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Sleep Impairment in Psychiatric Disorders

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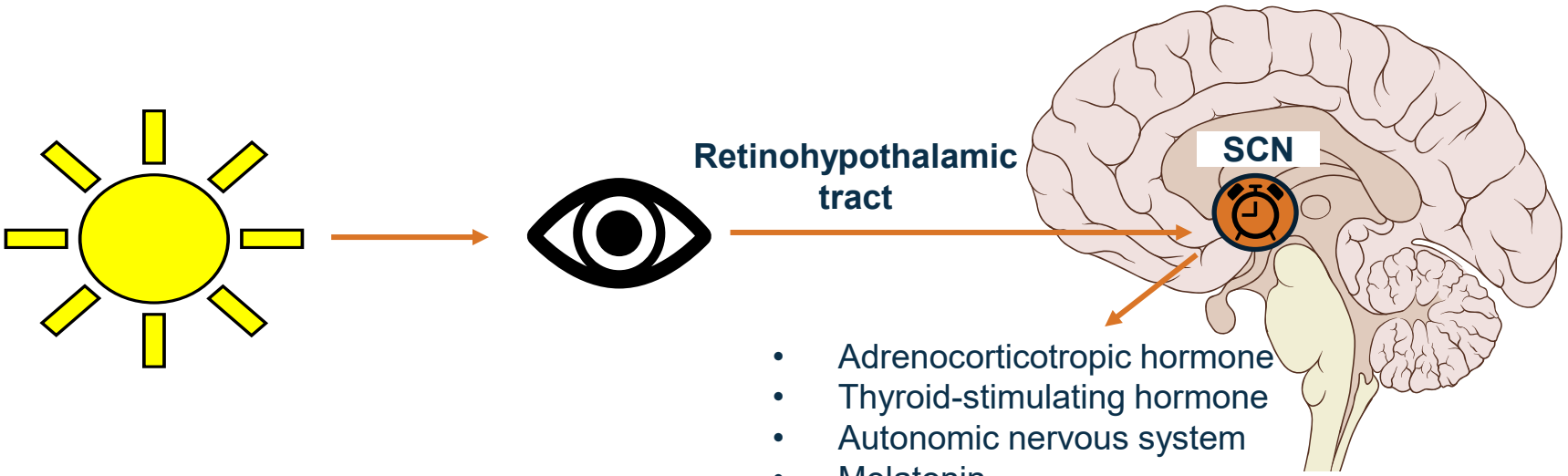
Chronobiology of Sleep

The Light-Dark Cycle is a Key Regulator of the Circadian Clock

Light signals from the eye to the superchiasmatic nucleus (SCN) in the brain are critical to setting the 24-hour cycle of the circadian period[1]



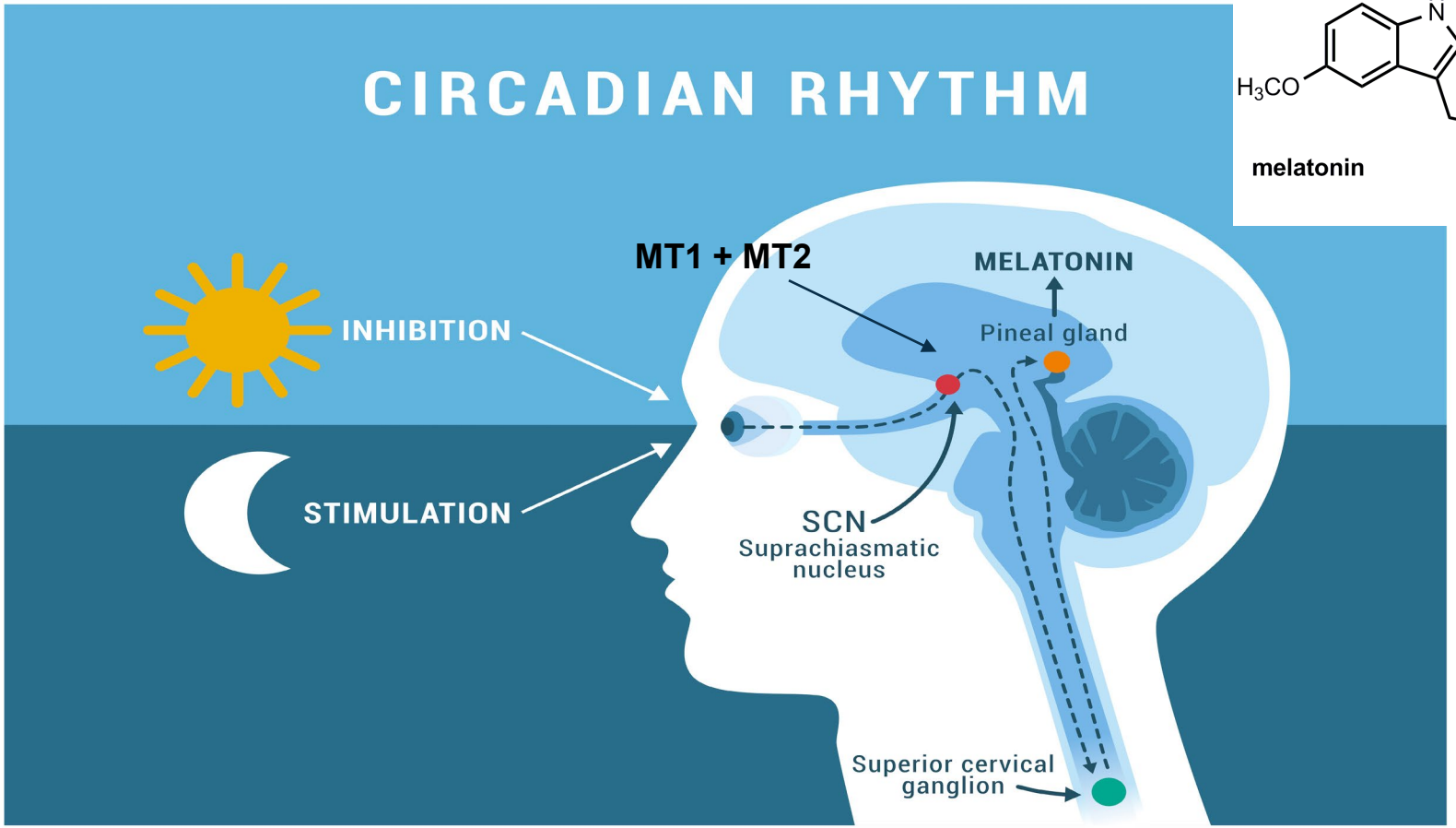
- Adrenocorticotropic hormone
- Thyroid-stimulating hormone
- Autonomic nervous system
- Melatonin
- Body temperature

Human rhythmicity is disrupted by artificial light and, when severely disrupted, has demonstrated links to poorer health, including increased risk of metabolic dysfunction, obesity, and certain cancers; patients with BD may have increased sensitivity to light[2,3]

SCN, superchiasmatic nucleus

1. Hickie et al. *BMC Medicine.* 2013;11:79. 2. Wyse et al. *Ann Med.* 2014;46:253-263. 3. Harvey. *Am J Psychiatry.* 2008;165:820-829.

