
The Physiology of Sleep: Effect of Opioids and Other Sedating Medications

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Dr. Paula Carvalho has no financial relationship to disclose.



Nothing to disclose

Topics:

- Normal sleep architecture
- Respiratory control during sleep
- Effects of opioids on sleep architecture and respiratory control
- Management of opioid-induced sleep disorders
- Effects of other sedative-anxiolytics on sleep



Physiologic sleep

Normal sleep:

Relaxed / Waking



Stage 1 Light Sleep



Stage 2 Light Sleep



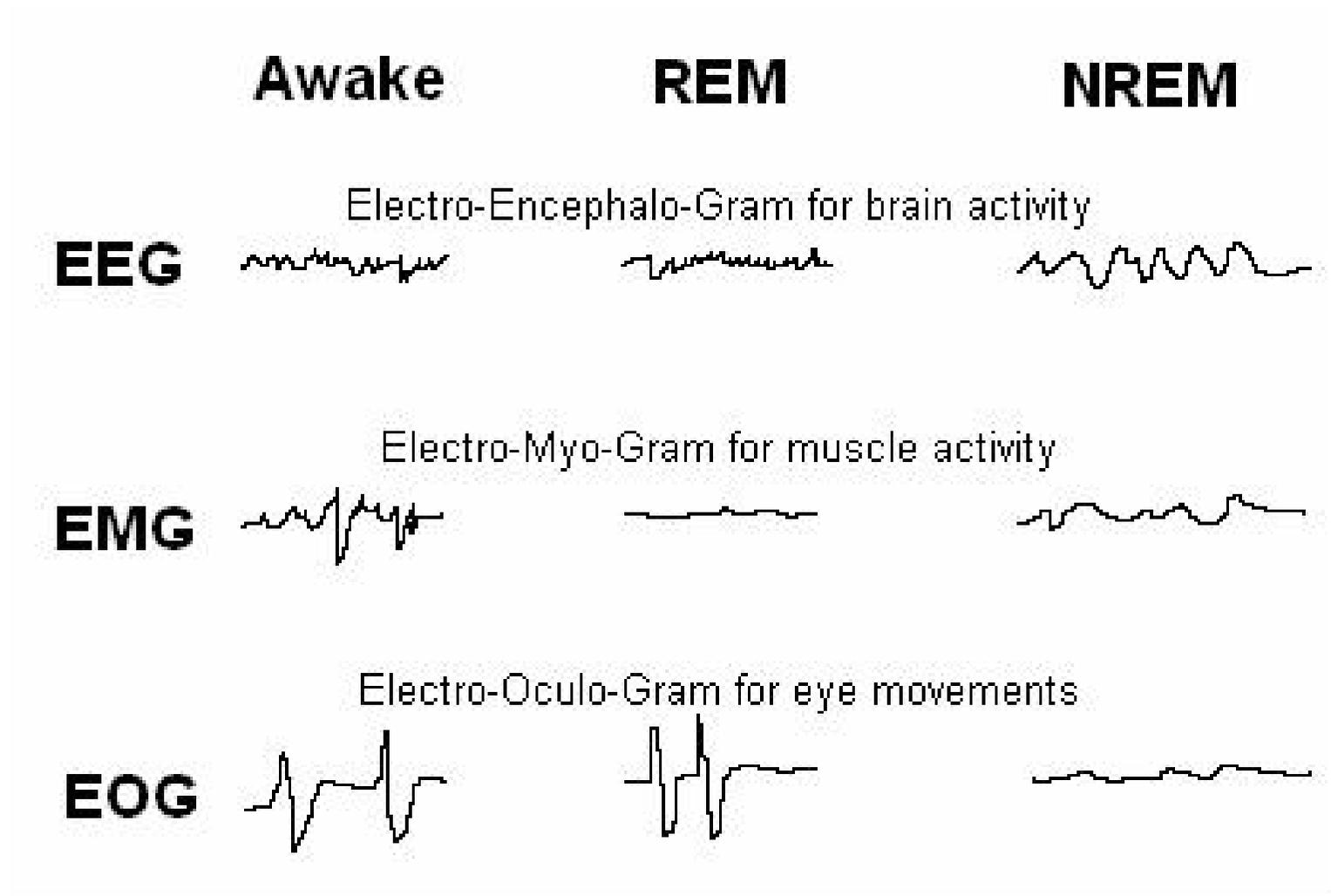
Deep Sleep



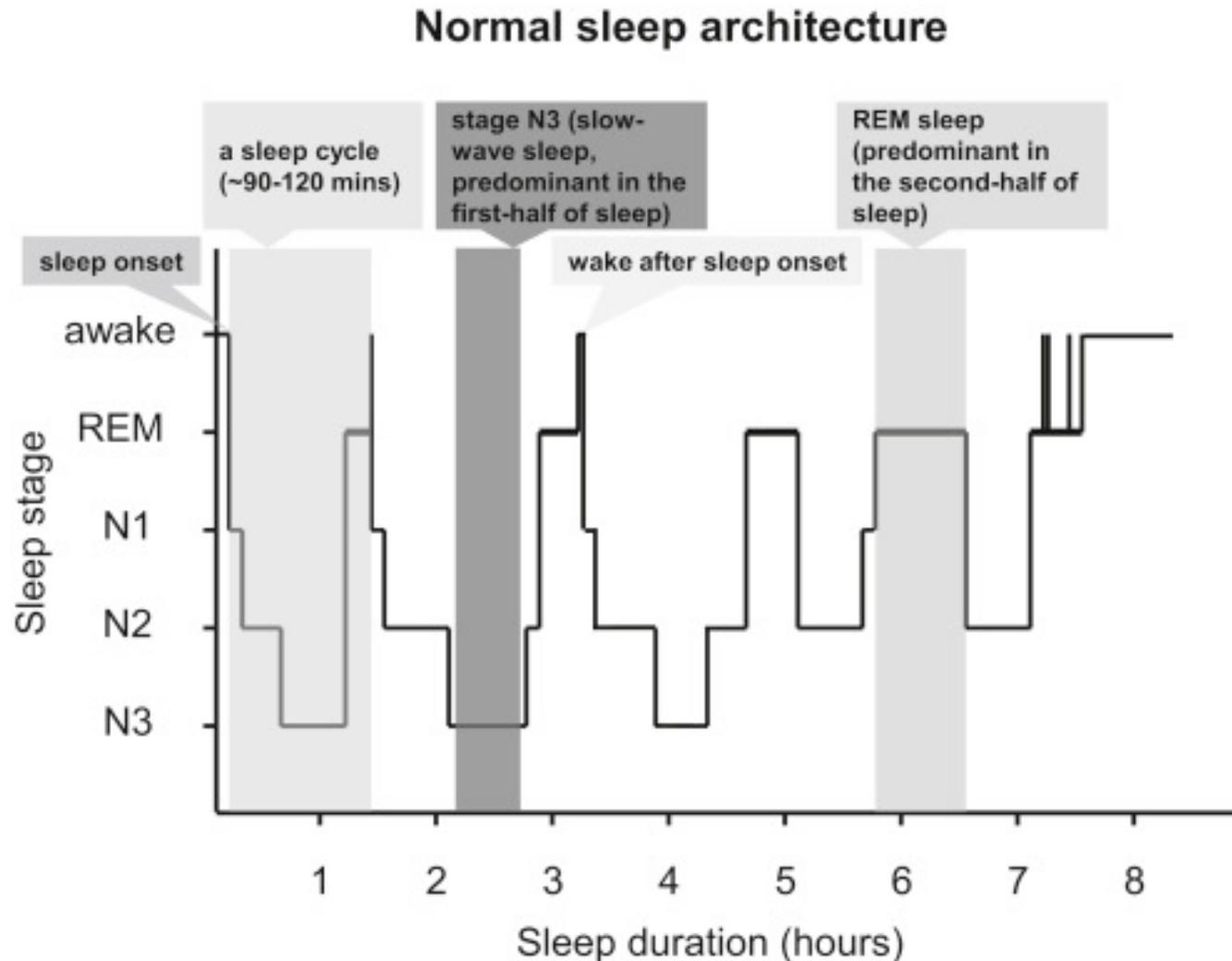
REM / Dreaming



Normal sleep: N-REM and REM

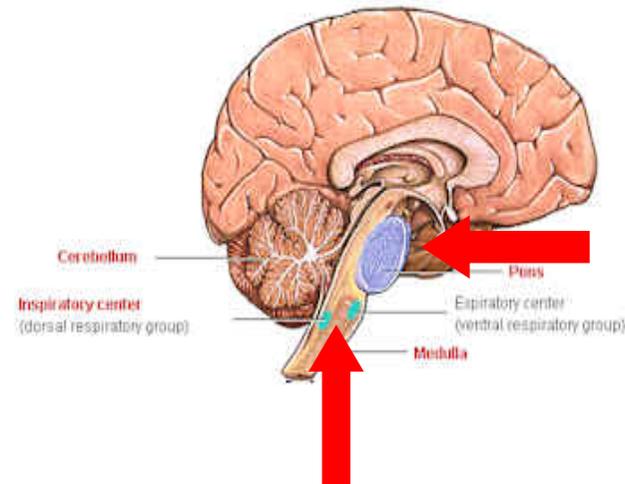


Normal sleep architecture:

