

# Non-Opioid Analgesics and Sleep

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# Disclosures

- Data Safety Monitoring Board Chair- sodium oxybate in pediatric narcolepsy (Jazz Pharma 13-005)
- Almost all drugs to be discussed remain “off-label” for children from the sleep-wake function standpoint

# Learning Objectives

- Understand the non-opioid analgesics effects on sleep
- Implement measures in chronic pain to improve sleep patterns
- Provide optimal care for pediatric pain associated sleep disorders

# Some Basic Concepts

Fragmented  
Sleep



Exacerbation of  
Pain



Increased peripheral nociception



Increased central sensitization

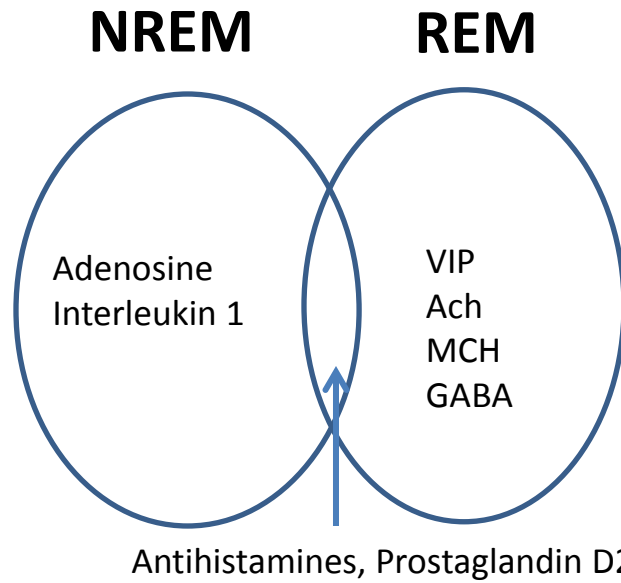


Depression / anxiety

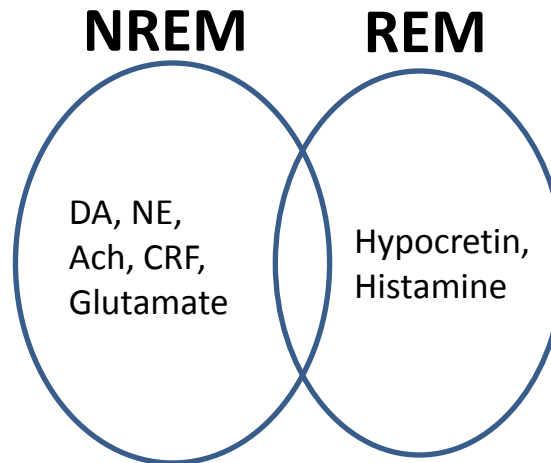


Autonomic dysfunction and  
physical deconditioning

Sleep promoting



Sleep inhibiting



# Factors Modulating the Effect of Drugs on Sleep

- Age
- Gender
- Genetic background
- Temperature
- Emotional stress
- Route of delivery
- Concentration
- Formulation

# Pediatric Psychopharmacology: Unique Features

- Drugs are metabolized more rapidly as compared to adults
- Paradoxical hyperactivity with sedatives and hypnotics
- Non-verbal children may be unable to indicate side effects
- Adherence to therapy dictated by the parent
- Timing of medication administration also dictated by parent



# Key Steps

- Try to make a specific sleep diagnosis, *e.g. inadequate sleep hygiene, limit setting disorder, circadian rhythm sleep disorder, restless legs syndrome*
- Document the extent to which sleep-wake function has been affected
- Identify and treat systemic co-morbidities, especially inflammation
- Identify and treat psychiatric co-morbidities, especially anxiety
- Team approach

# Specific Pharmacologic Agents

# Acetaminophen and Ibuprofen

2012

- FDA issued a black-box warning about use of codeine containing medications in children undergoing tonsillectomy for sleep apnea
- *Mattos JL, et al. Int J Pediatr Otorhinolaryngol, 2014*
  - N= 1065
  - Acetaminophen + ibuprofen = 73.5%
  - No ibuprofen = 26.5%
  - Post-tonsillectomy bleeding rate was 8.3%
  - Ibuprofen did not impact bleeding rate