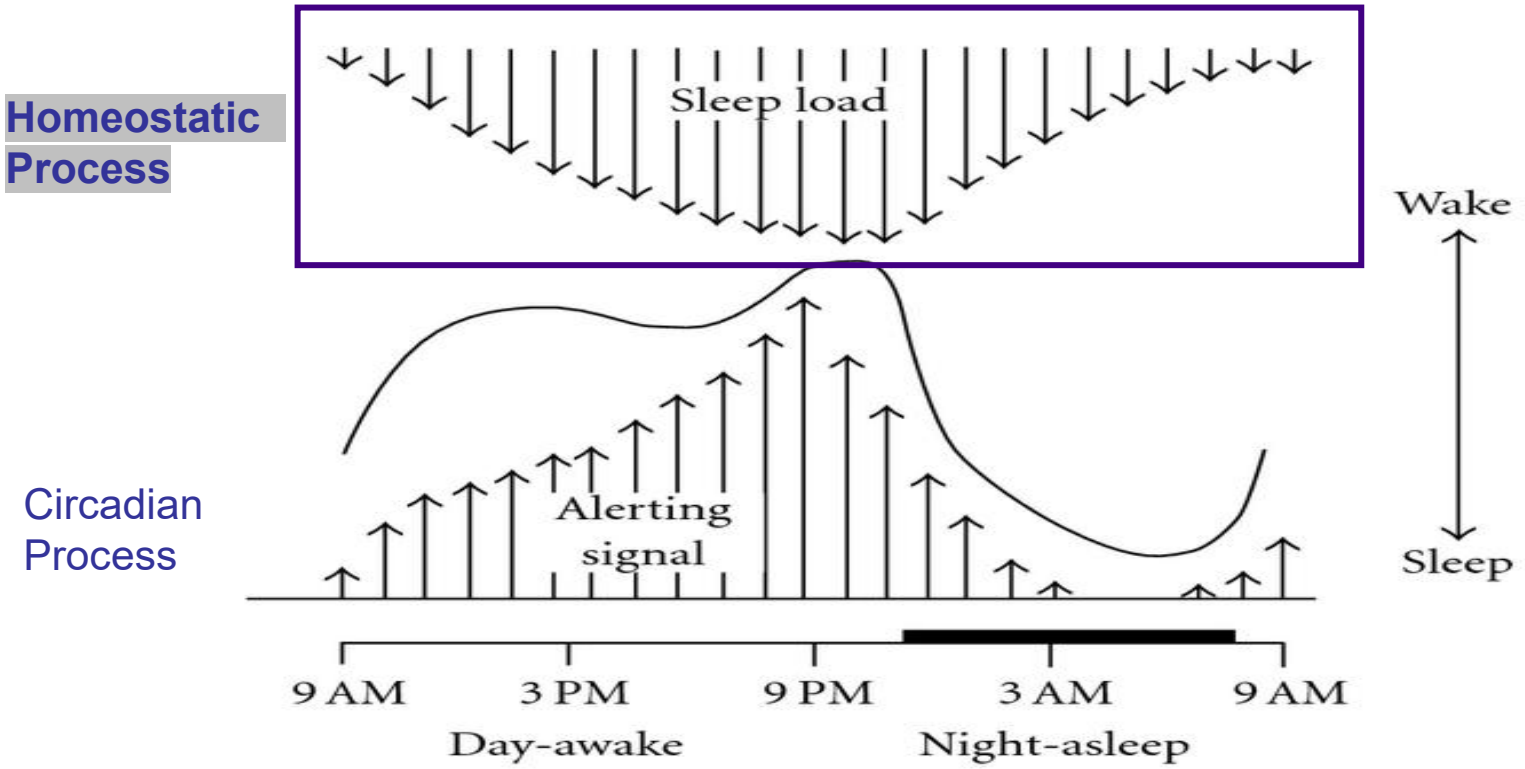
Receptors in the Circadian Cycle



MT1, melatonin receptor 1; MT2, melatonin receptor 2

Brzezinski, N Engl J Med 1997; 336:186-195

Homeostatic and Circadian Regulation of Sleep – Homeostatic Process

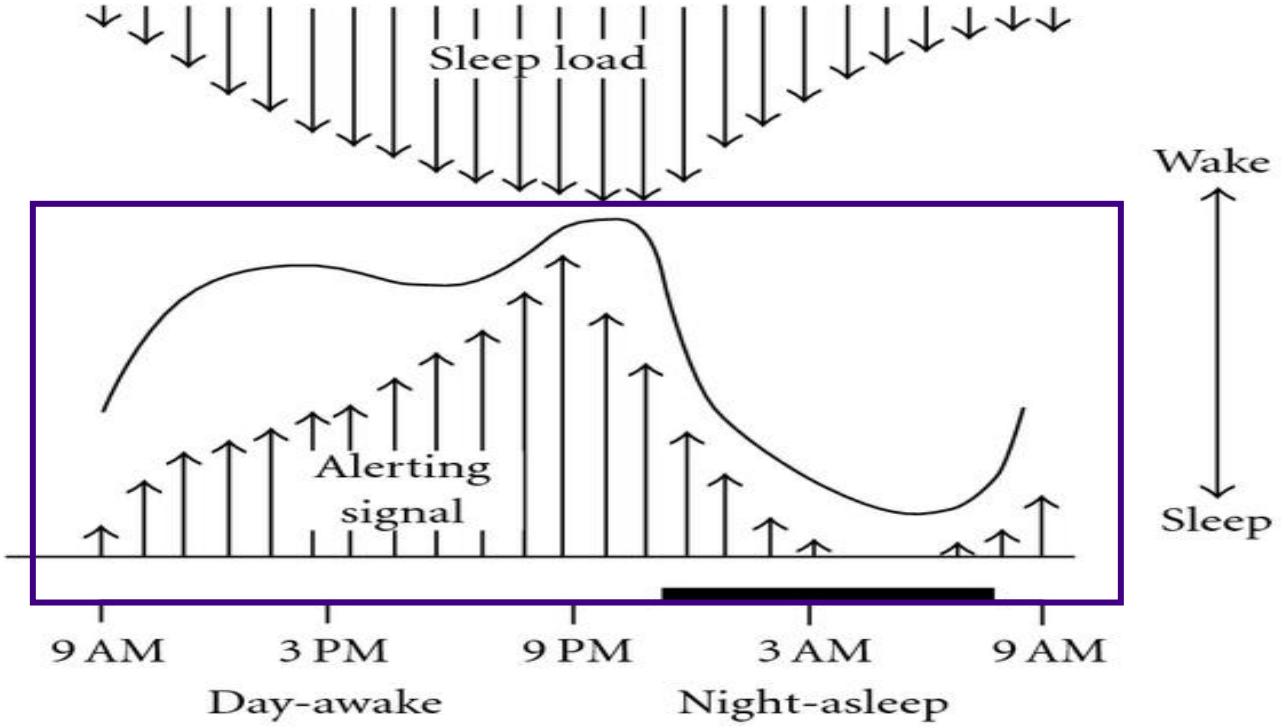


Shechter and Boivin. International Journal of Endocrinology Volume 2010, Article ID 259345, 17 pages doi:10.1155/2010/259345

Homeostatic and Circadian Regulation of Sleep - Circadian Process

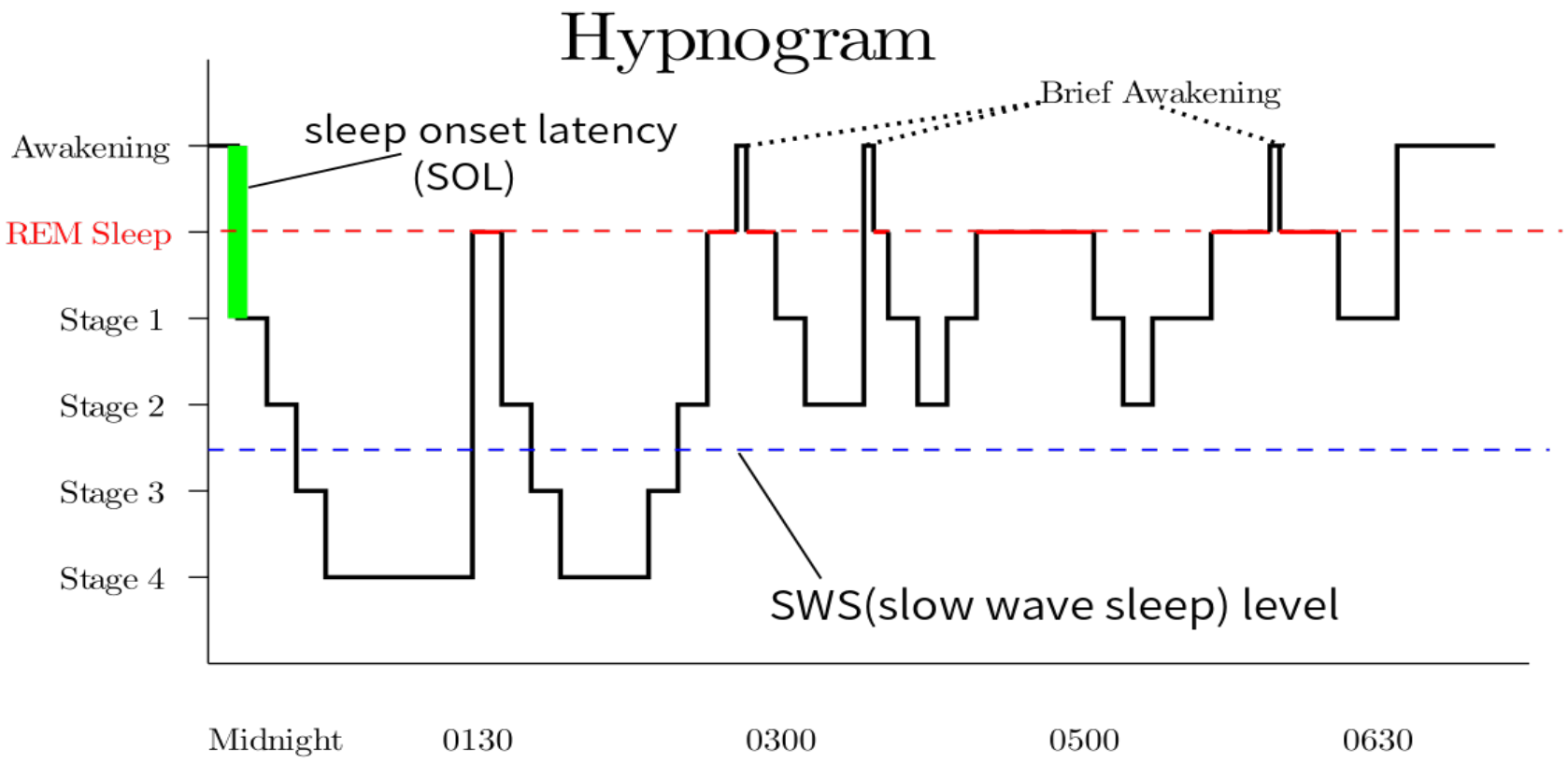
Homeostatic Process

Circadian Process



Shechter and Boivin. International Journal of Endocrinology Volume 2010, Article ID 259345, 17 pages doi:10.1155/2010/259345

