposure in AM and low toward bedtime
  - Limit electronics, engage in quieting activities, no caffeine nor alcohol
  - Cool, dark, comfortable space

# Sleep Duration by Age – Centers for Disease Control \*

<b>Age Group</b>		<b>Recommended hrs/24 hr day</b>
Newborn	0-3 months	14-17 hours (NSF)
Infant	4-12 months	12-16 hours (includes naps)
Toddler	1-2 years	11-14 hours (includes naps)
Preschool	3-5 years	10-13 hours (includes naps)
School age	6-12 years	9-12 hours
Teen	13-18 years	8-10 hours
Adult	18-60 years	7 + hours
	61-64 years	7-9 hours
	65 years +	7-8 hours

(\* How much sleep do I need? after AASM and NSF [https://www.cdc.gov/sleep/about\\_sleep/how\\_much\\_sleep.html#print](https://www.cdc.gov/sleep/about_sleep/how_much_sleep.html#print) )

# Circadian Sleep-Wake Rhythm Disorders

- Circadian System
  - Modulates physiologic rhythms
  - Environmental cues: light-dark, eating, activities
  - Without cues, longer oscillating period (24.2+ hr)
- Environmental disorders
  - Jet lag disorder
  - Shift work disorder
- Intrinsic disorders
  - Delayed sleep-wake phase disorder
  - Advanced sleep-wake phase disorder
  - Non-24-hour sleep-wake rhythm disorder
  - Irregular sleep-wake rhythm disorder





# Jet Lag

- Symptoms on crossing at least 2 time zones:
  - Insomnia
  - Excessive daytime sleepiness (EDS)
  - Somatic symptoms
  - Impaired performance
- Diagnosis ICSD-3
  - Insomnia or EDS associated with  $\downarrow$  TST and jet travel  $\geq 2$  time zones
  - Impaired daytime functioning within 2 days of travel
  - Not due to other disorder



# Jet Lag - Management

- Goal: align internal phase to destination
- Eastward vs Westward travel
- **Timed – Melatonin** (primarily Eastward travel)
  - Typically - 3 mg IR
  - At desired bedtime on arrival and up to 5 days
  - Review of 12 placebo-controlled trials:
    - Improved symptoms
    - Improved sleep duration and quality
    - Cortisol and oral temperature entrained to destination time more quickly



# Shift workers

- Internal biology and external schedule mis-aligned
- Sleep disturbances affect two-thirds
- Symptoms-risks:
  - Excessive sleepiness
  - Impaired cognitive functioning and psychomotor control
  - Impaired emotion and stress management
  - Adverse health outcomes
- Shift Work Disorder (ICSD-3)
  - Report of insomnia and/or excessive sleepiness; ↓ TST
  - Symptoms associated with shift work for  $\geq 3$ mo
  - Clinically significant distress/impairments
  - Evidence of disturbed S-W pattern (sleep log, actigraphy)
  - Not better explained by other disorder



# Shift workers - Management

- General
  - Non-pharmacologic strategies:
    - Sleep hygiene
    - Regularity of schedule across days (even non-work days)
    - CBT-I and bright light therapy
    - Promoting wakefulness during shifts
  - Pharmacologic strategies: hypnotics and melatonin
- **Melatonin**
  - Meta-analysis of small randomized trials (melatonin v placebo) in night workers
  - Total sleep time improved with use 1-3 mg melatonin (IR)
  - Recommendation:
    - Limit to 1-3 mg
    - 30 minutes before desired sleep onset



# Delayed Sleep-Wake Phase Disorder (DSWPD)

- Most common circadian disorder in teens
  - 3-5% teens and up to 1.7% adults
- Clinical symptoms
  - Delayed bedtime and waketime
  - Sleep insufficiency
  - Co-occurring psychiatric disorders
- Diagnosis ICSD-3
  - Significant delay of sleep and wake time relative to that desired/required
  - Symptoms present for  $\geq 3$  months
  - Improved sleep quality / duration on ad lib schedule
  - Sleep log and actigraphy evidence
  - Not better explained by other disorder



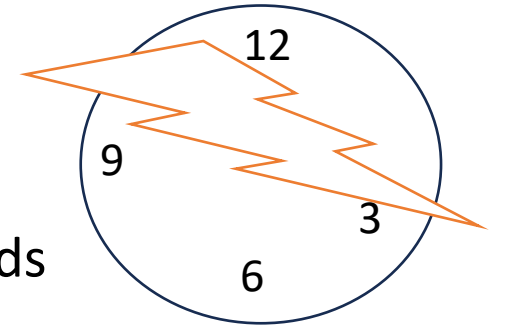
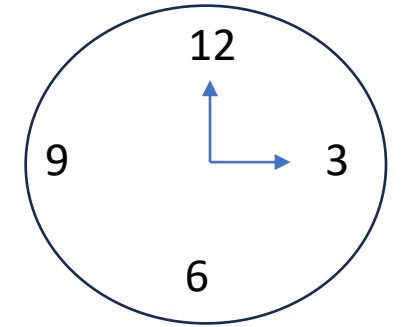
# DSWPD - Management

