



Assessment and Management of Sleep Disorders in the Context of Anxiety

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Disclosures

If you have disclosures, state:

“My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

I am the author of the book “Almost Depressed” and have received payments from Harvard health Publications

“...The subject of sleeplessness is once more under discussion. The hurry and excitement of modern life is quite correctly held to be responsible for much of the insomnia of which we hear; and most of the articles and letters are full of good advice to live more quietly and of platitudes concerning the harmfulness of rush and worry.”

Sleeplessness. The British Medical Journal 1894:719.

“Expected” Sleep Parameters in Youth

<u>Age</u>	<u>Total sleep time</u>	<u>Naps (on average)</u>
• 0 to 2 months	16 to 18 hours	3.5 per day at 1 month of age
• 2 to 12 months	12 to 16 hours	2 per day at 12 months of age
• Most children 6 to 9 months of age sleep through the night		
• 1 to 3 years	10 to 16 hours	1 per day at 18 months of age
• 3 to 5 years	11 to 15 hours	50% of 3-year-olds do not nap
• 5 to 14 years	9 to 13 hours	5% of Cau & 39% of AA nap at 8 years of age
• 14 to 18 years	7 to 10 hours	Napping in this age group suggests insufficient sleep or a possible sleep disorder

Iglowstein I, Jenni OG, Molinari L, and Largo RH: Sleep duration from infancy to adolescence: reference values and generational trends. Pediatrics 2003; 111: pp.302-307

Crosby B, LeBourgeois MK, and Harsh J: Racial differences in reported napping and nocturnal sleep in 2- to 8-year-old children. Pediatrics 2005; 115: pp. 225-232

Common Sleep Disorders in Youth

- INSUFFICIENT SLEEP
- DELAYED SLEEP-PHASE SYNDROME
- POOR SLEEP HYGIENE
- RESTLESS LEG SYNDROME
- OBSTRUCTIVE SLEEP APNEA
- PARASOMNIAS
- NARCOLEPSY
 - POST H1N1 VACCINATION in EUROPE

Reiter, Joel & Rosen, Dennis. The diagnosis and management of common sleep disorders in adolescents. *Current Opinion in Pediatrics*. 26(4):407-412, August 2014.

Sleep-Wake Disorders in DSM-5

- **Breathing-Related Sleep Disorders**
 - obstructive sleep apnea hypopnea, central sleep apnea, and sleep-related hypoventilation.
- **Circadian Rhythm Sleep-Wake Disorders**
 - advanced sleep phase syndrome, irregular sleep-wake type, and non-24-hour sleep-wake type; jet lag type removed.
- **Rapid Eye Movement Sleep Behavior Disorder and Restless Legs Syndrome**
 - In DSM-IV, both were included under dyssomnia not otherwise specified

DSM-V, APA 2013

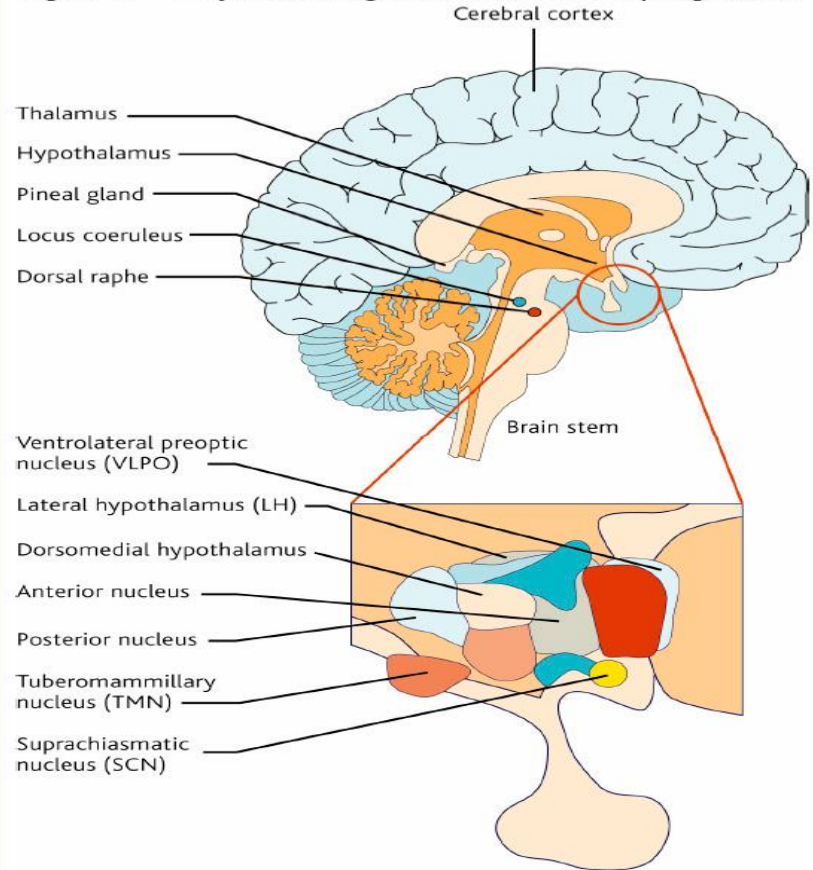
Disordered Sleep in Common Psychiatric Conditions