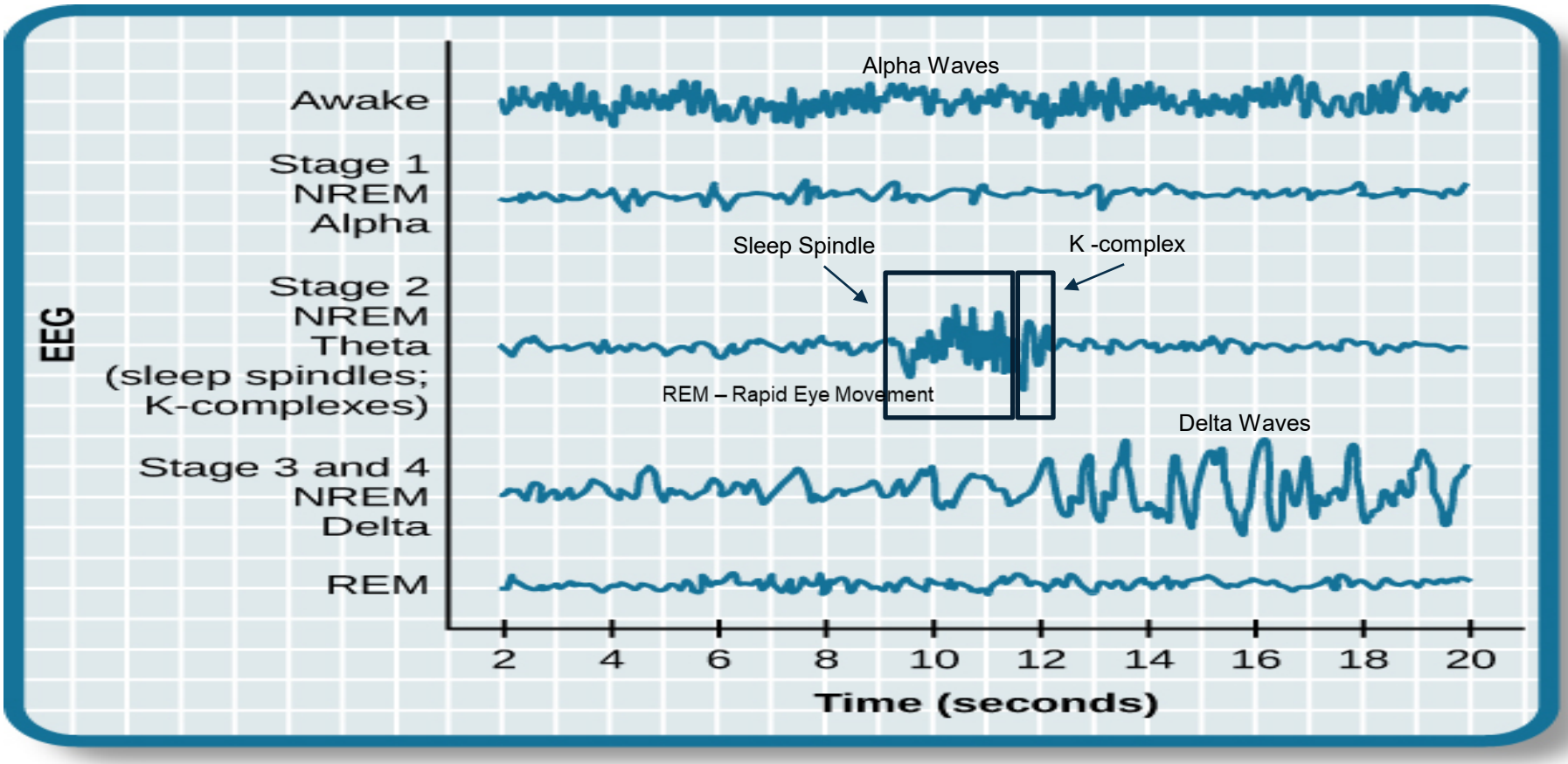
Normal/Healthy Sleep Characteristics



REM, rapid eye movement

https://en.wikipedia.org/wiki/Rapid_eye_movement_sleep. Accessed February 12, 2021.

Sleep Waves as Measured by PSG



PSG, polysomnography; NREM, non-rapid eye movement; REM, rapid eye movement;

https://courses.lumenlearning.com/suny-hccc-ss-151-1/chapter/stages-of-sleep/ Accessed February 12, 2021.

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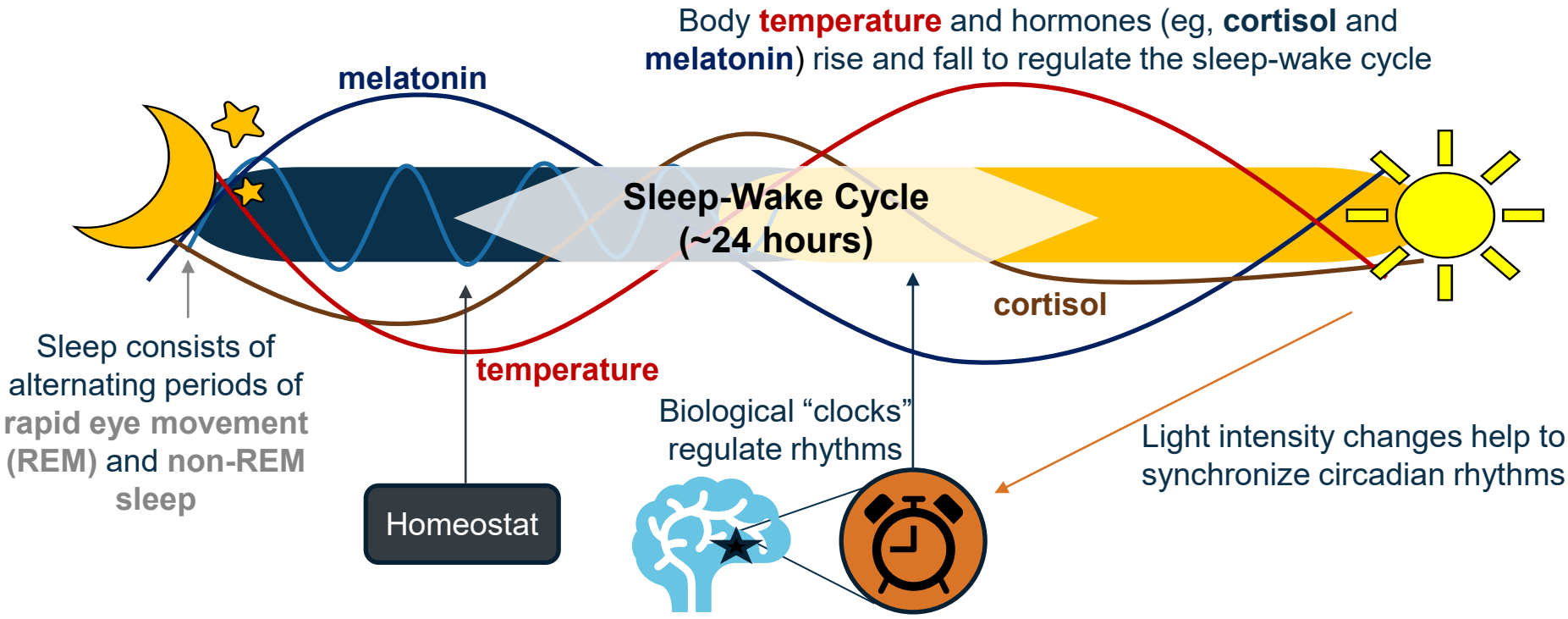
Sleep Pathology & Economic Impact

Sleep Pathophysiology

Sleep/Wake rhythm involves many factors influencing sleep onset and maintenance over 24-hour periods, including circadian oscillations, hormone levels, and light intensity



Thase. *Dialogues Clin Neurosci*. 2006;8:217-226.

