Opioids and Sleep: Fueling the Fire?

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Disclosures

- None

Research Support

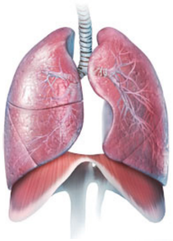
- FAER Research in Fellowship Grant
- Institutional K12
- Society for Anesthesia and Sleep Medicine (SASM)
- Johns Hopkins Sommer Scholars Program

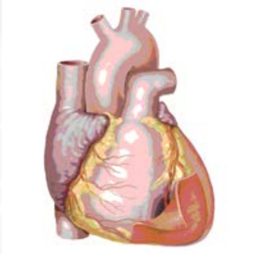
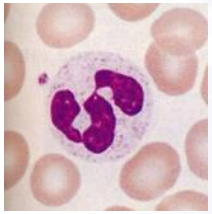
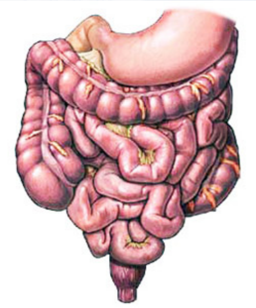
Learning Objectives

- Review the current understanding of opioids on sleep architecture
- Discuss the management of patients with obstructive sleep apnea and postop sleep disturbances who require appropriate analgesia
- Develop guidelines for optimizing pain management and sleep

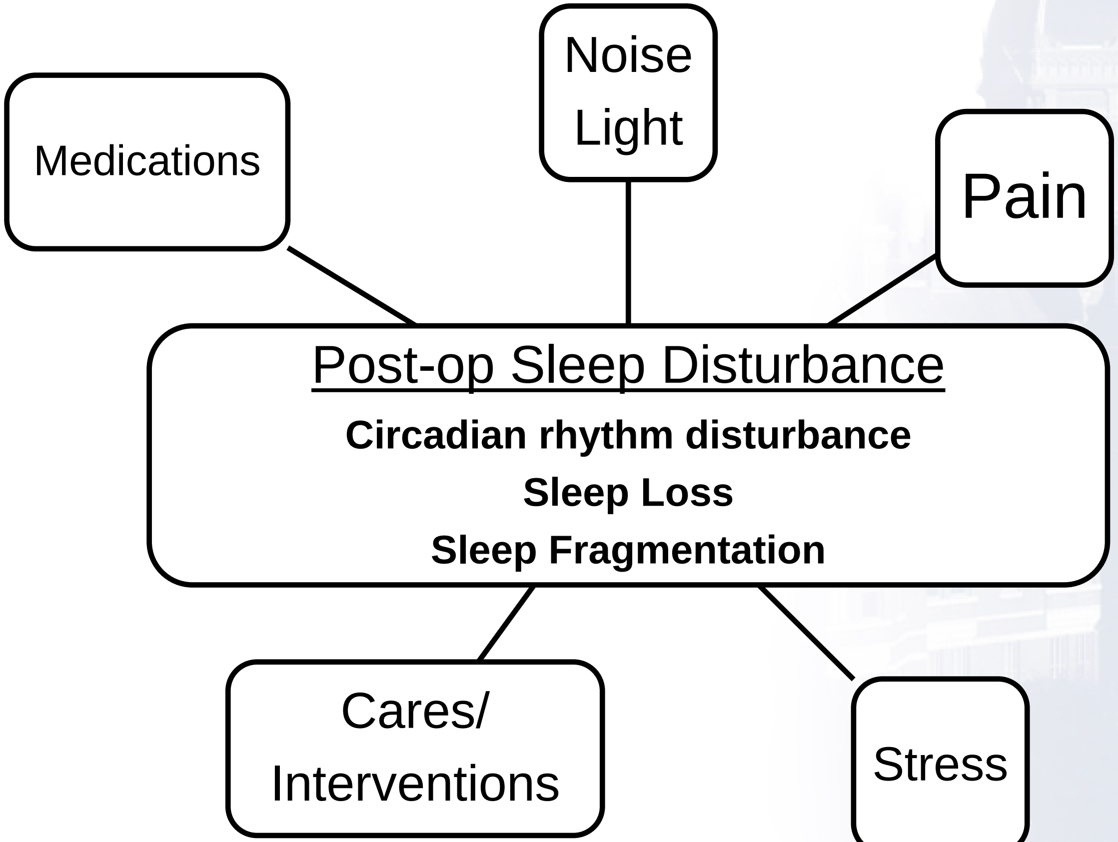
Why study sleep in the post-operative period?

- Natural sleep is integral to physiologic homeostasis
  - Thermoregulation
  - Respiratory
  - Cardiovascular
  - Gastrointestinal
  - Immune defenses
  - Endocrine



Postoperative Sleep Disturbances



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Hospital sleep is not a priority

Sleep of critically ill children in the pediatric intensive care unit: A systematic review

Sapna R. Kudchadkar[a,*], Othman A. Aljohani[a], Naresh M. Punjabi[b]

- Multitude of studies of sleep in the NICU
- Nine publications about sleep in the PICU
  - Four publications from same RCT
  - Two studies using subjective assessment (PSBOT)

Kudchadkar et al., Sleep Med Rev 2014

Sedation, Sleep Promotion, and Delirium Screening Practices in the Care of Mechanically Ventilated Children: A Wake-Up Call for the Pediatric Critical Care Community

Sapna R. Kudchadkar, MD[1,2]; Myron Yaster, MD[1,2]; Naresh M. Punjabi, MD, PhD[3,4]

- Surveyed 341 pediatric intensivists internationally
- <15% aware of any efforts made to optimize sleep of critically ill children in their unit including any of following:
  - Noise reduction
  - Lighting
  - Earplugs/eyemasks

Crit Care Med 2014.