- AUTISM
- ATTENTION-DEFICIT/HYPERACTIVITY DISORDER
- ANXIETY DISORDERS
- DEPRESSION
- BIPOLAR
- SUBSTANCE USE DISORDERS
- TRAUMA RELATED CONDITIONS

The Balance of Sleep and Wakefulness

- Tubermammillary nucleus (TMN) of the hypothalamus promotes wakefulness (produces histamine) = **WAKE PROMOTER**
- Suprachiasmatic nucleus (SCN) of the hypothalamus is activated by light, melatonin; this area acts as **THE SWITCH** and **INTERNAL CLOCK**; promoting either sleep or wakefulness
- Ventrolateral preoptic area (VLPO) of the hypothalamus promotes sleep (produces GABA)= **SLEEP PROMOTER**

Figure 1 : Major brain regions involved in sleep regulation



Based on controlled clinical trials, we can conclude that...

- Behavioral treatments for young children result in significant improvements for
 - sleep-onset latency,
 - night waking frequency, and
 - night waking duration.
- Currently very low-quality evidence exists for the treatment of insomnia in
 - older children and adolescents,
 - children with neurodevelopmental disorders, mood disorders, and/or chronic illnesses

Meltzer LJ, Mindell JA. Systematic Review and Meta-Analysis of Behavioral Interventions for Pediatric Insomnia. (2014) *Journal of Pediatric Psychology* 39 (8): 932-948

Summary of Cognitive Behavior Therapy for Insomnia

- Cognitive therapy
 - Focuses on changing false beliefs and attitudes about sleep (e.g., everyone needs at least 8 hours of sleep for good health)
- Sleep hygiene education
 - No pets in the bedroom
 - No caffeine consumption after 4 p.m.
 - Keep bedroom cool and conducive to sleep
 - No watching the bedroom clock

Pediatric Sleep Pharmacotherapy

- Need for sleep biologic
- Children learn how to sleep and/or form associations with sleep from families
 - Parental Expectations
 - Cultural Background
- Paucity of Evidence
 - Off label use of Medications for Sleep
 - Antihistamine & clonidine most used
 - Use of Antipsychotics “concerning”

Stojanovski SD, Rasu RS, Balkrishnan R, et al. Trends in medication prescribing for pediatric sleep difficulties in US outpatient settings. Sleep 2007;30:1013–7

2007;30:1013–7

Pediatric Sleep Pharmacotherapy

- Sedation ≠ Refreshing Sleep
 - “...she became hyper” or
 - “...he didn’t sleep at all!” or
 - “...got a second wind”
- Dose
 - Inclination to give lowest dose
 - If too low then may be drowsy without sleep
- Timing
 - Empty stomach (except Trazodone)

Pelayo R & Yuen K. Pediatric Sleep Pharmacology. Child Adolesc Clin N Am (2012) 861-883.

Diphenhydramine (Benadryl)

- Lipid Soluble Competitive H₁-Blocker
- Peaks within 2 hours
- Decrease in sleep latency Number of awakenings
- Half-life in children 5.4 ± 1.8 hours
- Usual duration of effect 4-6 hours
- Dose in children 0.5 mg/kg to 25 mg
- AEs: impaired consciousness; anticholinergic effects

Simons KJ, Watson WT, Martin TJ, et al. Diphenhydramine: pharmacokinetics and pharmacodynamics in elderly adults, young adults, and children. *J Clin Pharmacol* 1990;30:665–71.

Chloral Hydrate

- Produces sleep within 1 hour; Tolerance possible
- Half-Life 8-12 hours in children, longer in infants
- Usual dose range: 25-50 mg/kg to max 1 gram; Higher doses 80-100 mg/kg have been given with good effect and minimal toxicity
- AE:
 - Respiratory in OSA, wheezing, Encephalic White Matter Diseases & Brain Stem Disorders
 - In youth on stimulants, rare reports of malignant cardiac arrhythmias
 - Increased sedation reported in pt on fluoxetine

Pershad J, Palmisano P, Nichols M. Chloral hydrate: the good and the bad. *Pediatr Emerg Care* 1999;15:432–5.

Melatonin

“...no evidence that melatonin is effective in treating secondary sleep disorders or sleep disorders accompanying sleep restriction, such as jet lag and shift work disorder.”

Buscemi N, Vandermeer B, Hooton N, et al. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. BMJ 2006;332:385–93.

Using Melatonin

- OTC: pursue well made grade
- Not FDA regulated
- Timing of the dose is the Key
- **Most effective Time to dose is 5-6 hours before Dim Light Melatonin Onset (DLMO)**
- DLMO roughly occurs 9-10 hours after awakening
- Usual dose range: 500 mcg to 10 mg
- National Sleep Foundation warms about use due to concerns regarding immune effects

van Geijlswijk IM, Korzilius HP, Smits MG. The use of exogenous melatonin in delayed sleep phase disorder: a meta-analysis. *Sleep* 2010;33:1605–14.

George

- 7 yo fraternal twin with Smith-Magenis Syndrome; not sleeping; built his own room; risperidone 0.5 mg TID helpful for aggression.
- Beta-blocker in AM
- Melatonin 6 mg given at 4 PM

Hoebert M, van der Heijden KB, van Geijlswijk IM, et al. Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. J Pineal Res 2009;47:1–7.