- Behavioral modifications
  - Address external factors
  - Sleep hygiene, consistent schedules
  - Consider later school start time
  - If DSWPD mild: gradual phase advancement
  - If DSWPD moderate/+: chronotherapy
  - DLMO does advance as well
- **Timed melatonin**
  - 3-5 mg ~1.5 hr before desired bedtime
  - Treatment duration individualized
- Light therapy

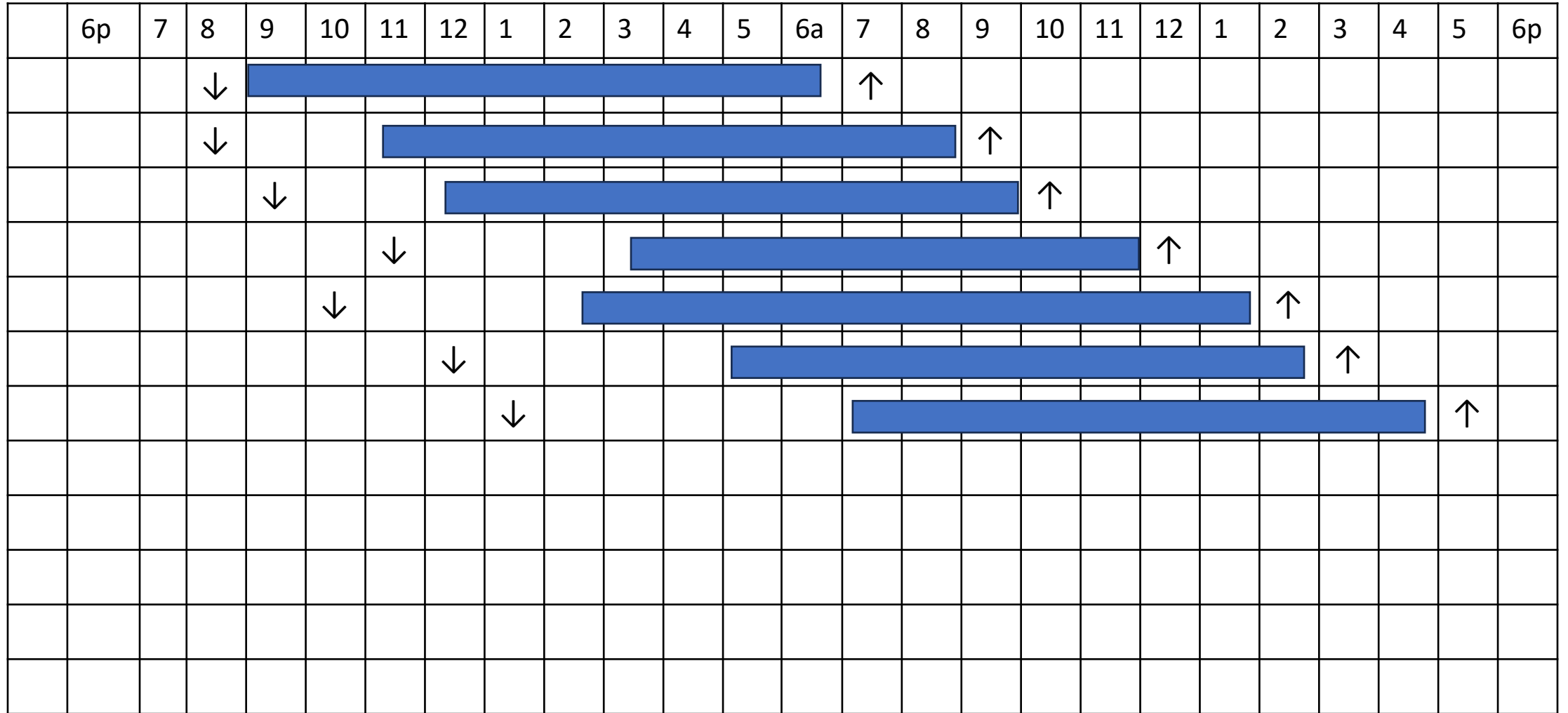


# Non-24-hour Sleep-wake Rhythm Disorder (N24SWD)

- Unable to maintain alignment with 24-h environment
- Shift of sleep-wake pattern apart from external time.
- 63% of blind and 31% of sighted individuals
- Pathophysiology
  - Light not received by brain
  - Progression from DSWPS, other impairment
  - Important to review patterns over several weeks (sleep log/actigraphy)
- Diagnosis (ICSD-3):
  - Alternating periods of insomnia or EDS with absence of symptoms periods
  - Symptoms for 3+ months
  - Evidence from sleep logs and actigraphy
  - Not better explained by another diagnosis.