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Pediatric Intensive Care and Sleep: Is it a priority?

- >85% still using a combination of benzodiazepine and opioid for sedation in mechanically ventilated children
  - Fentanyl and midazolam infusions most preferred

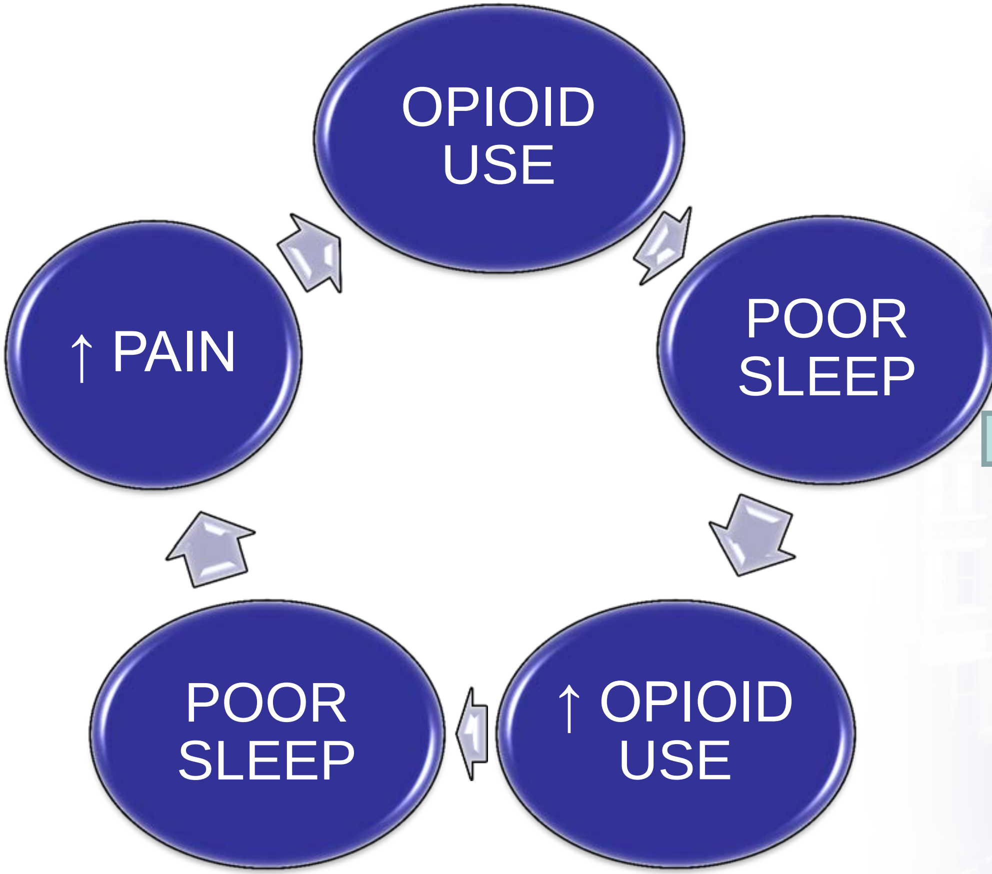
- <10% utilize dexmedetomidine as a primary sedative agent

Kudchadkar et al. 2014, *Crit Care Med.*

OPIOID FACTS

- Opioids are here to stay as a central component of pain management..for now
- Despite sedating qualities, opioids paradoxically alter the sleep-wake cycle and decrease restorative sleep
- We are still defining the mechanisms through which opioid disrupts normal sleep architecture--even more complex in the developing brain

A vicious cycle



Physiologic dependence, prolonged hospital stay for withdrawal

History of Sleep Science

1953: Aserkinsky & Kleitman investigate rolling eye movements of infants during sleep– also noted in adults and associated with dreaming

Regularly Occurring Periods of Eye Motility, and Concomitant Phenomena, During Sleep[1]

Eugene Aserinsky[2] and Nathaniel Kleitman

Department of Physiology, University of Chicago, Chicago, Illinois

Slow, rolling or pendular eye movements such as have been observed in sleeping children or adults by Pietrusky (*1*), De Toni (*2*), Fuchs and Wu (*3*), and Andreev (*4*), and in sleep and anesthesia by Burford (*5*) have also been noted by us. However, this report deals with a different type of eye movement—rapid, jerky, and binocularly symmetrical—which was briefly described elsewhere (*6*).