Clonidine

- Centrally acting alpha₂ agonist
- Half-life 6-24 hours
- Onset of Action 1 hour
- Duration of Effect 2-4 hours
- AEs: hypotension, bradycardia, irritability, nightmares, anticholinergic effects, REM Suppression
- Usual Dose Range: 0.025-0.3 mg

Prince JB et al., Clonidine for sleep disturbances associated with attention-deficit hyperactivity disorder: a systematic chart review of 62 cases. J Am Acad Child Adolesc Psychiatry. 1996 May;35(5):599-605.

Benzodiazepines

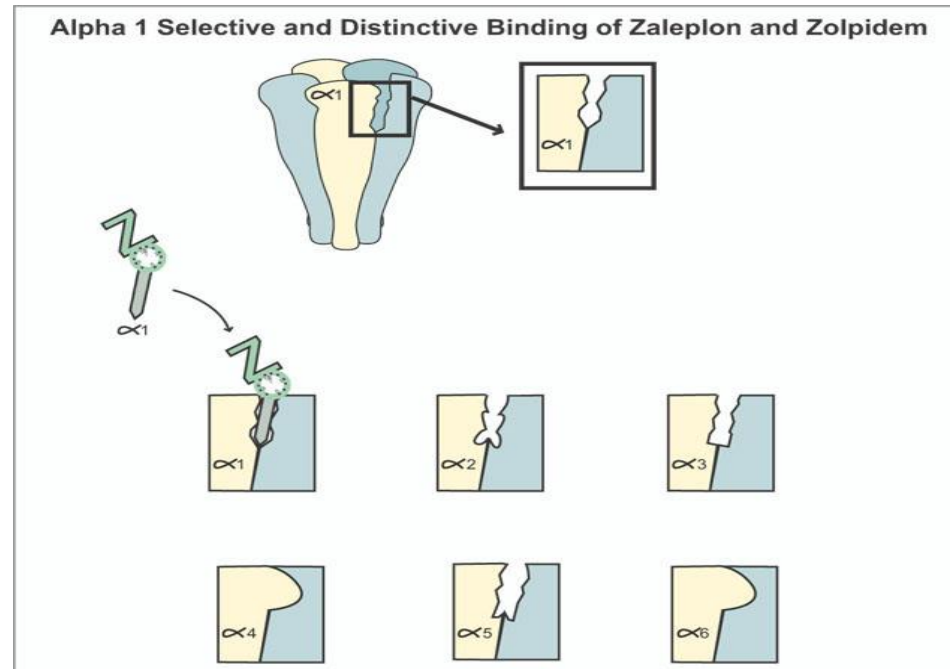
- Used extensively in adults, less commonly in youth
- Activation of GABA receptor
- May alter normal sleep architecture
 - Atypical sleep spindles
 - Suppression of SWS
- Exception is clonazepam (discussed later)

Nonbenzodiazepine Hypnotics

- Zolpidem (IR and XR; Ambien)
- Eszopiclone (Lunesta)
- Zaleplon (Sonata)
- Off label in Children
 - Adjunctive to behavioral treatments
- Preserve overall sleep architecture
- Do not usually have insomnia rebound seen with BZDs.
- Administer “..as being put to...” bed

Alpha 1 Selective Hypnotics - Zaleplon and Zolpidem

- The hypnotics zaleplon and zolpidem bind selectively to GABA-A receptors that contain the **alpha 1 subunit (sleep)**. This subunit is important for sedation and possibly for anticonvulsant and amnesic actions.



Zolpidem (Ambien): FDA Warning

“...announcement was focused on women because they take longer to metabolize the drug than men. An estimated 10 percent to 15 percent of women will have a level of zolpidem in their blood that could impair driving eight hours after taking the pill, while only about 3 percent of men do, said Dr. Robert Temple, an official in the agency’s Center for Drug Evaluation and Research.

“Drug Agency Recommends Lower Doses of Sleep Aids for Women.” By S. TAVERNISE NYT January 10, 2013

Zolpidem (Ambien)

- Standard Adult Dose
 - 5-10 mg of IR; 12.5 mg ER; Empty stomach helpful
- Rapid Onset of action, shorten sleep latency
- Half-Life 2.5 hours (may be longer in women)
- Recommended dose range: 0.25 mg/kg-20 mg
- Clearance in Children 3 times higher than in adults
- In youth, lower doses may be ineffective or associated with frightening epiphenomena
- Not efficacious in 8-wk DBPC Trial with ADHD

Salva P, Costa J. Clinical pharmacokinetics and pharmacodynamics of zolpidem. Therapeutic implications. Clin Pharmacokinet 1995;29:142–53.

Blumer JL, Findling RL, Shih WJ, et al. Controlled clinical trial of zolpidem for the treatment of insomnia associated with attention-deficit/hyperactivity disorder in children 6 to 17 years of age. Pediatrics 2009;123:e770–6.

Zaleplon (Sonata)

- Standard Adult Dose 10 mg
- Rapid Onset of action, shorten sleep latency
- Half-Life 1 hour
 - ? Minimize next day sedation
 - May be Useful in Middle of Night Awakenings?