Insomnia is Common

Definition	*Prevalence Range (%)*
Insomnia symptoms	
• Any	30-48%
• ≥3 nights/wk, “often” or “always”	16-21%
• Moderate to extreme severity	10-28%
Insomnia symptoms + Daytime consequences	9-15%
Insomnia by DSM-IV criteria	6%

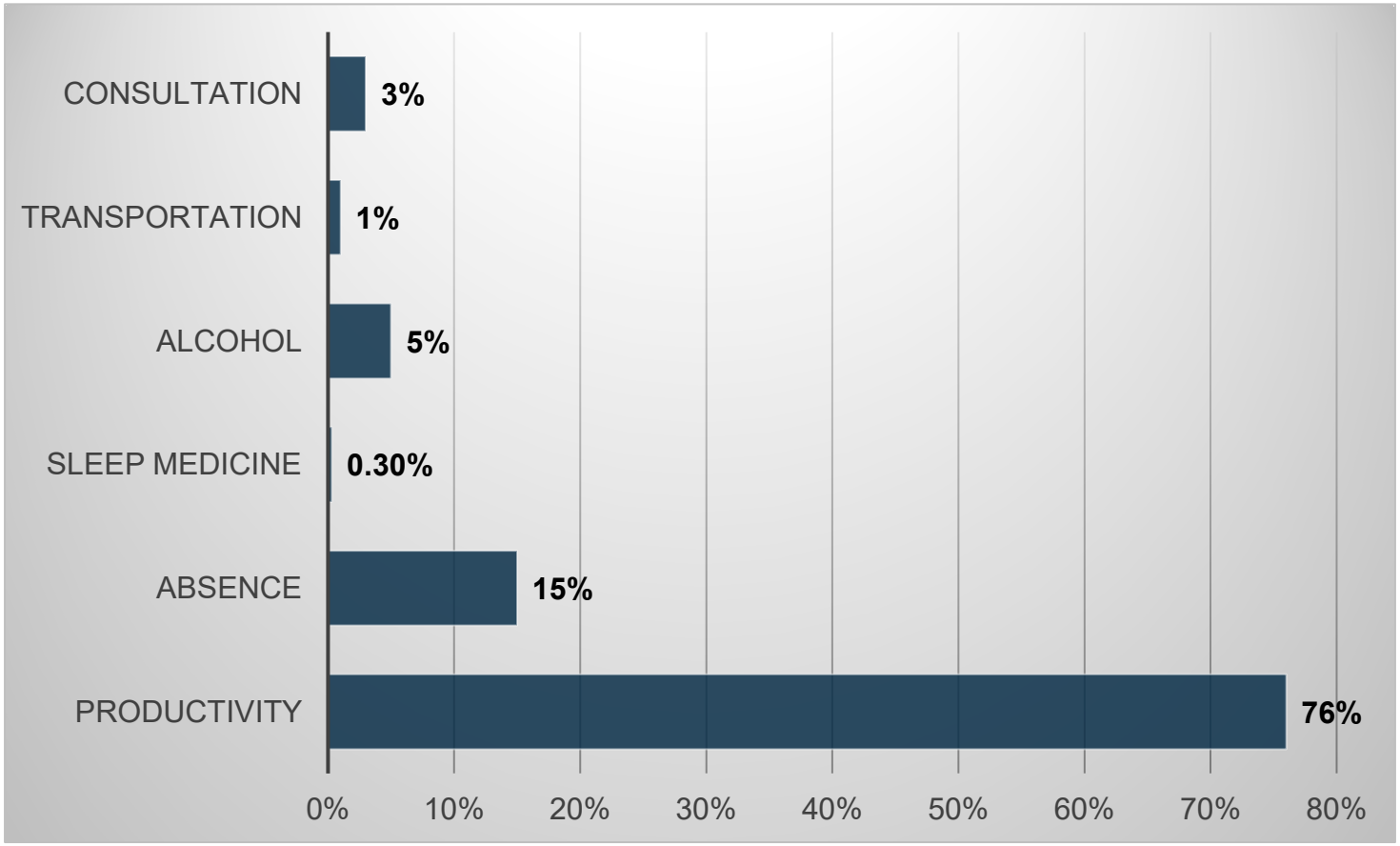
Ohayon MM. *Sleep Med Reviews* 2002;6(2):97-111

The Average Annual Per-Person Costs in Quebec

- **Direct and indirect combined**:
  - $5,010 for individuals with insomnia syndrome
  - $1431 for individuals presenting with symptoms
  - $421 for good sleepers

Daley M et al; Sleep 2009;.32(1):55-64

Estimated proportional contribution of direct and indirect costs to the overall economic burden of insomnia to a sample of Quebec patients



Daley M et al. Sleep 2009; Vol. 32, No. 1:55-64

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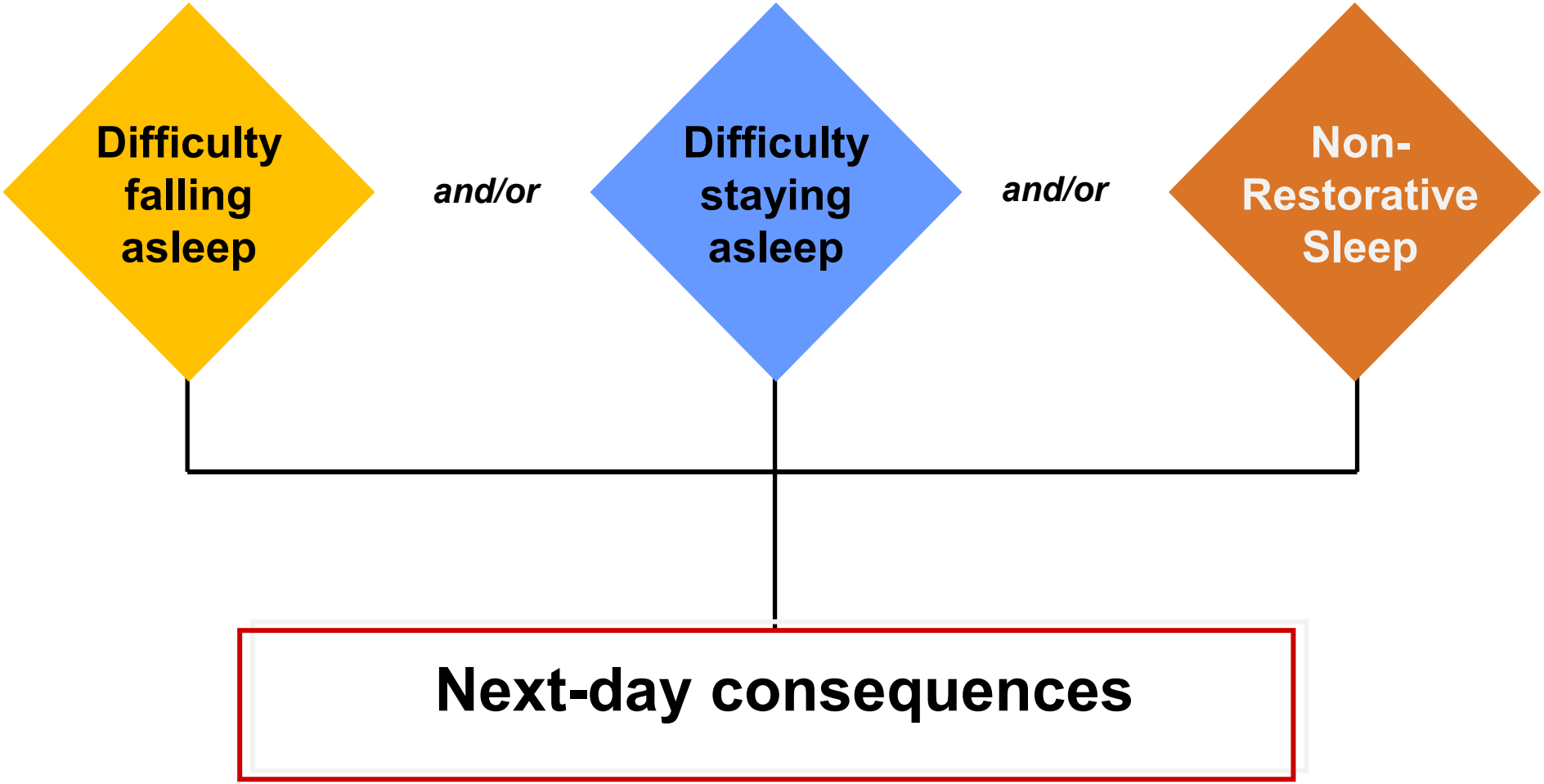
Diagnostic Measurements

What is Insomnia?