Science 1953

Sleep– not such a quiet time

Changes in respiration, heart rate, and systolic blood pressure in human sleep

FREDERICK SNYDER, J. ALLAN HOBSON,[1] DONALD F. MORRISON,[2] AND FREDERICK GOLDFRANK
National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland

Journal of Applied Physiology, 1964

Opioids and Sleep

Psychopharmacologia (Berl.) 14, 404—416 (1969)

Morphine Effects on Human REM State, Waking State and NREM Sleep *

David C. Kay, Richard B. Eisenstein, and Donald R. Jasinski

National Institute of Mental Health, Addition Research Center, Lexington, Kentucky, U.S. Department of Health, Education and Welfare, Public Health Service

Received October 14, 1968

Opioids and Sleep: Kay 1969

Summary. After 4 adaptation nights, IM doses of morphine sulfate (7.5, 15, 30 mg/70 kg) and placebo were studied in 8 male postaddicts, using a cross-over design with randomized block analysis to demonstrate significant drug effect. Morphine decreased the number and duration of REM periods, delayed the onset of the first REM period, and possibly increased the time between REM period onsets. Thus, morphine significantly decreased REM state (REMS), but did not alter the pattern of maximum REMS in late night. Morphine significantly increased waking state (WS) but did not alter the pattern of maximum WS in early night. Morphine significantly increased tension, and shifted maximum tension from early night to middle night. Morphine altered EEG sleep patterns; although NREM definitions were thus less certain, morphine appeared to increase NREM light sleep (stages 1 and 2) and decrease NREM deep sleep (stages 3 and 4). After an initial decrease in REMS by 30 mg/70 kg of morphine, an increase in REMS was noted in the third night of the 2 pilot study subjects. The arousal response to morphine seen in post-addicts needs further study in other populations and during the course of chronic morphine use.

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Opioids and REM-sleep Inhibition: What's the issue?

- 2 mechanisms for opioid-induced respiratory depression
  - Direct effect on chemosensitive and respiratory nuclei in CNS
  - Indirect effects via sleep-dependent respiratory depression
- **REM sleep deprivation leads to REM sleep rebound**

Physiologic changes during REM Sleep

- Ventilatory depression due to:
  - Upper airway hypotonia
  - Hypopneas
  - ↑ apneas
- Episodic cardiovascular changes
  - Hypertension, tachycardia
  - ↑ coronary blood flow

British Journal of Anaesthesia 1995; 74: 188–192

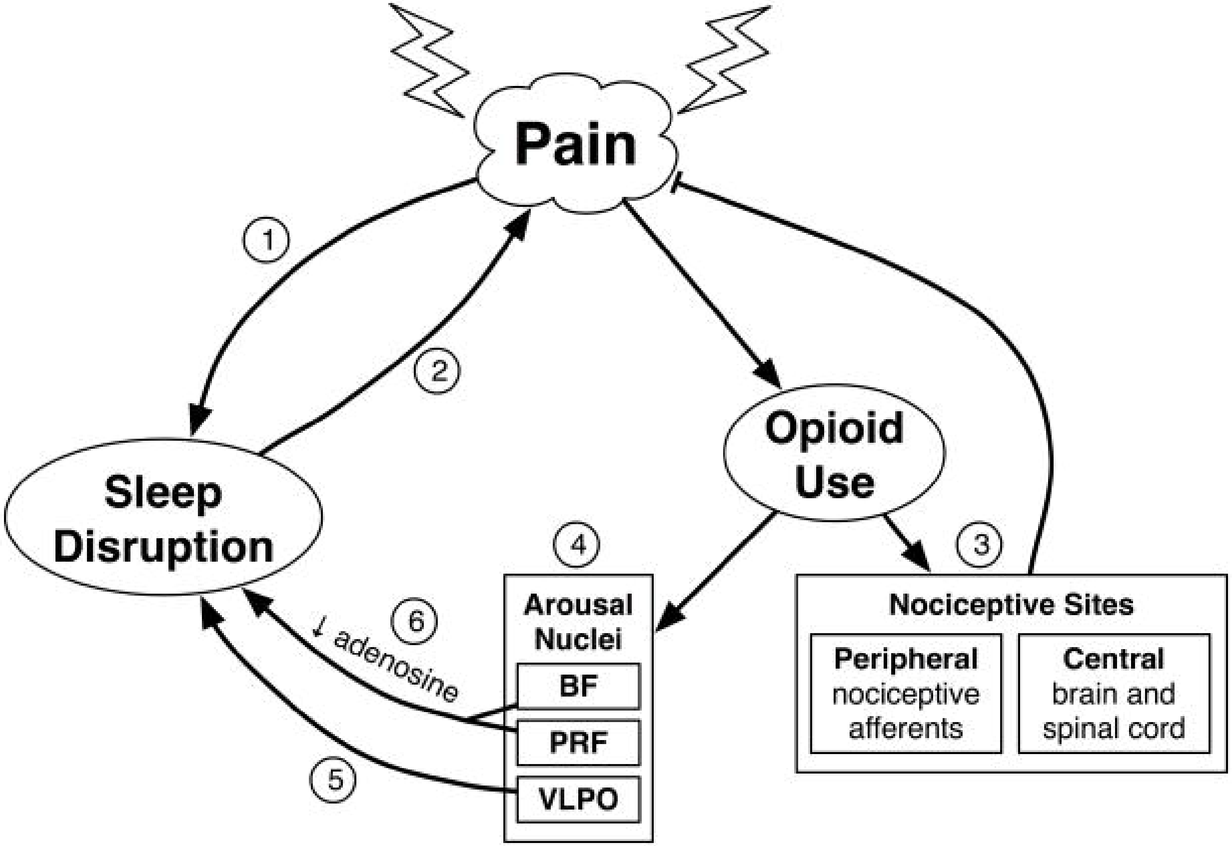
LABORATORY INVESTIGATIONS

Opioid inhibition of rapid eye movement sleep by a specific mu receptor agonist

A. Cronin, J. C. Keifer, H. A. Baghdoyan and R. Lydic

- Hypothesis: Specific subtypes of opioid receptors within the medial pontine reticular formation (mPRF) mediate inhibition of REM sleep
- Synthetic opioid agonists selective for mu, delta and kappa subtypes were injected into mPRF of cats
- Only the mu agonist significantly inhibited REM sleep

Opioids, Sleep and Pain: The Adenosinergic Link



Moore & Kelz, Anesthesiology 2009

What about NREM sleep?