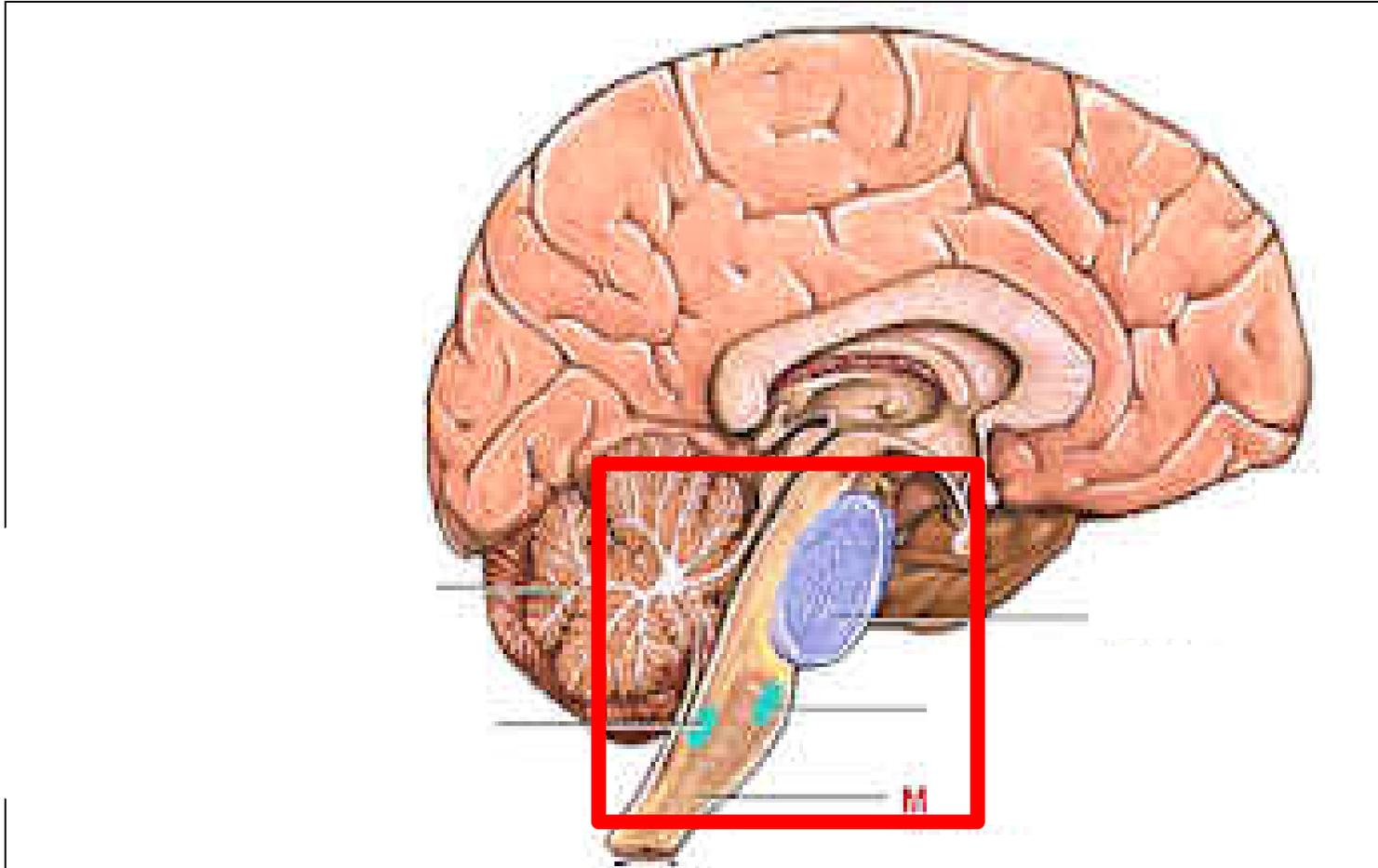


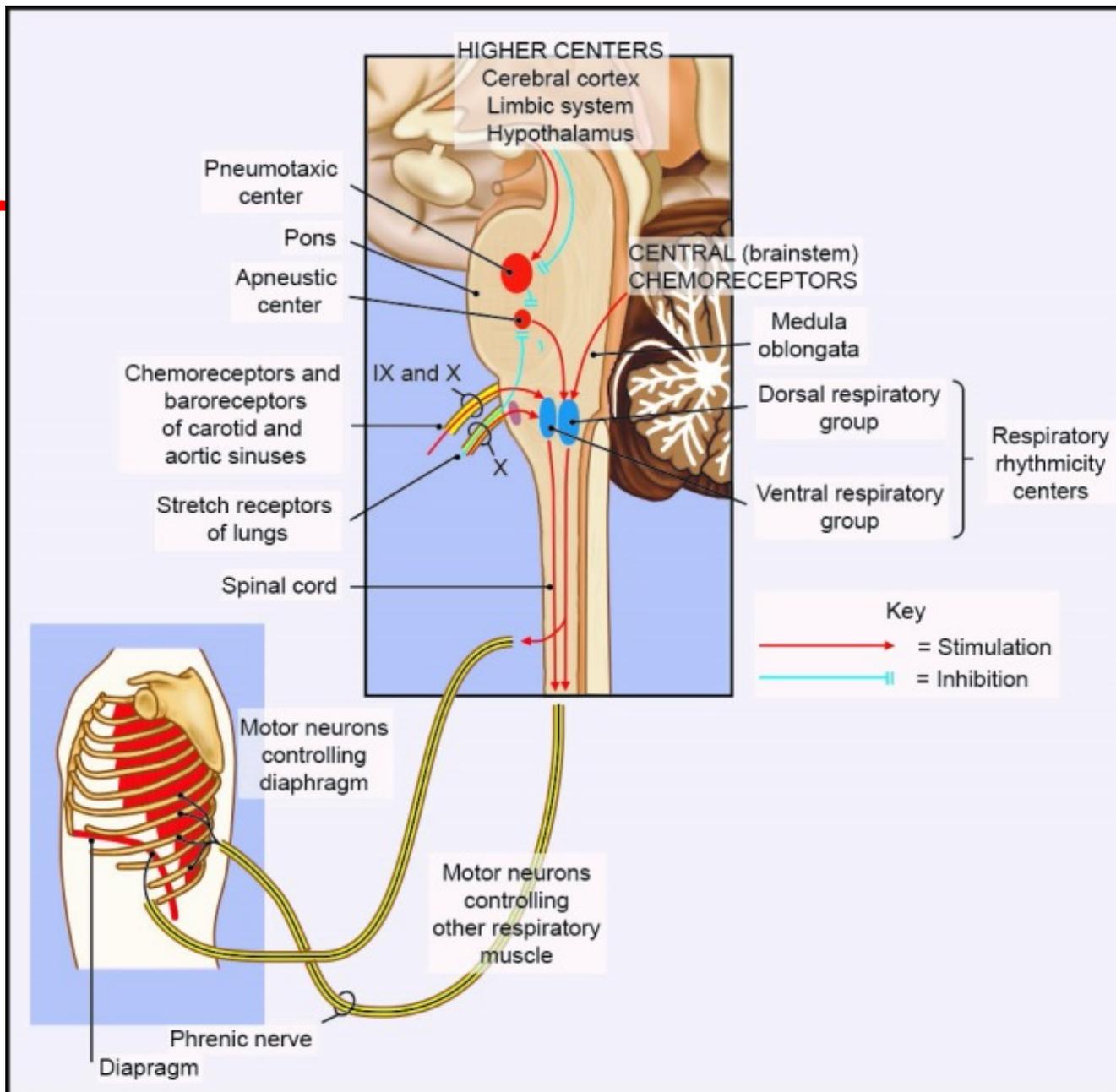
Where are the central chemoreceptors located?