American Psychiatric Association. DSM-IV-TR. Washington DC: APA, 2000:1-982

Insomnia: Definition and Classification

DSM-IV TR Definition

- Difficulty initiating sleep *and/or*
- Difficulty maintaining sleep *and/or*
- Non-restorative sleep

PLUS

- Next-day consequences

Duration

- Transient (acute)
- Chronic (long-term)

Etiology

- Primary
- Secondary

American Psychiatric Association. DSM-IV-TR. Washington DC: APA, 2000:1-982

Insomnia: Definition & Classification in DSM-5

Classification changes from DSM-IV-TR to DSM-5
Insomnia renamed as insomnia disorder
Primary and secondary distinction removed
Frequency criteria changed to at least 3 nights per week
Duration changed to 3 months

Center for Behavioral Health Statistics and Quality (2016). Impact of the DSM-IV to DSM-5 Changes on the National Survey on Drug Use and Health. Substance Abuse and Mental Health Services Administration, Rockville, MD: 1-262.

Insomnia Efficacy Measures

- Sleep onset latency: duration of time it takes to transition from wakefulness to sleep
- Subjective sleep latency: subject's perspective of sleep latency via self assessment
- Total sleep time (TST): total amount of time spent sleeping
- Sleep efficiency: percentage of time spent sleeping
- Wake after persistent sleep onset (WASO): period of wakefulness after sleep onset
- Sleep diary: self-reported tool used to document sleep quality

1. McCall C., McCall W. Comparison of actigraphy with polysomnography and sleep logs in depressed insomniacs. J Sleep Res. 2012 (DOI: 10.1111/j.1365-2869.2011.00917.x)
2. Shrivastava D, et al.J Comm Hospital Internal Med Perspectives. 2014. 25;4(5):24983 3. O'Donnell D et al. J Sleep Res. 2009;18(2): 254–263,
4. https://encyclopedia.thefreedictionary.com/Sleep+diary Accessed February 13, 2021.

Insomnia and Specific Sleep Disturbances Can Be Assessed in Clinical Interviews

Insomnia is primarily diagnosed by clinical evaluation through sleep, medical, substance use, and psychiatric history[1]

- Self-administered questionnaires, at-home sleep logs, symptom checklists, psychological screening tests, and bed partner interviews are used for evaluation[1]
- Interviews can help explain the nature, history, and severity of sleep difficulties[2]

Reliable, efficient, and validated self-report instruments are available for use in adults[3]

- Insomnia Severity Index (ISI)
- Athens Insomnia Scale (AIS)
- Pittsburgh Sleep Quality Index (PSQI)
- Sleep Quality Index (SQI)
- Epworth Sleepiness Scale (ESS)
- 12-Item General Health Questionnaire (GHQ-12)

PSQI has 19 self-rated questions assessing sleep quality factors, including[4]

Subjective sleep quality
Sleep latency
Sleep duration
Habitual sleep efficiency
Sleep disturbances
Use of sleeping medications
Daytime dysfunction

1. Schutte-Rodin et al. *J Clin Sleep Med.* 2008;4:487-504. 2. Bastien et al. *Sleep Med.* 2001;2:297-307. 3. Chung et al. *Sleep Med.* 2011;12:463-470. 4. Buysse et al. *Psychiatry Res.* 1988;28:193-213.

Measurements

- **Polysomnography** – laboratory study used to diagnose sleep disorders usually occurring overnight. Consists of several measures including the following
  - Electroencephalogy (EEG) – measures brain activity
  - Eletrooculography (EOG) – measures eye movements
  - Electromyography (EMG) – measures muscle activity
  - Electrocardiography (EKG) – measures heart activity

- **Actigraphy** – device that monitors rest and/or activity cycles usually worn for several days

1. Armon PSG Medscape 2020. https://emedicine.medscape.com/article/1188764 Accessed February 13, 2021.
2. McCall C., McCall W. Comparison of actigraphy with polysomnography and sleep logs in depressed insomniacs. J Sleep Res. 2012 (DOI: 10.1111/j.1365-2869.2011.00917.x

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Sleep Impairment in Psychiatric Disorders

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Sleep Disturbances in Patients with Major Depressive Disorder (MDD)

Sleep Pathology in MDD

- Sleep in depression exhibits pathognomonic changes:
  - Prolonged sleep latency
  - Early awakening in the morning
  - Slow wave sleep reduction
  - REM sleep latency shortened
  - First REM sleep period prolonged

MDD, major depressive disorder; REM, rapid eye movement

Winokur et al. Depression and Anxiety 2001;14:19–28

Sleep Pathology in MDD

- Reduction of slow wave sleep
- The *pattern* of **REM sleep** is altered
  - REM sleep latency shortened
  - Increased REM during first ½ of night
- The *density* of REM sleep
- Increased sleep latency, wake time and early morning awakenings

MDD, major depressive disorder; REM, rapid eye movement

Winokur et al. Depression and Anxiety 2001;14:19–28.

Antidepressants Effects on Sleep Architecture

- SSRIs decrease REM sleep
- Reduction in the overall amount of REM sleep observed with most antidepressants
- Increased REM onset latency
- Mixed effects on sleep continuity
- Mixed effects on slow wave sleep

SSRI, selective serotonin reuptake inhibitor; REM, rapid eye movement

Winokur et al. Depression and Anxiety 2001;14:19–28.

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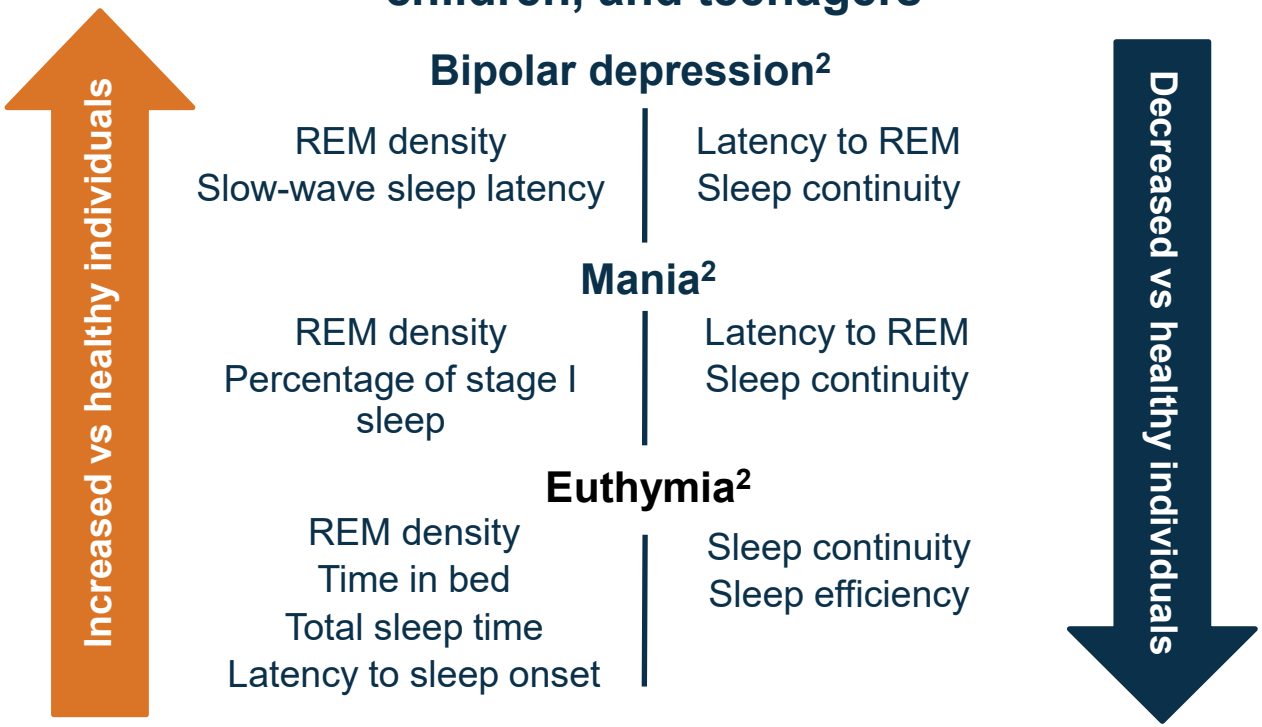
Sleep Disturbances in Patients with Bipolar Disorder (BD)

Sleep May be Altered in All BD Phases

Sleep disturbance throughout BD phases is common in adults, children, and teenagers[1]



Evening chronotype, measured by actigraphy and questionnaires, is characteristic of patients with BD[3,4]

BD, bipolar disorder; REM, rapid eye movement.