JCSM
Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

The Effect of Opioids on Sleep Architecture

Joel E. Dimsdale, M.D.[1]; Daniel Norman, M.D.[2]; Douglas DeJardin[1]; Mark S. Wallace, M.D.[3]

[1]*Department of Psychiatry,* [2]*Department of Medicine,* [3]*Department of Anesthesiology, University of California, San Diego, CA*

- 42 healthy young adults
- Double-blind multiple crossover
- MSContin (15mg), methadone (5mg) or placebo

Hypothesis

Journal of Clinical Sleep Medicine

"We hypothesized that morphine, a relatively pure μ-agonist, would have particular effects on REM sleep, while methadone, a μ-agonist with NMDA antagonist properties, would have increased actions on NREM sleep."

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Findings

Journal of Clinical Sleep Medicine

- 30-50% decrease in restorative, deep sleep (NREM Stage 3) with both drugs
- No significant decrease in REM sleep
- Conclusion: REM sleep inhibition is likely dose dependent, but low dose opioid adversely affects restorative NREM sleep
- Limitation: Pain free patients– complex pain-sleep-opioid interaction not studied

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NREM Sleep and Children

The evolution of slow wave sleep (NREM) during infancy and childhood reflects constant changes in brain organization and biology during development

NREM sleep in healthy children

Am J Physiol Regul Integr Comp Physiol 304: R296–R303, 2013.
First published November 28, 2012; doi:10.1152/ajpregu.00422.2012.

Longitudinal sleep EEG trajectories indicate complex patterns of adolescent brain maturation

Irwin Feinberg and Ian G. Campbell
Department of Psychiatry and Behavioral Sciences, University of California, Davis, California

Cerebral Cortex March 2011;21:607-615
doi:10.1093/cercor/bhq129
Advance Access publication July 12, 2010

EEG Sleep Slow-Wave Activity as a Mirror of Cortical Maturation

Andreas Buchmann, Maya Ringli, Salomé Kurth, Margot Schaerer, Anja Geiger, Oskar G. Jenni and Reto Huber

Children's Hospital, University of Zurich, CH-8032 Zurich, Switzerland

- NREM delta power increases significantly in childhood and then begins to decline
- SWA (δ and θ) strongly positively correlated with gray matter volumes

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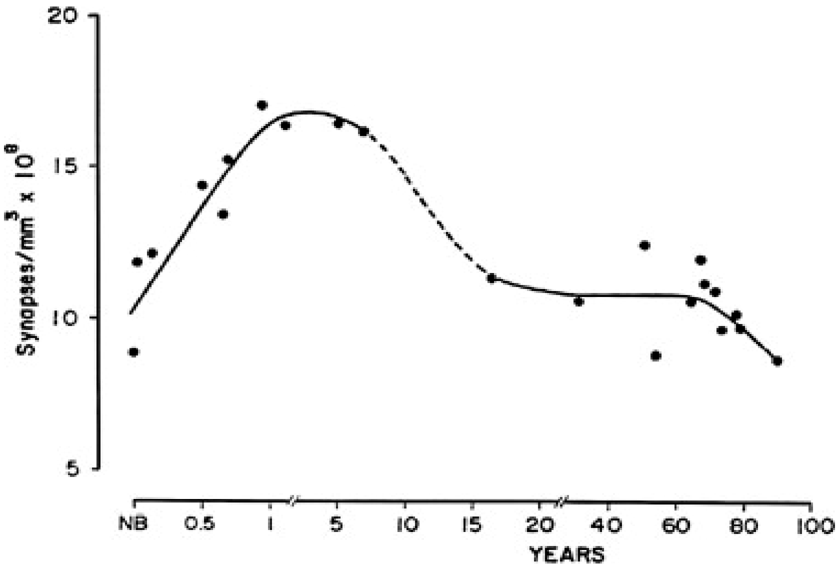
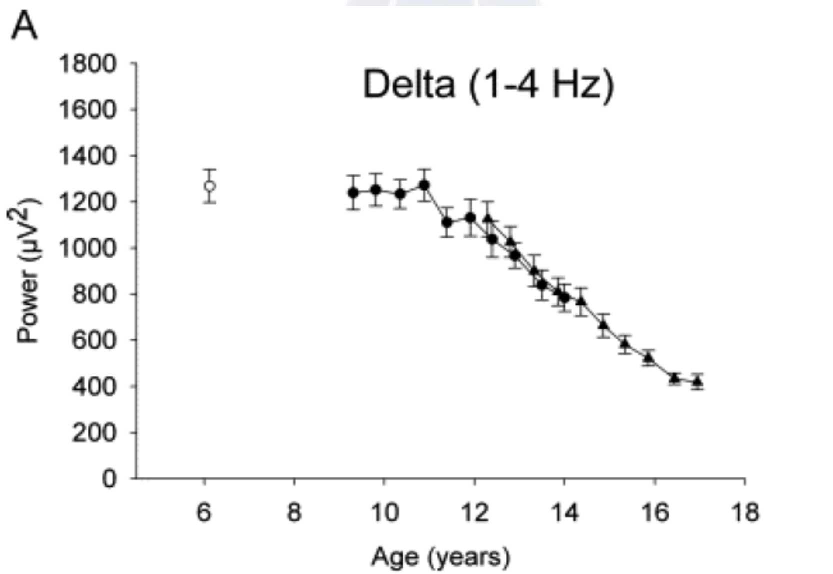
Synaptic density and delta sleep