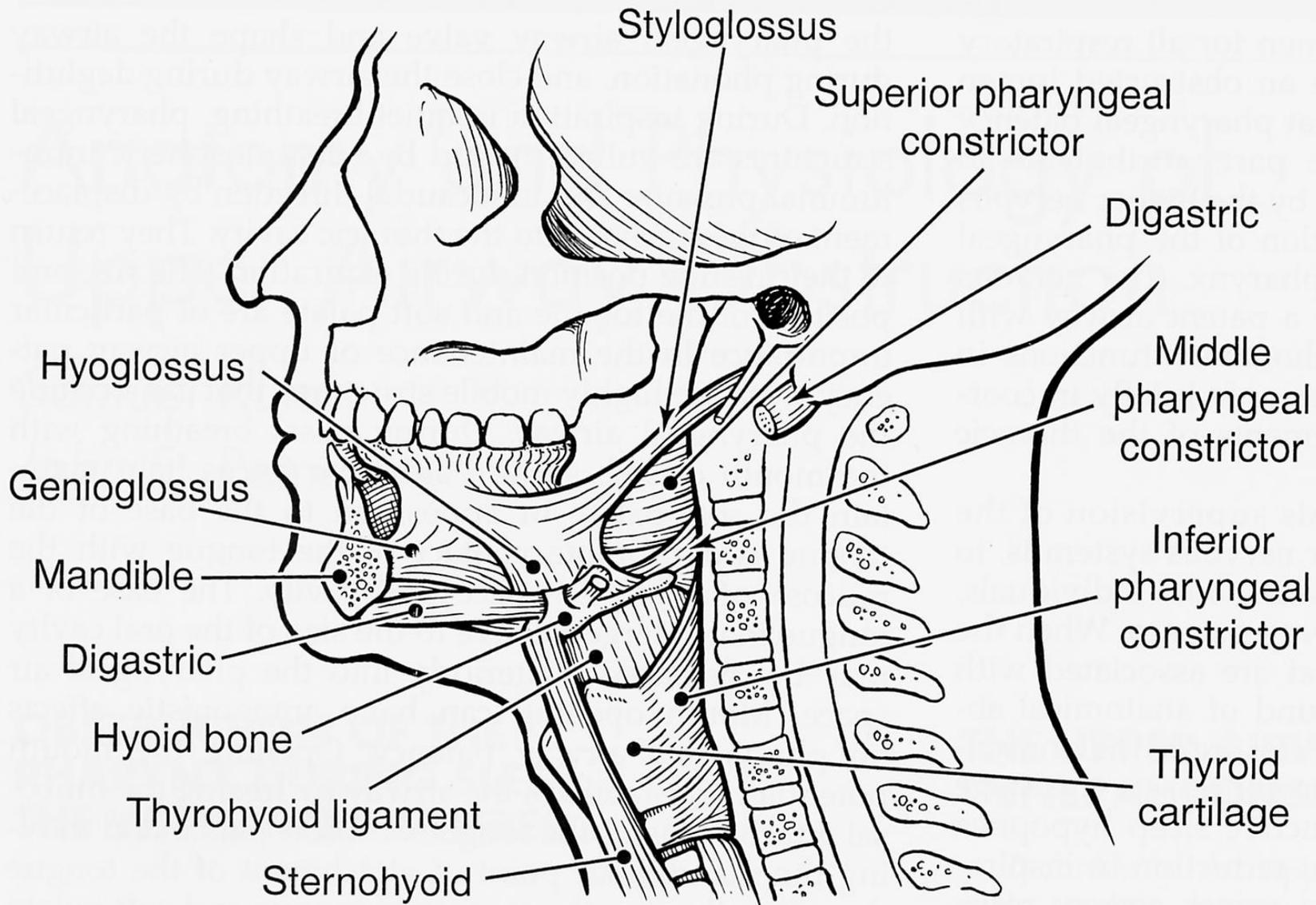
- Central nervous system chemoreceptors are located on the ventral surface of the **medulla oblongata and mid-brain**.
- Chemoreceptors respond immediately to changes in **pH**.