Zammit GK, Corser B, Doghramji K, et al. Sleep and residual sedation after administration of zaleplon, zolpidem, and placebo during experimental middle-of-the-night awakening. J Clin Sleep Med 2006;2:417–23

Eszopiclone (Lunesta)

- Longer half-life (6 hours in adults)
- No studies in youth

Roth T, Walsh JK, Krystal A, et al. An evaluation of the efficacy and safety of eszopiclone over 12 months in patients with chronic primary insomnia. Sleep Med 2005;6:487–95.

Off Label Use of Neuroleptics

- Facilitate Sleep
- May Increase SWS
- Used off label to treat insomnia in adults
- Tempting to consider for insomnia in youth
- Routine Use to Treat Sleep Disorders in Youth **not recommended**

Pelayo R & Yuen K. Pediatric Sleep Pharmacology. Child Adolesc Clin N Am (2012) 861-883.

Parasomnias

- Undesirable events or experiences during onset, within or during arousal from sleep.
- Sleep paralysis, night terrors, sleepwalking & confusional arousals.
- Nocturnal Seizure or Parasomnia?
- Epilepsy versus Parasomnia

International classification of sleep disorders. 2nd edition. Westchester (IL): American Academy of Sleep Medicine; 2005.

Lahorgue Nunes M, et al. Sleep organization in children with partial refractory epilepsy. *J Child Neurol* 2003;18:763–6.

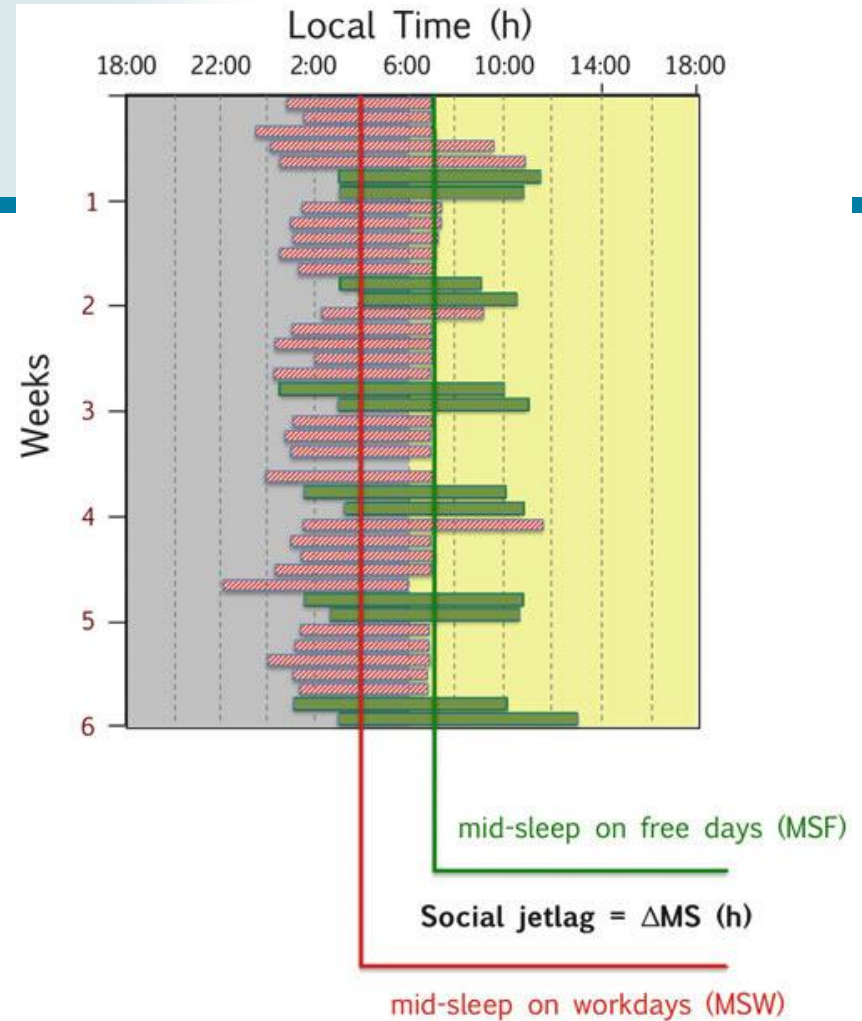
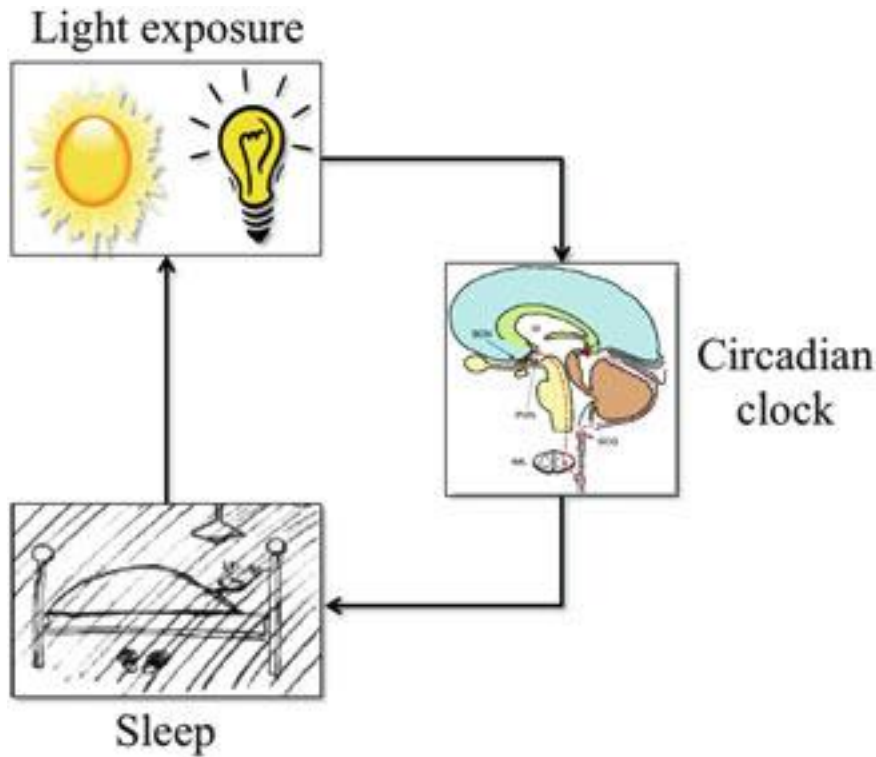
Kotagal P. The relationship between sleep and epilepsy. *Semin Pediatr Neurol* (2001);8:241–50.