1. Harvey et al. *Clin Psychol (New York)*. 2009;16:256-277. 2. Gold and Sylvia. *Nat Sci Sleep*. 2016;8:207-214. 3. Melo et al. *Sleep Med Rev*. 2017;34:46-58. 4. Gershon et al. *J Affect Disord*. 2018;225:342-349.

Sleep Alterations Differ Between Mania and Bipolar Depression

Mania: decreased sleep[1]

- Unmedicated manic patients demonstrate[1]
  - Shortened total sleep time
  - Increased time awake in bed
  - Shortened REM latency
  - Daytime motor hyperactivity

Bipolar depression: hypersomnia and severe insomnia[1,2]

- Hypersomnia has been reported in 17% to 78% of patients with BD
- Hypersomnia in bipolar depression may differ from unipolar depression and primary sleep disorders with[1]
  - More early morning awakenings
  - Greater total REM density
  - Fatigue instead of true excessive daytime sleepiness

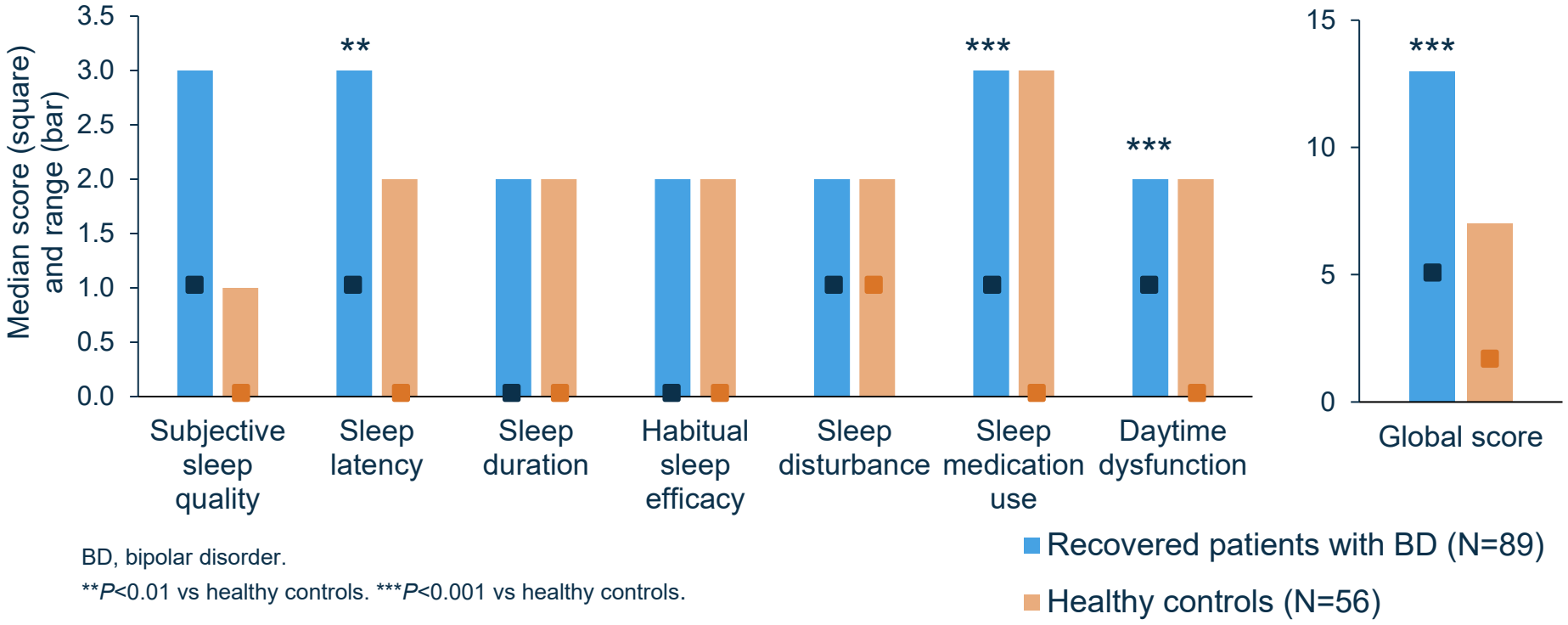
It remains unknown whether sleeplessness is a prodromal symptom or a cause of mania[1]

BD, bipolar disorder; REM, rapid eye movement.

1. Plante and Winkelman. *Am J Psychiatry*. 2008;165:830-843. 2. Gold and Sylvia. *Nat Sci Sleep*. 2016;8:207-214. 3. Kaplan and Harvey. *Sleep Med Rev*. 2009;13:275-285.

Sleep Disturbance is Common in Patients with BD, Even in Recovered Phase

Compared with healthy controls, recovered patients with BD had worse global sleep, including longer sleep latency and more daytime dysfunction, and more sleep medication use



BD, bipolar disorder.

**P<0.01 vs healthy controls. ***P<0.001 vs healthy controls.

Cretu et al. *J Affect Disord*. 2016;190:162-166.

Sleep Affects Many Aspects of Life in Patients with BD

Sleep loss can

- Impair quality of life[1]
- Worsen health and reduce likelihood of engaging in healthy behaviors[1,2]
- Contribute to relapse and mood episode recurrence[1,2]
- Disrupt affect regulation[1]
- Adversely affect cognitive functioning[1,2]
- Contribute to impulsivity and risk taking[1]

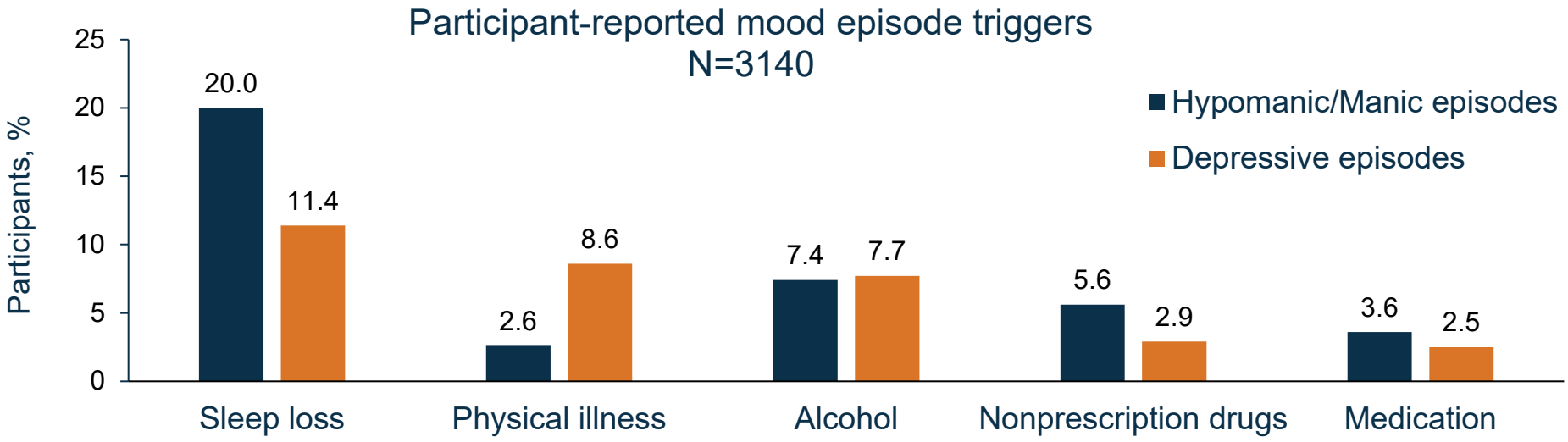
Sleep loss is associated with

- Increased substance use[1]
- Increased risk of suicidal ideation and attempts[2]

1. Harvey et al. *Clin Psychol (New York)*. 2009;16:256-277. 2. Gold and Sylvia. *Nat Sci Sleep*. 2016;8:207-214.

Sleep Loss is a Reported Trigger of Mood Episodes in BD

Patients with BD reported that sleep loss was the most common trigger for hypomanic/manic episodes



More patients with BD I than BD II, and more women than men, reported that sleep loss was a trigger for a manic or hypomanic episode

BD, bipolar disorder; BD I, bipolar I disorder; BD II, bipolar II disorder.

Lewis et al. *Br J Psychiatry*. 2017;211:169-174.