# Sleep Log

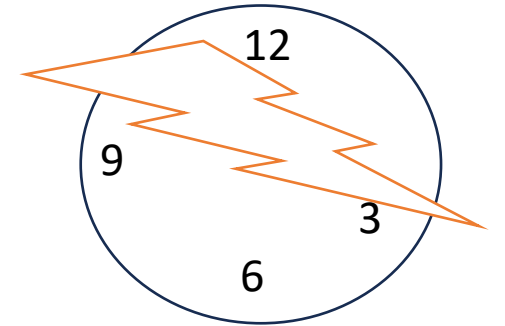
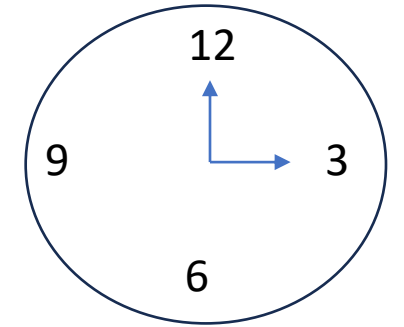


In bed ↓ Asleep ■ Arousal-awake ↑

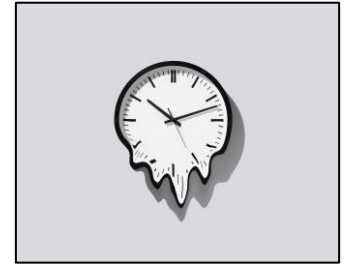


# Non-24- SWD - Management

- General:
  - Entrain-synchronize circadian pacemaker to 24-hr day for both
  - Behavioral: regular S-W schedule and strengthen daytime cues
- Blind
  - **Melatonin** or melatonin agonist 1 h prior to bedtime or at a fixed clock time.
  - TST ↓ 27 min; SOL ↓ 29 min
- Sighted (more challenging)
  - **Melatonin** 2 hr prior to bedtime and avoid bright light
  - Bright light exposure for 30+ min on awakening.
  - Maintain fixed rise time



# Insomnia



## • Pediatrics

- Behavioral Insomnia
  - Sleep Onset Association Type (Z73.810)
  - Limit Setting Type (Z73.811)
  - Combined type (Z73.812)
  - Unspecified type (Z73.819)
- Insomnia not otherwise specified

## • Adult

### • Insomnia

- Due to medical condition (G47.0)
- Due to mental disorder (F51.05)
- Not due to substance or known physiological condition (F51.0-)
- Psychophysiologic insomnia (F51.04)

## **General management**

- Determine and address underlying medical sleep disorders
- Determine and address other precipitants
- Eliminate/minimize contributors
  - Pediatric: sleep hygiene-habits, parent limit setting, child mental health
  - Adult: sleep hygiene-habits, chronic medical/mental health, substance use
  - Medication side effects
  - Environment

# Agents for Insomnia in Children

(none FDA approved for sleep in younger children)



<b>Drug</b>	<b>Mechanism</b>
<b>Antihistamines</b>	<b>Histamine H1 receptor antagonist</b>
<b>Melatonin</b>	<b>Melatonin receptor agonist</b>
Clonidine, Guanfacine	Alpha-adrenergic agonists
Trazodone	5-HT <sub>2A</sub> , alpha-1 adrenergic and Histamine H1 receptor antagonism
Fluvoxamine, Paroxetine, Citalopram	SSRI with sedating effects
Eszopiclone, Zaleplon, Zolpidem	Benzodiazepine receptor agonist
Estazolam, Flurazepam, Temazepam, Triazolam, Quazepam	Benzodiazepine hypnotic