Clonazepam for Parasomnias in Youth

- Rapidly absorbed after oral administration
- Onset 20-60 minutes
- Peaks 1-3 hours
- Duration 6-8 hours in youth
- Half-life 30-40 hours
- Extensively hepatically metabolized
- Initial dosing 0.25-0.5 mg
- Extensively studied in adults by Schenck et al.

Attarian H. Treatment options for parasomnias. *Neurol Clin* 2010;28:1089–1106.
Pelayo R, Dubik M. Pediatric sleep pharmacology. *Semin Pediatr Neurol* 2008;
15:79–90.

Social Jet Lag



Till Roenneberg, Thomas Kantermann, Myriam Juda, Céline Vetter, Karla V. Allebrandt.
 Light and the Human Circadian Clock. Handbook of Experimental Pharmacology
 Volume 217, 2013, pp 311-331.

Children's Media Use and Sleep Problems: Issues and Unanswered Questions

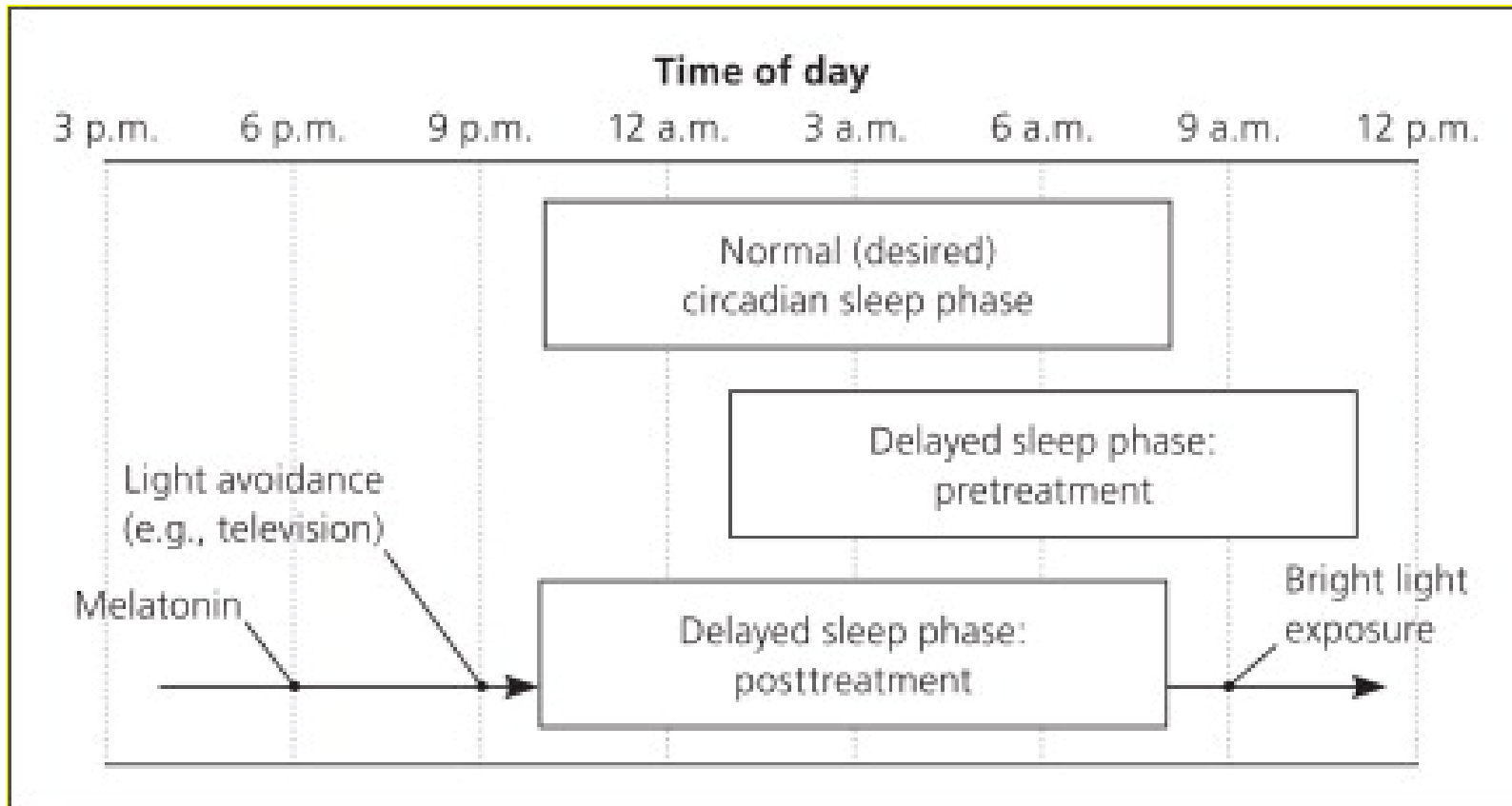
- TV in Bedroom 8.5 hours/day
- No TV in Bedroom 5.5 hours/day