Some Insomnia Pharmacotherapies May Affect BD Symptoms

Benzodiazepines	• Unknown whether use in patients with BD alters mood stability •Risks can include abuse, tolerance, withdrawal, daytime sedation, and motor/cognitive impairment
Benzodiazepine receptor agonists	• Less daytime carryover and side effects than benzodiazepines • Risks can include tolerance and withdrawal
Low-dose sedating antidepressants	• Most commonly used to treat chronic insomnia • Risks can include rare mania induction in patients with BD
Anticonvulsants	• Not associated with mania; some anticonvulsants may help stabilize mood • Can improve sleep quality, decrease light sleep, and increase REM sleep and possibly slow-wave sleep • Risks can include cognitive impairment and daytime sedation
Atypical antipsychotics	• Potential to increase total sleep time and sleep quality in healthy subjects • Paradoxically, some can induce or worsen sleep-related disorders • Risks can include weight gain, metabolic abnormalities, daytime sedation, and extrapyramidal symptoms (eg, akathisia)

BD, bipolar disorder; REM, rapid eye movement.

Plante and Winkelman. Am J Psychiatry. 2008;165:830-843.

Schizophrenia and Bipolar Disorder May Share Sleep-Circadian Rhythm Phenotypes

- Patients with remitted schizophrenia may have a sleep-circadian phenotype distinguished by:
  - Longer total sleep time, extended sleep latency, elevated wake after sleep onset, and decreased motor activity
- Comparable findings are found in patients with bipolar disorder however the effects are greater for patients with schizophrenia

Meyer N, et al. Sleep and circadian rhythm disturbance in remitted schizophrenia and bipolar disorder: a systematic review and meta-analysis [published online March 10, 2020].Schizophr Bull.doi:10.1093/schbul/sbaa024

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Sleep Disturbances in Patients with Schizophrenia (SZ)

Sleep Pathology in Schizophrenia

- Between 30-80% of individuals diagnosed with schizophrenia (SZ) experience sleep disturbances
- Different sleep dysfunctions may be present throughout the course of their illness-transient
- Sleep medication or antipsychotics with sedative properties may influence sleep quality

The Interplay Between Sleep & Physical Activity For Patients Living With Schizophrenia. Mental Health and Physical Activity, April 2018

Sleep Pathology in Schizophrenia

Figure 1. Common Sleep Disturbances Experienced By Individuals Living With Schizophrenia

Difficulty Initiating / Maintaining Sleep

Advanced Sleep Syndrome

Hypersomnia With Short Naps

Reduced Sleep Efficacy
(Ratio Of Time Asleep To Time Spent In Bed)

Reduced Total Sleep Time

Increased Sleep (Onset) Latency
(Amount Of Time It Takes To Fall Asleep)

Decreased Slow Wave Sleep
(Deep Sleep, Non-Rapid Eye Movement (REM))

Decreased REM Latency
(Time From Sleep Onset To First REM Sleep)

Figure 1 developed by PsychU. Source: Costa, R., et. al. (2018). Sleep quality in patients with schizophrenia: The relevance of physical activity. *Mental Health & Physical Activity, 14*, pp. 140-145. Retrieved from http://doi.org/10.1016/j.mhpa.2018.04.004.

Sleep Pathology in Schizophrenia: Positive and Negative Symptoms

Positive symptoms

- Short REM latency
- Reduced sleep efficiency
- Proportion of hours slept to hours spent in bed-poor sleep efficiency
- Increased sleep latency

Negative symptoms

- Short REM latency
- Slow-wave sleep deficits

REM, rapid eye movement

Costa R et al. Mental Health and Physical Activity 2018;14:140–145

Sleep Pathology in Schizophrenia

- Patients often express treatment goals involving taking less medication, **nonpharmacological interventions**
- Patients with schizophrenia exhibit unhealthy lifestyle choices such as:
  - Lack of physical activity
  - Poor diet
  - High rates of cigarette smoking
- Around 30–80% of patients suffer from disturbed sleep in the early phase
- Sleep disturbance occurs before psychotic symptoms and often after other symptoms have been treated
- Increased physical activity may provide an alternative avenue to addressing sleep dysfunction

Costa R et al. Mental Health and Physical Activity. 2018;14:140-145.

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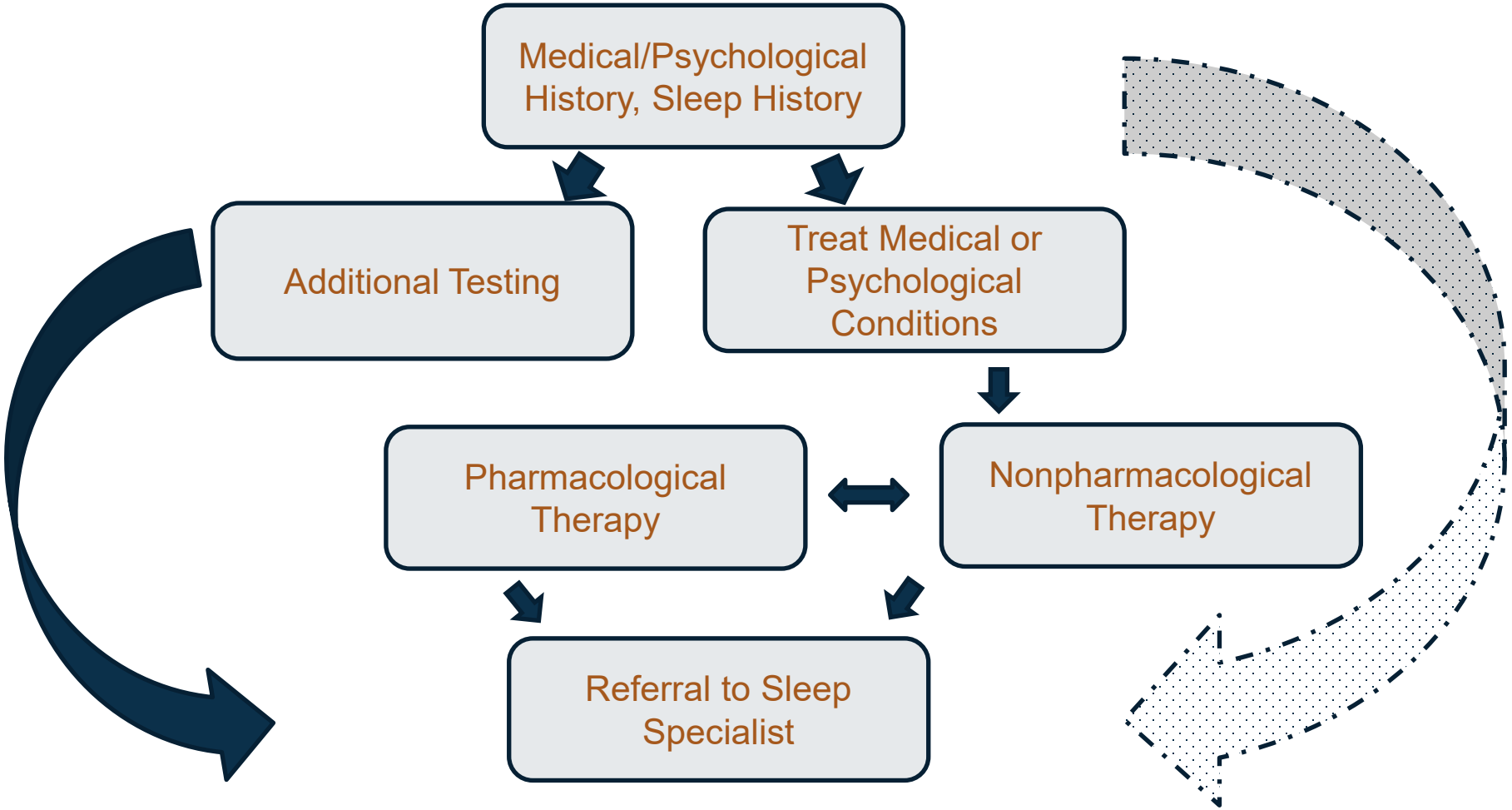
Sleep Medicine Therapeutics

Management of Insomnia



Maness DL and Muneeza K. American Family Physician 2015;92(12):1058-1064

Classes of Sleep Medicines

- Benzodiazepine receptor agonists
- Melatonin receptor agonists
- Dual orexin receptor antagonists
- Histamine H1 receptor antagonists
- Sedating antidepressants