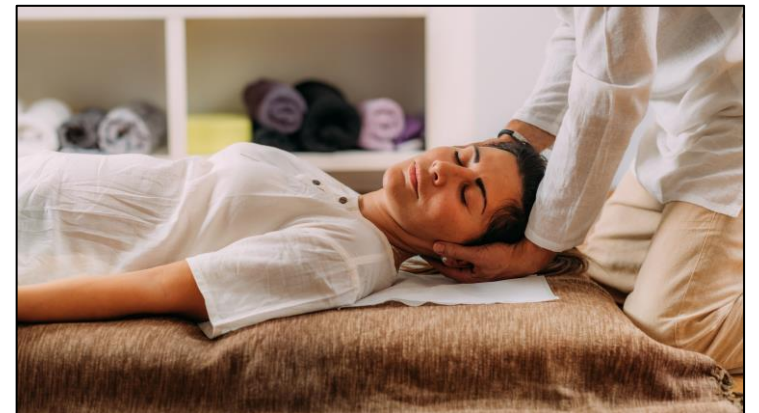
# Agents for Insomnia in Adults



<b>Drug</b>	<b>Mechanism</b>
Doxepin	Histamine H1 receptor antagonist
Ramelteon (or melatonin)	Melatonin receptor agonist
Lemborexant; Suvorexant, Daridorexant	Orexin receptor antagonist
Trazodone	5-HT <sub>2A</sub> , alpha-1 adrenergic and Histamine H1 receptor antagonism
Eszopiclone, Zaleplon, Zolpidem	Benzodiazepine receptor agonist
Estazolam, Flurazepam, Temazepam, Triazolam, Quazepam	Benzodiazepine hypnotic

# Safety of Melatonin

- Adverse effects
- Interactions
- Oversight, manufacturing and purity
- Increasing overdose risks



# Melatonin - Adverse Effects

- Side effects
  - Vivid dreams – nightmares, daytime sleepiness
  - Dizziness, headache, stomachache
  - Depressed mood, irritability
- Potential side effects but less evidence
  - Suppression of hypothalamic-gonadal axis
  - Increased immune reactivity
  - Endogenous melatonin suppression
- Reviews of 3 RCTs not reveal serious adverse side effects



# Melatonin – Interactions (not exhaustive)

- CYP1A2 inhibitors:
  - tricyclic antidepressants
  - Fluvoxamine
  - Cimetidine
  - Ciprofloxacin
  - Erythromycin
  - Verapamil
  - Grapefruit juice
- CYP1A2 inducers:
  - Carbamazepine
  - Phenobarbital
  - Rifampin
  - Omeprazole
  - Modafinil
  - Dexamethasone
  - Smoking

Besag 2022; UpToDate 2023:  
Pharmacotherapy for insomnia in adults





# Oversight of Dietary Supplements

- US Congress regulation of FDA involvement dates back to 1906.
- 1989: Eosinophilia-Myalgia Syndrome thought related to a contaminated batch of L-tryptophan or 5-hydroxytryptophan
- 1994: Dietary Supplement Health and Education Act
- Currently
  - FDA does not approve dietary supplements for safety and effectiveness
  - Supplement companies - responsible for safe and appropriate labelling of products



# Manufacture and Purity

- Variable content and concentration
- 2017 study of 16 local brands
  - Melatonin content -83% to 478% of labelled content
  - Lot to lot variability up to 465%
    - Tablets and sublingual strips were most reproducible.
    - Capsules greater variability
    - Simple mix of ingredients less variable
  - Serotonin in 50% of the supplements (1-75 µg)
- 2023 study of 25 melatonin/CBD gummy products
  - No melatonin in one
  - Others: 1.3-31.1 mg melatonin (74-347% labelled quantity)
  - CBD 104-118% of labelled quantity; no serotonin.



## Pediatric Melatonin Ingestions — United States, 2012–2021

Karima Lelak, MD<sup>1</sup>; Varun Vohra, PharmD<sup>2</sup>; Mark I. Neuman, MD<sup>3</sup>; Michael S. Toce, MD<sup>3</sup>; Usha Sethuraman, MD<sup>1,4</sup>

- Between 2012-2021 reported melatonin ingestions increased 530%
- Sales increased: 2016-\$285 mil to 2020-\$821 mil.
- 2020: melatonin most frequently ingested substance in children.
- Most unintentional,  $\leq 5$ yo, male and occurred at home,
- Most asymptomatic (84%) but of ~28K receiving care at health facility, 14.7% hospitalized, 1% required ICU, 2 died.

# Conclusions

- Melatonin is commonly used in children and adults
- Most effective for Circadian Rhythm Disorders
- Determine if other medical, mental health, psychosocial concern
- Provide education about sleep hygiene
- Implement with targeted outcome depending on condition
- Strive for short-term use
- Be watchful for drug-drug interactions
- Be aware of product variability
- Use safety measures to protect children

*Thank you*



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- UpToDate: Delayed sleep-wake phase disorder; Jet lag; Non-24-hour sleep-wake rhythm disorder; Overview of circadian sleep-wake rhythm disorders; Sleep-wake disturbances in shift workers.