<http://justgetflux.com/>

Zimmerman, FJ. Kaiser Family Foundation. June 2008.

Delayed Phase Disorder



Carter KA, Hathaway NE & Lettieri CF. Common Sleep Disorders in Children. (2014). American Family Physician 89 (5): 368-377.

Sleep and Headache in Children

- Treatment (behavioral &/or pharmacologic) of insomnia, sleep apnea, sleep bruxism and restless legs syndrome often leads to an improvement of migraine
- Serotonergic and Dopaminergic compounds are commonly used
 - for sleep disorders and
 - for migraine prophylaxis and treatment
- Pharmacological Treatment, Education and Lifestyle Modification including sleep hygiene can significantly reduce migraine

Guidetti V, Dosi C, Bruni O. Cephalalgia. 2014 Sep;34(10):767-76.

Sleep Disorders in Youth

KEY POINTS

- Sleep disorders in adolescents are both very common and underdiagnosed.
 - Insufficient sleep is ubiquitous in adolescents and affects both physical and mental health.
 - Delayed sleep-phase syndrome is often the cause of insufficient sleep and easily amenable to treatment.
 - Additional sleep disorders in adolescents include obstructive sleep apnea, parasomnias, and narcolepsy.
-

Reiter, Joel & Rosen, Dennis. The diagnosis and management of common sleep disorders in adolescents. *Current Opinion in Pediatrics*. 26(4):407-412, August 2014.

“...people worry whether they get sufficient sleep, especially if they sleep less than the magic number...”

van Vugt H. Sleep in context. In: Westerink J, Ouwerkerk M, Krans M, eds. *Sensing emotions: the impact of context on experience measurements.* New York: Springer, 2011.

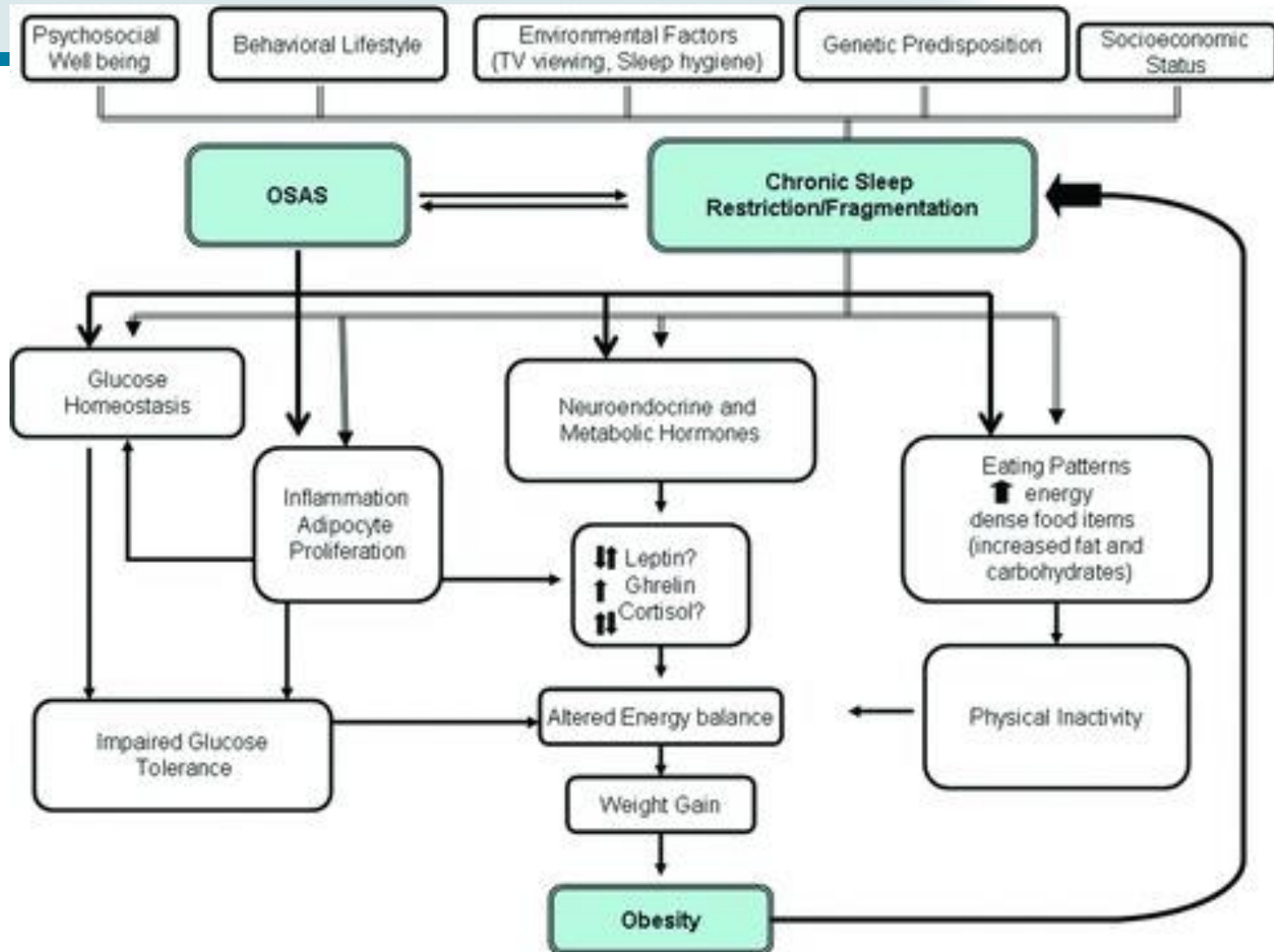
“...my most significant finding is that ignorance is the worst sleep disorder of all.”