# Impact of anti-depressants on sleep

Medication	Sleep-related pharmacology	Effect on sleep architecture
SSRI	5-HT reuptake inhibition	REM suppression, increased REM latency
SNRI	5-HT, NE reuptake inhibition	REM suppression, increased REM latency
Triazolopyridines, e.g. trazodone	5-HT antagonism	Decreased sleep latency, increased slow wave sleep (SWS)
Tetracyclics, e.g. mirtazapine	5-HT <sub>2</sub> antagonism, H <sub>1</sub> antagonism	Decreased sleep latency, increased SWS
Tricyclics, e.g. amitriptyline, doxepin	5-HT, NE reuptake inhibition, H <sub>1</sub> antagonism	Decreased SWS, REM suppression, increased REM latency

# Trazodone

- Antidepressant, triazolopyridine class
- Selectively inhibits neuronal uptake of serotonin; also alpha 1 adrenergic receptor antagonist
- Dose: 25-50 mg at bed time
- Side effects include lowering seizure threshold, priapism, orthostatic hypotension

# Tricyclic Agents

- Sedating: amitriptyline, doxepin, clomipramine;
  - have more prominent effect on serotonin system
  - Shorten sleep latency, increase total sleep time
- Less sedating: desipramine, protriptyline;
  - More effect on norepinephrine system
  - Prolong sleep latency, shorten total sleep time, increase night awakenings
- Dose for sleep enhancement:
  - Amitriptyline 25-50 mg at bedtime
  - Doxepin 3-6 mg at bed time
- If ineffective, *taper off gradually* to avoid withdrawal symptoms

# Gabapentin

- GABA precursor, approved initially in 1993 for treatment of partial seizures
- Also approved for treating neuropathic pain and restless legs syndrome
- Improved sleep quality in an open label study of adults by increasing slow wave sleep and sleep efficiency

# Gabapentin (continued)

- Open label study of sleep in children (*Robinson AA and Malow BA, J Child Neurol 2013*)
- 78% showed improved sleep (parental response)
- Dose for sleep enhancement was 3-15 mg/kg *q hs* while dose for seizure control is ~ 40 mg/kg/day in 2-3 divided doses



# Other Anti-epileptic Agents

- Older anti-epileptic drugs
  - Carbamazepine: ↑ N3 and ↓ REM sleep
  - Phenobarbital: ↓ REM sleep
- Newer agents (tiagabine, gabapentin, pregabalin): ↑ N3 sleep

# Pregabalin

- $\alpha$ -2  $\delta$  binding neuromodulator that acts in the region of neuronal voltage gated  $\text{Ca}^{++}$  channels
- Prevents the amplification of nociceptive influences
- Also approved for generalized anxiety and neuropathic pain
- Dose 50-200 mg / day in 2-3 divided doses

# Pregabalin

*Arnold LM, et al. Pain Medicine, 2014*

## Fibromyalgia

- *Post-hoc* analysis of four phase 2-3 placebo-controlled trials
  - 12 pregabalin treatment arms, N = 2069
  - 4 placebo arms, N = 689
- **39.8 %** of pregabalin group showed improved pain control vs. **27.7%** in placebo group ( $p < 0.0001$ )
- **51.9 %** of pregabalin vs. **34.4%** of placebo had improvement in sleep ( $p < 0.0001$ )

# Duloxetine

- Combined serotonin and norepinephrine reuptake inhibitor
- Enhances central nervous system arousal
- Improves central diffuse noxious inhibitory control
- Dose 30-120 mg once a day
- Common side effects: fatigue, dizziness, headache
- Combining with pregabalin may be more efficacious

# “Sleeping Pills”

## Are They Ever Indicated?

- The underlying etiology is also being addressed, but:
  - insomnia persists, or shows minimal improvement
  - school and social life have been adversely impacted

# Sleeping Pills Overview

- Interact with benzodiazepine receptors
- Zaleplon (SONATA), ultra-short  $\frac{1}{2}$  life, dose 5-10 mg
- Zolpidem (AMBIEN), short half life; dose 5-10 mg
- Eszopiclone (LUNESTA), 1-2 mg
- Caution about respiratory depression, especially if sleep apnea coexists; dependence; parasomnias with zolpidem

Some general comments about  
enhancing sleep quality

# Incorporate Advice About Sleep Hygiene into Management

- Try to awaken at the same time each morning
- Avoid napping during the day
- Exercise during the day
- Avoid exercise or warm showers close to bedtime
- Stop use of electronic devices 1-2 hours prior to bedtime
- Worry “before getting into bed” rather than later
- Avoid caffeine in the 2-3 hours prior to bedtime
- Avoid nicotine