Work by Huttenlocher and Feinberg: Although synaptic density begins to decrease significantly between ages 6-15, there is limited data about the evolution of delta sleep among children in the younger range of this age group

Huttenlocher et al. *Brain Research*, 1979
Campbell et al. *Proc Natl Acad Sci USA*, 2009

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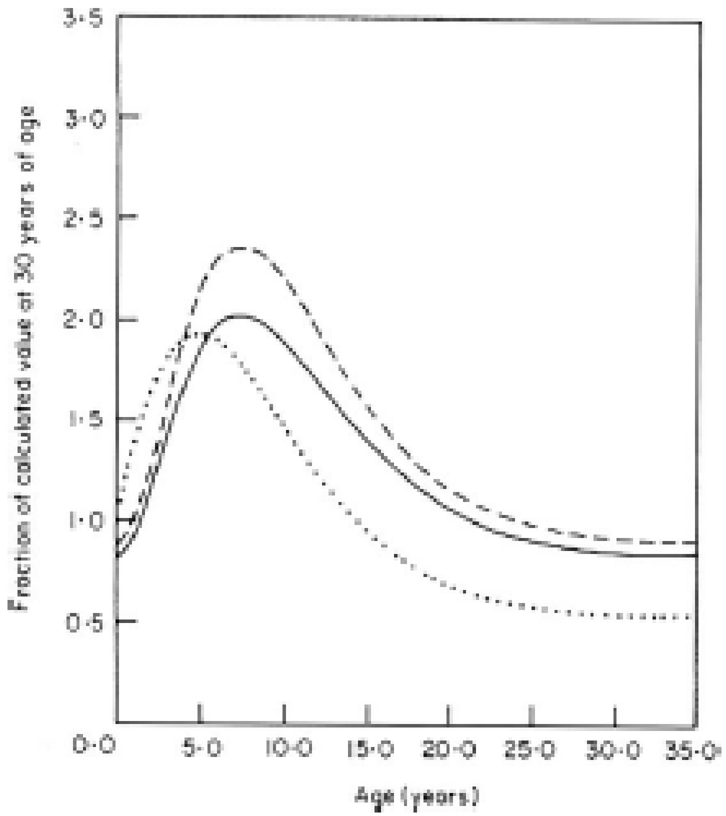
Synaptic density, $CMRO_2$ and delta wave amplitude: parallels



Gamma distribution model of growth in childhood and decline in adolescence

..... synaptic density

---- delta wave amplitude

___cerebral metabolic rate

Changes in delta power are a reflection of synaptic pruning, brain maturation and reorganization

Feinberg et al, 1990. Journal of Theoretical Biology

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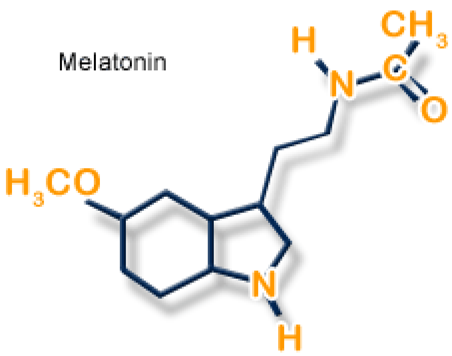
Synthesis

- NREM and REM sleep are both integral to normal brain development during infancy and childhood

Opioids and the Circadian Rhythm: Melatonin

- Produced by the pineal gland
- Under control of circadian pacemaker of suprachiasmatic nuclei
- Peaks at 2 a.m., decreases to daylight levels by 8 a.m.
- Nocturnal melatonin suppression noted in ICU and post-operative patients



Preliminary Data: Melatonin in Children after Major Surgery

Anesthesiology 2008; 108:627–33

Remifentanil Inhibits Rapid Eye Movement Sleep but Not the Nocturnal Melatonin Surge in Humans

Christopher P. Bonafide, M.D., Natalie Aucutt-Walter, M.D.,† Nicole Divittore, B.A.,‡ Tonya King, Ph.D.,§ Edward O. Bixler, Ph.D.,‖ Arthur J. Cronin, M.D.#*

- 10 healthy volunteers
- Remifentanil did not decrease melatonin concentration
- Exogenous melatonin did not prevent remifentanil-induced sleep disturbances

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Postoperative Sleep Disturbances

Medications

Noise
Light

Pain

Post-op Sleep Disturbance

Circadian rhythm disturbance

Sleep Loss

Sleep Fragmentation

Cares/
Interventions

Stress

Obstructive Sleep Apnea (OSA)

- Pathophysiology of pediatric OSA is multifactorial (anatomy, obesity, genetics)
- No consensus regarding safest anesthetic technique for children with significant OSA
- No clear criteria for post-op monitoring/admission

OSA: Mechanisms of increased sensitivity

- Central and peripheral mechanisms
- Up-regulation of μ-opioid receptors due to recurrent hypoxemia→↑ risk resp. depression
- Decreased ventilatory response to hypoxemia

Obstructive Sleep Apnea

- Increased sensitivity to intraoperative and postoperative opioids is well known

Anesthesiology 2004; 100:806–10

Recurrent Hypoxemia in Young Children with Obstructive Sleep Apnea Is Associated with Reduced Opioid Requirement for Analgesia

Karen A. Brown, M.D., André Laferrière, B.A.,† Immanuela Ravé Moss, M.D., Ph.D.‡*

Anesthesiology 2006; 105:665–9

Recurrent Hypoxemia in Children Is Associated with Increased Analgesic Sensitivity to Opiates

Karen A. Brown, M.D., André Laferrière, B.A.,† Indrani Lakheeram, M.D.,‡ Immanuela Ravé Moss, M.D., Ph.D.§*

What about IV PCA?