William Dement, a professor at Stanford University and a leading sleep researcher



**EXTRA SLIDES/INFORMATION FOR
COMPLETENESS**

Childhood obesity and sleep: relatives, partners, or both?



Gozal D, Kheirandish-Gozal L. Ann N Y Acad Sci. 2012 August; 1264(1): 135–141.

AAP's (2012) PP on Obstructive Sleep Apnea

- (1) All children/adolescents should be screened for snoring.
- (2) Polysomnography should be performed in children/adolescents with snoring and symptoms/signs of OSAS; if polysomnography is not available, then alternative diagnostic tests or referral to a specialist for more extensive evaluation may be considered.
- (3) Adenotonsillectomy is recommended as the first-line treatment of patients with adenotonsillar hypertrophy.
- (4) High-risk patients should be monitored as inpatients postoperatively.
- (5) Patients should be reevaluated postoperatively to determine whether further treatment is required. Objective testing should be performed in patients who are high risk or have persistent symptoms/signs of OSAS after therapy.
- (6) Continuous positive airway pressure is recommended as treatment if adenotonsillectomy is not performed or if OSAS persists postoperatively.
- (7) Weight loss is recommended in addition to other therapy in patients who are overweight or obese.
- (8) Intranasal corticosteroids are an option for children with mild OSAS in whom adenotonsillectomy is contraindicated or for mild postoperative OSAS.

I'M SLEEPY (Parent version):

- I – Is your child often **I**rritated or angry during the day?
- M – Body **M**ass index above 85%?
- S – Child usually **S**nore?
- L – Does your child sometimes have **L**abored breathing at night?
- E – **E**ver noticed a stop in your child's breathing at night?
- E – Does your child have **E**nlarged tonsils and/or adenoids?
- P – Does your child have **P**roblems with concentration?
- Y – Does your child often **Y**awn or is often tired/sleepy during the day?

Kadmon G· Chung SA and Shapiro CM. I'M SLEEPY: A short pediatric sleep apnea questionnaire. International Journal of Pediatric Otorhinolaryngology. Available online 8 October 2014. In Press,

Corrected Proof

I'M SLEEPY (Child version):

- I – Are you angry a lot?
- M – Filled in by the doctor: body mass index above 85%?
- S – Do you snore at night?
- L – Did your parents or a friend tell you that your breathing is “difficult” at night?
- E – Did your parents or a friend tell you that you stop breathing at night?
- E – Do you have problems with your tonsils or adenoids (glands inside your mouth)?
- P – Is it difficult for you to focus (at school or at home)?
- Y – Do you feel tired or sleepy a lot?

Kadmon G· Chung SA and Shapiro CM. I'M SLEEPY: A short pediatric sleep apnea questionnaire. *International Journal of Pediatric Otorhinolaryngology*. Available online 8 October 2014. In Press, Corrected Proof

Pharmacotherapy of Sleep-Disordered Breathing

- Oxygen and Protriptyline no longer mainline treatments
- Current Mainline: Adenotonsillectomy and Continuous Positive Airway Pressure (CPAP)
- Option: Orthodontics
 - rapid maxillary expansion
- Medications may have a role in pts intolerant to CPAP or if residual Sx despite surgery

Marcus CL, et al. Use of nasal continuous positive airway pressure as treatment of childhood obstructive sleep apnea. *J Pediatr* 1995;127: 88–94.