# Consider the role of concurrently administered wakefulness-promoting drugs on sleep

- Psychostimulants, e.g. methylphenidate
- Antihypertensives, e.g. beta blockers
- Bronchodilators, e.g. albuterol, theophylline
- Corticosteroids
- Nasal decongestants, e.g. phenylephrine
- Psychotropics, e.g. SSRI agents

# Timing is Everything



When you buy it



When you put it on your bag

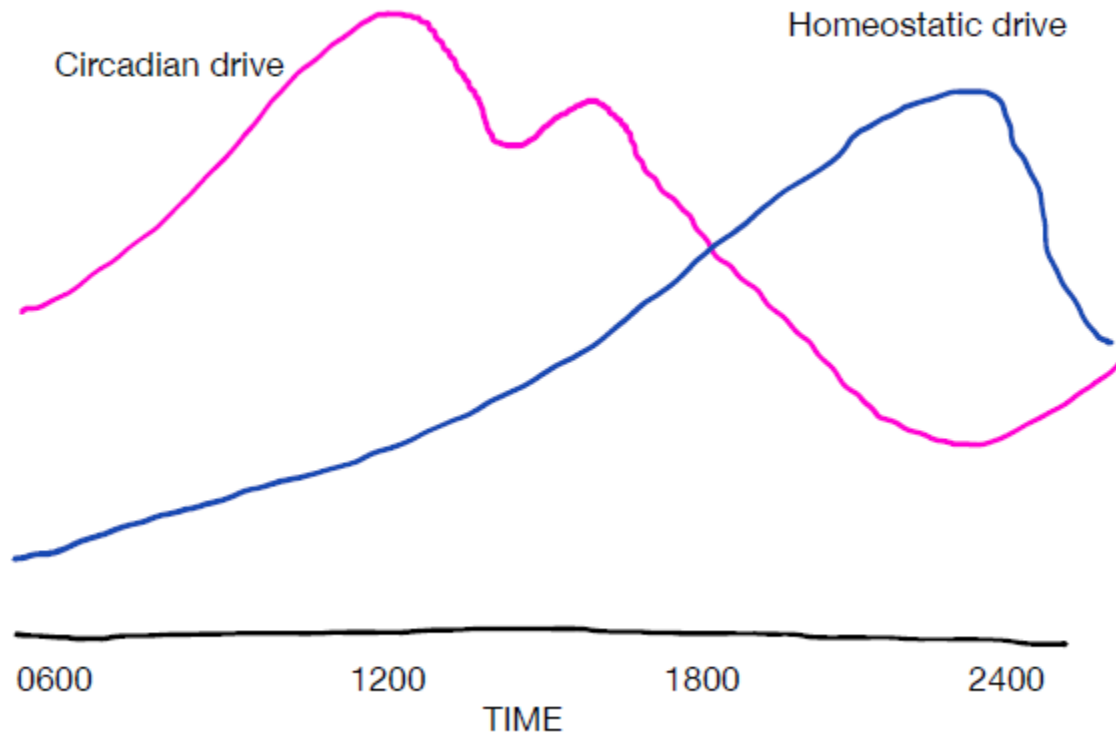


When you want to eat it

truthfacts.com

*Michael Wulff and Anders Morgenthaler*

# Time of day/night may influence the effects of medications on sleep



# Conclusions

- There is a bi-directional relationship between sleep and chronic pain
- Medications *per se* can help only partially
- Patients with chronic pain and sleep initiation /maintenance difficulty often require a multi-specialty team approach
- Emphasize wellness over illness

# Suggested Reading

- Mannion R and Woolf CJ. Pain mechanisms and management: a central perspective. *The Clinical Journal of Pain* 2000; 16: S144-S156
- Patel A, Davidson M, Tran MC, et al. Dexmedetomidine infusion for analgesia and prevention of emergence agitation in children with obstructive sleep apnea syndrome undergoing tonsillectomy and adenoidectomy. *Anesthesia and Analgesia* 2010; 111: 1004-10
- Angeletti C, Guetti C, Piroli A, et al. Duloxetine and pregabalin for pain management in multiple rheumatic disease associated fibromyalgia. *Pain Practice* 2013; 13: 657-662
- Senba E. A key to dissect the triad of insomnia, chronic pain and depression. *Neuroscience Letters*, 2015.01.012
- Finan PH, Smith MT. The comorbidity of insomnia, chronic pain and depression: dopamine as a putative mechanism. *Sleep Med Rev* 2013; 17: 183-83

**Thank You!**