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IV PCA and Sleep

- Seems beneficial– immediate delivery of pain medication when needed
- Ability for low-dose basal dose--Less arousals due to pain at night? Better sleep?

Anesthesiology
76:362–367, 1992

Effects of a Nighttime Opioid Infusion with PCA Therapy on Patient Comfort and Analgesic Requirements after Abdominal Hysterectomy

Robert K. Parker, D.O.,* Barbel Holtmann, M.D.,† Paul F. White, Ph.D., M.D., F.F.A.R.A.C.S.‡

- No difference in pain scores, nocturnal awakenings or nighttime bolus doses between continuous infusion vs. no infusion

Peds PCA and Sleep

Pediatric Anesthesia 2006 **16**: 1051–1056 doi:10.1111/j.1460-9592.2006.01932.x

Postoperative sleep disturbance in pediatric patients using patient-controlled devices (PCA)

J.J. KELLY MBBS FRACP*, SUSAN DONATH†, KRIS JAMSEN† AND G.A. CHALKIADIS MBBS FANZCA‡

**Department of General Medicine, Royal Children's Hospital, Parkville, Vic., †Clinical Epidemiology and Biostatistics Unit, The Royal Children's Hospital, Melbourne and ‡Department of Anaesthesia and Director of Pain Management, Royal Children's Hospital, Parkville, Vic., Australia*

Background infusion predictive of increased button pushes, no objective indicator of sleep

Peds PCA and Sleep

Pediatric Anesthesia

Pediatric Anesthesia ISSN 1155-5645

ORIGINAL ARTICLE

Pain management following major intracranial surgery in pediatric patients: a prospective cohort study in three academic children's hospitals

Lynne G. Maxwell[1], George M. Buckley[2], Sapna R. Kudchadkar[2], Elizabeth Ely[3], Emily L. Stebbins[4], Christine Dube[5], Athir Morad[2], Ebaa A. Jastaniah[2], Navil F. Sethna[5] & Myron Yaster[6]

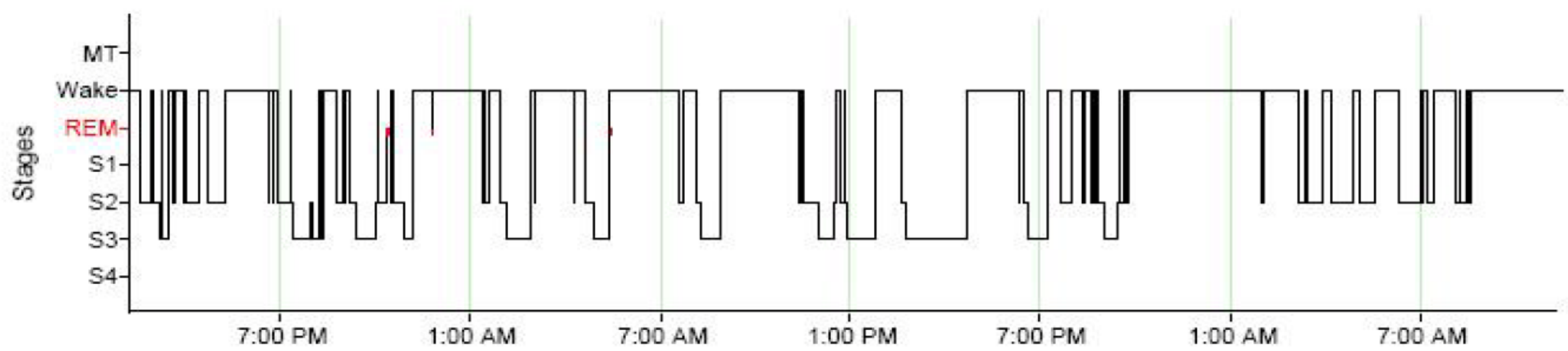
Parkville, Vic., Australia

Patients on IVPCA received significantly more opioid than those receiving PRN intermittent dosing

The Question

What role does sleep play as a modulator outcomes in children receiving opioids after major surgery?

Pilot data: 9 y/o on a fentanyl PCA



- Only 2 periods of REM sleep in a 36 hour period
- Several awakenings from sleep with no clear day-night cycle
- What happens long term?
- Does visual scoring offer enough insight into the the sleep state of this child?