Villa MP, et al. Efficacy of rapid maxillary expansion in children with obstructive sleep apnea syndrome: 36 months of follow-up. *Sleep Breath* 2011;15:179–84.

Bhattacharjee R, et al. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study. *Am J Respir Crit Care Med* 2010;182:676–83.

Sodium Oxybate (GHB; Xyrem) for Narcolepsy in Youth

- No DBPC Trials in Youth
- Approved in Adults Helpful for EDS & Cataplexy
 - Increase SWS
 - Half-life 90-120 minutes
 - 1st dose at HS; 2nd dose 2.5-4 hours later
 - Starting dose in adults 2.25 g/dose; range 6-9 g daily
- Case series from Stanford & Mayo
 - Positive effects, well tolerated

Mansukhani MP, Kotagal S.
Sodium oxybate in the treatment of childhood narcolepsy cataplexy: a retrospective study. Sleep Med.
2012 Jun;13(6):606-10.

Aran A et al., Clinical and therapeutic aspects of childhood narcolepsy-cataplexy: a retrospective study of 51 children. Sleep. 2010 Nov;33(11):1457-64.

Stimulants & Modafinil for Narcolepsy in Youth

- Amphetamines
 - Widely used in adults; MPH as alternative
- Modafinil
 - First line in adults for EDS
 - Additive effects with GHB
 - Half-life 10-to-12 hours
 - Dose 200-400 mg/day; dosed AM and Noon
 - Report of erythema multiforme/Stevens-Johnson
 - Used in Pts with Prader-Willi; MS
- Aromodafinil not studied in youth

Antidepressants for Cataplexy in Children and Adolescents

- TCAs: IMI and CMI use limited by anticholinergic and Cardiovascular AEs
- SSRIs: option
- SNRIs: Venlafaxine often used in adults; 75-150 mg/day; youth start 37.5 mg; may be helpful to dose BID
- Atomoxetine: 18-100 mg; QD or BID

Billiard M. Narcolepsy: current treatment options and future approaches. Neuropsychiatr Dis Treat 2008;4:557–66.

Restless Leg Syndrome (RLS)

- Chronic Familial Neurologic Disorder
- Leg discomfort may be characterized by “growing pains”
- May mimic ADHD
- Associated with iron deficiency
- Monitor serum ferritin; Vitamin C may help iron absorption

Picchietti DL, Arbuckle RA, Abetz L, et al. Pediatric restless legs syndrome: analysis of symptom descriptions and drawings. *J Child Neurol* 2011;26:1365–76.

Patrick LR. Restless legs syndrome: pathophysiology and the role of iron and folate. *Altern Med Rev* 2007;12:101–12.

Pharmacotherapy of Restless Leg Syndrome (RLS) in Youth

- Dopamine Precursors and Agonist
- Levodopa (Sinemet)
 - Restless leg augmentation
- Pramipexole (Mirapex) and Ropinirole (Requip)
 - Approved in adults; commonly used
 - 0.125 mg tablet Pramipexole now available
 - Case report of 11 yo improved with 0.5 mg ropinirole
- Rotigotine (Neupra)
 - New DA agonist approved in adults; patch
- Gabapentin? Opiates (not recommended)

Frenette E. Restless legs syndrome in children: a review and update on pharmacological options. *Curr Pharm Des.* 2011;17(15):1436-42.

Littner MR, Kushida C, Anderson WM, et al. Practice parameters for the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. *Sleep* 2004;27:557-9.

Sleep Disorders in Rare Hereditary Diseases

- **Inborn Errors of Metabolism**
- **Chromosomal Anomalies**
 - Rett Syndrome
 - Down Syndrome
 - Fragile X Syndrome
 - Fragile X Associated Tremor/Ataxia Syndrome
 - Angelman Syndrome
 - Prader–Willi Syndrome
 - Williams–Beuren Syndrome
 - Smith–Lemli–Opitz Syndrome
 - Segawa’s Disease
 - Sepiapterin Reductase Deficiency

Gadoth N, Oksenberg A. *Front Neurol.* 2014 Jul 17;5:133.

Sleep Disorders in Rare Hereditary Diseases

- **Storage Diseases**
 - Mucopolysaccharidosis
 - Glycogen Storage Disease
 - Aspartylglucosaminuria
 - Neuronal Ceroid Lipofuscinosis
 - Wilson's Disease
 - Friedreich Ataxia
- **Autonomic Dysfunction**
 - Familial Dysautonomia
 - Congenital Central Hypoventilation Syndrome
- **Sleep in Hereditary Skeletal Deformities**
 - Achondroplasia
 - Marfan Syndrome (MS)
 - Treacher Collins Syndrome

Sleep Disorders in Rare Hereditary Diseases

- **Sleep in Hereditary Neuromuscular Disorders**
 - Duchenne Muscular Dystrophy
 - Myotonic Muscular Dystrophy Type 1 (MMD-1)
 - Myotonic Muscular Dystrophy Type 2
 - Spinal Muscular Atrophy
- **Hereditary Cerebellar Degeneration**
- **Congenital Neuropathies**
 - Hereditary Motor and Sensory Neuropathy AKA CMTD
 - Congenital Myopathies
 - Nemaline Myopathy