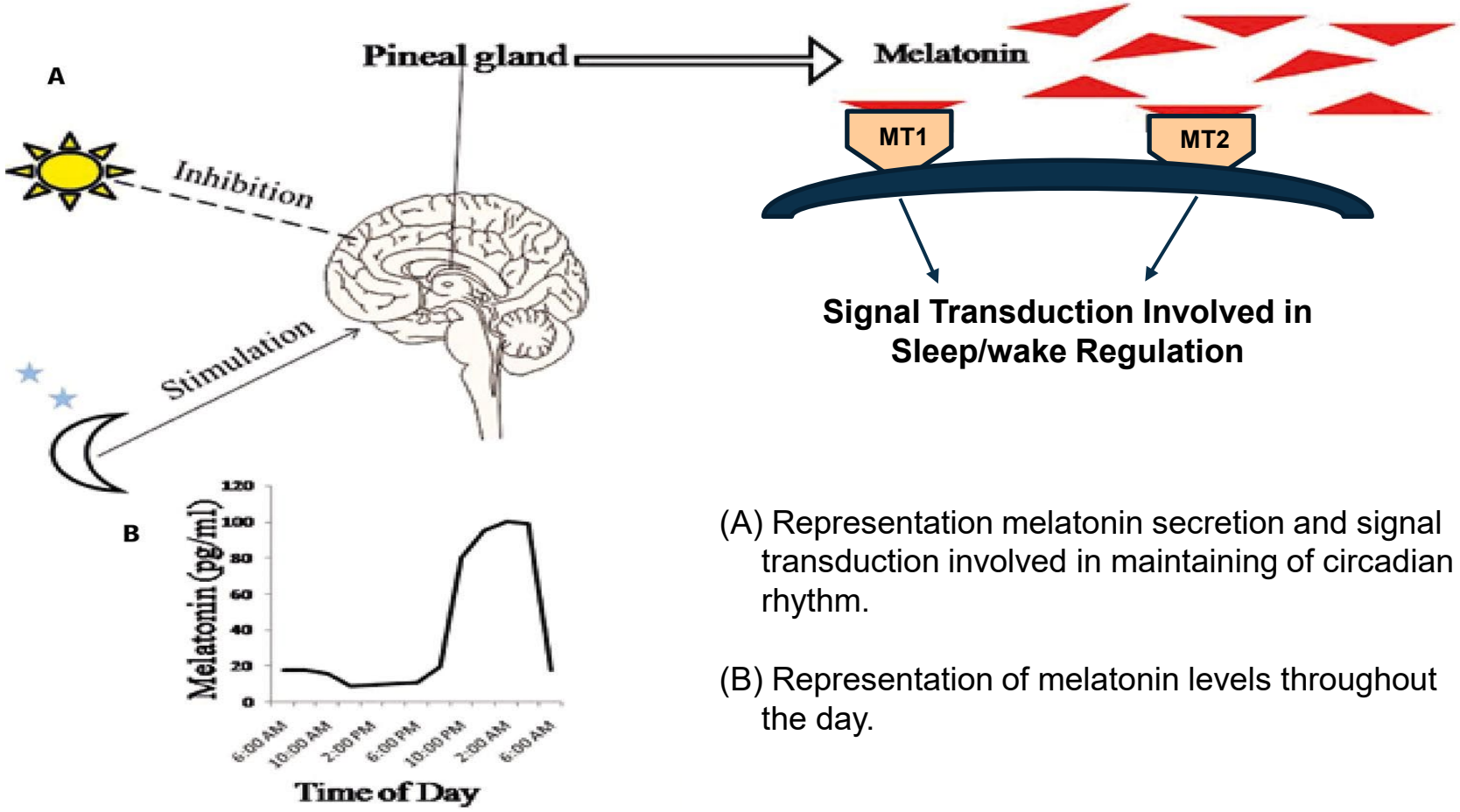
1. E.S. Ford et al. Trends in Outpatient Visits for Insomnia, Sleep Apnea, and Prescriptions for Sleep Medications among US Adults: Findings from the National Ambulatory Medical Care Survey 1999-2010. SLEEP 2014;37(8):1283-1293..
2. Lie E et al. Pharmacological Treatment of Insomnia. P&T. 2015;40(11):759-765.

Benzodiazepine Receptor Antagonists (BzRAs)

- Many of the agents in this drug class are FDA approved for insomnia
- All bind to the $GABA_A$ receptor
  - **Benzodiazepines** are full and non-selective GABA receptor alpha subunit agonists.
  - **Non-benzodiazepines** (also identified as 'Z drugs') are selective alpha-1 subunit agonists. This selectivity at this subunit is thought to result in fewer abusive side effects.
- Due to the addictive nature of this class, all are Schedule IV controlled substances

1. Mendelson WB. Sleep Med Reviews 2004;8:7-17.
2. Lie E et al. Pharmacological Treatment of Insomnia. P&T. 2015;40(11):759-765.

Melatonin Receptor Agonists



(A) Representation melatonin secretion and signal transduction involved in maintaining of circadian rhythm.

(B) Representation of melatonin levels throughout the day.

MT, melatonin receptor

Sharma S et al. Arch. Endocrinol. Metab. 2015;59(5):391-399

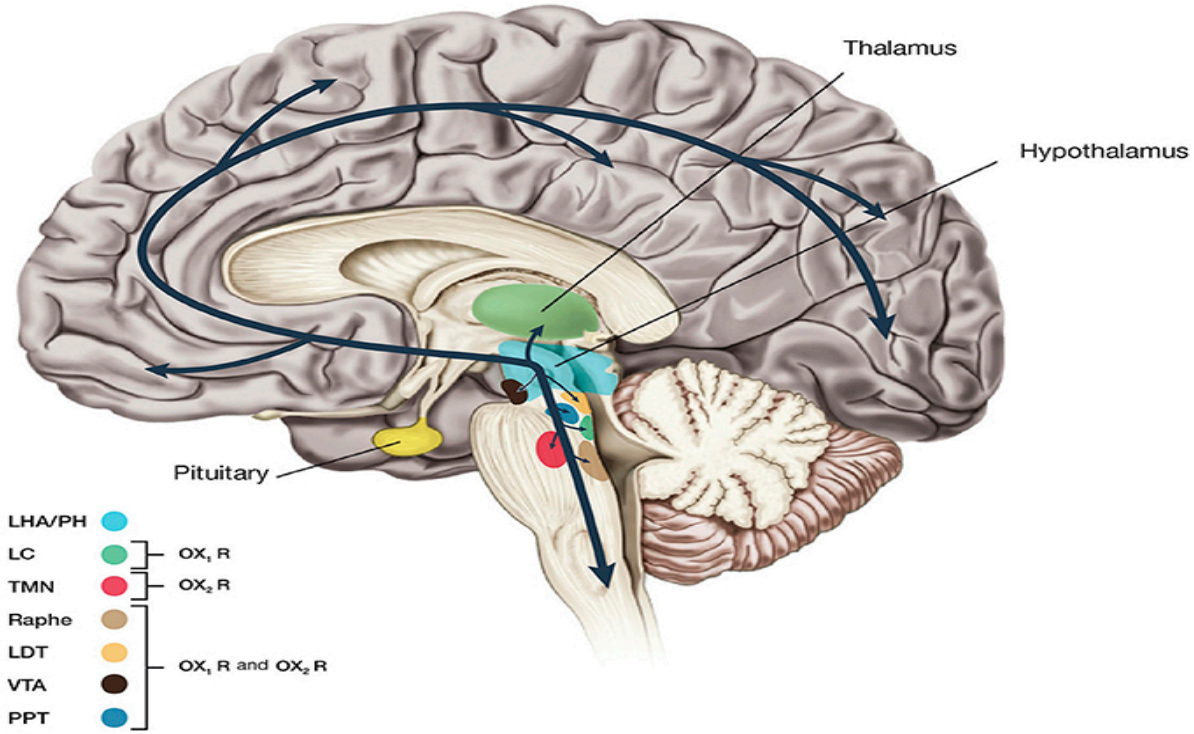
Histamine Receptor Agonist/Antagonist

- Histamine H1 receptors also known as ‘Antihistamines’
- Strong and consistent evidence exist to suggest that histamine, acting via H_1 and/or H_3 receptor has a pivotal role in the regulation of sleep-wakefulness
- Administration of histamine or H_1 receptor agonists induced wakefulness, whereas administration of H_1 receptor antagonists promoted sleep

M. Thakkar. Sleep Med Rev. 2011 February ; 15(1): 65–74.

Orexin/Orexin Receptors

- Orexins-hypothalamus. Orexins are involved in wakefulness and arousal.



The orexin neuropeptide signaling system is a central promoter of wakefulness. Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors orexin receptor type 1 (OX1) and orexin receptor type 2 (OX2) is thought to suppress wake drive.

LHA, lateral hypothalamic area; PH, posterior hypothalamus; LC, locus ceruleus; OX1R, orexin 1 receptor; OX2R, orexin 2 receptor; TMN, tuberomammillary nucleus; LDT, laterodorsal tegmental nucleus; PPT, pedunculopontine tegmental nucleus; VTA, ventral tegmental area

1. Chieffi et al. Orexin System: The Key for a Healthy Life. Frontiers in Physiology 2017;8:357
2. Wang C et al. Front. Mol. Neurosci. 2018;11:220. Section A and B

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