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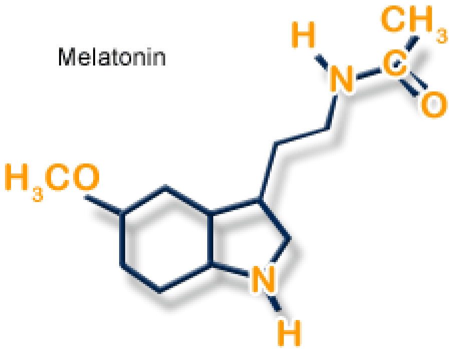
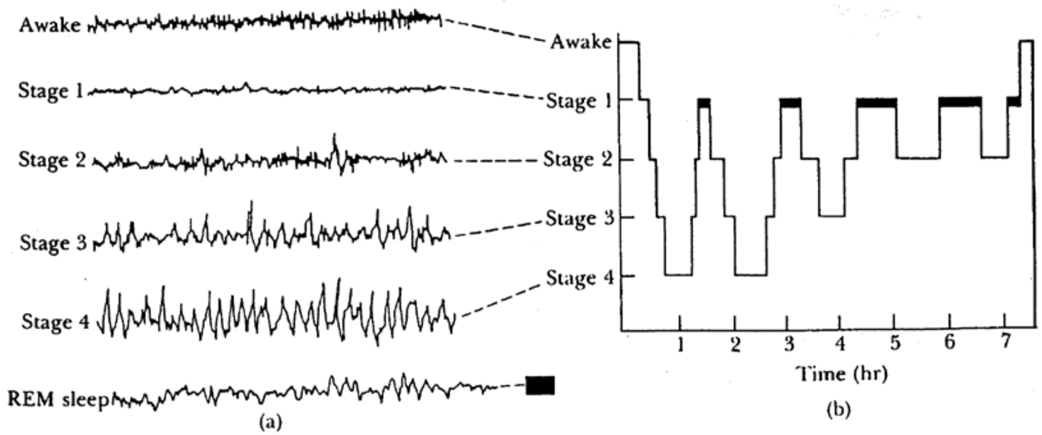
Objective Data: Postop sleep disturbances in children receiving opioids

- Sleep fragmentation
- Circadian dysrhythmia
- Decreased restorative sleep

Melatonin





What is actigraphy?

- Actigraphy, a non-invasive objective method using an internal accelerometer that measures activity levels

- It can be used to assess sleep-wake cycles in infants and children

- Algorithms have been developed to estimate: [4]
  - Sleep Fragmentation Index (SFI)
  - Total Sleep Time (TST)
  - Sleep Efficiency
  - Sleep Latency
  - Wake after Sleep Onset

- Little is known about the sleep-wake cycles of children hospitalized after major surgery

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Sleep-wake cycles after Major Surgery

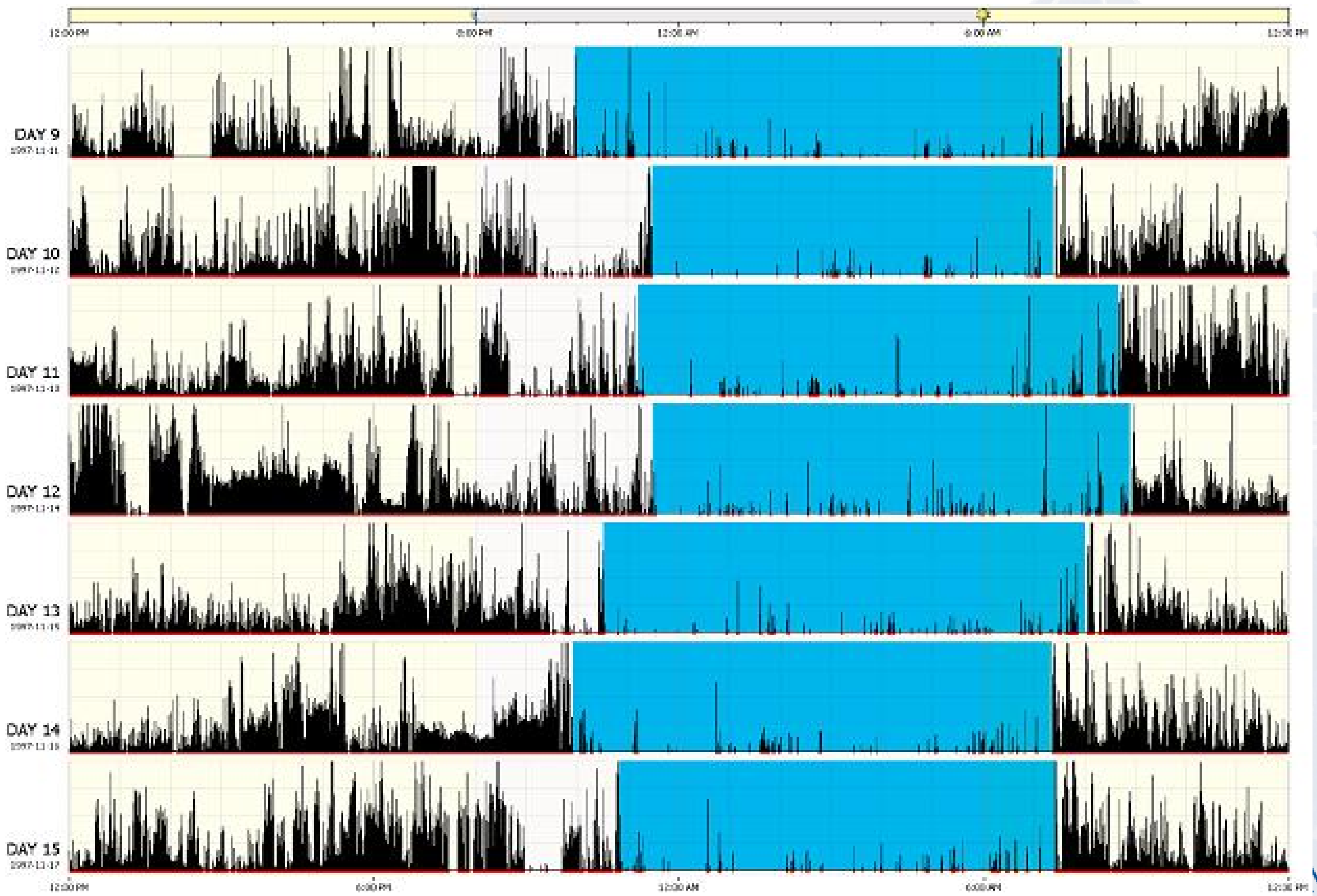
- How fragmented is the sleep of a child after major surgery as demonstrated by actigraphy?

- Does sleep continue to be fragmented after cessation of opioids and discharge to home?

Hypothesis

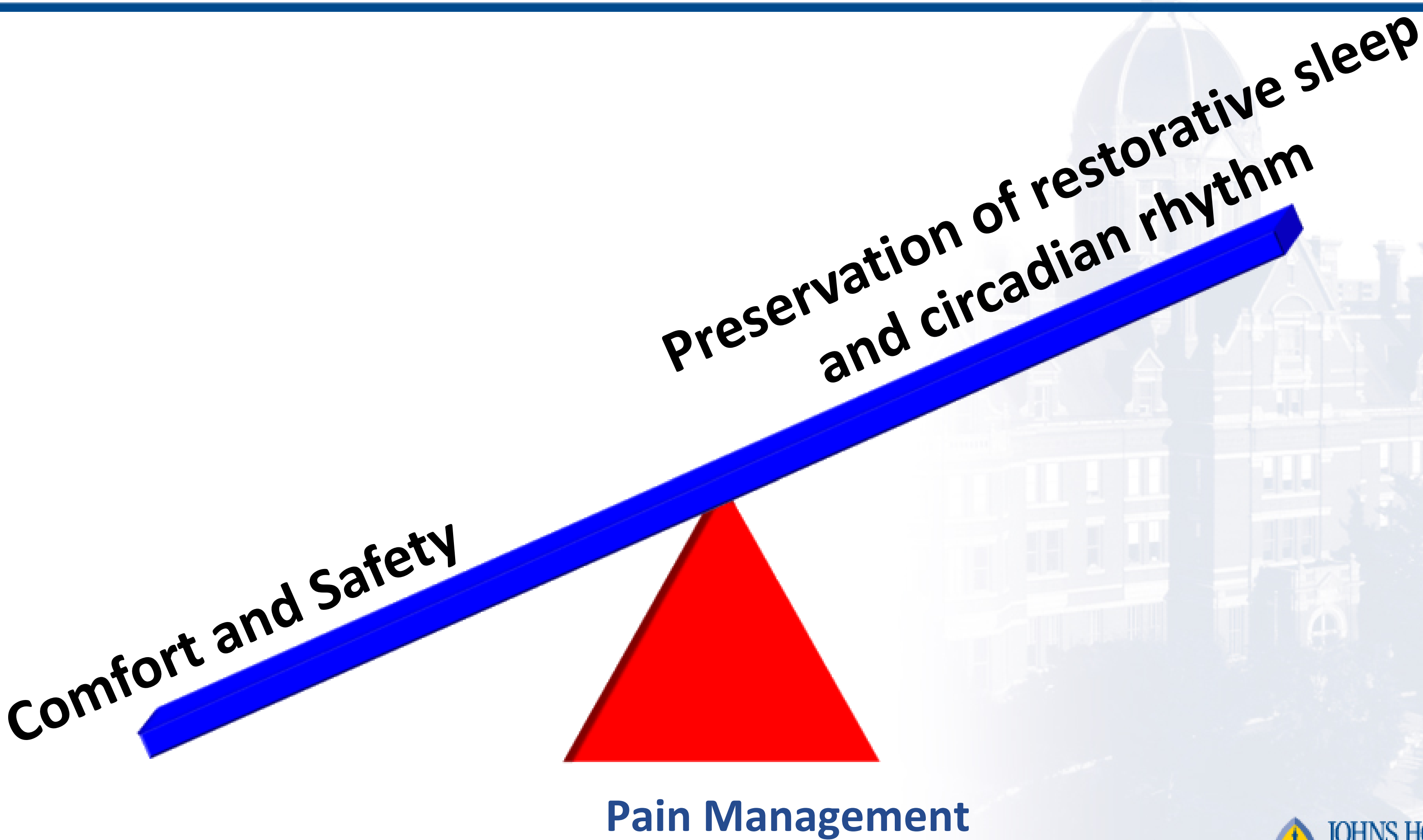
- Long-term continuous actigraphy in children receiving opioids after surgery will demonstrate significant disruption of sleep-wake cycles with prolonged recovery to normal cycles after discharge from the hospital.

Actigraphy plot demonstrates normal sleep-wake cycles



Research Data

Finding the Balance: Changing a Paradigm



Summary

- Children are at high risk for sleep disturbances after surgery that may play a role in recovery and brain maturation
- Optimization of extrinsic factors and opioid dosing is key to any pain management regimen
- Much work to be done!