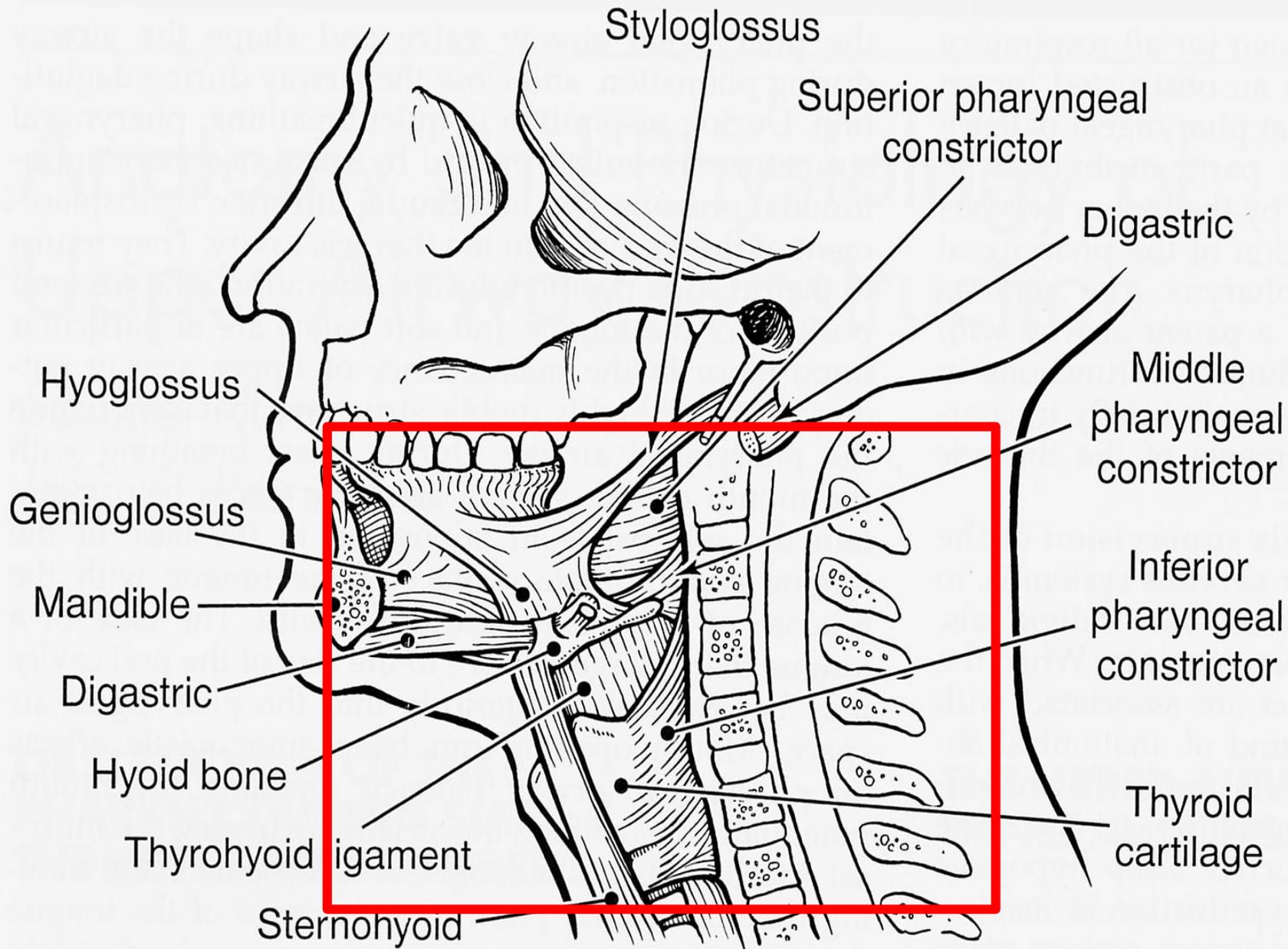


High density of opioid receptors: Pons and medulla

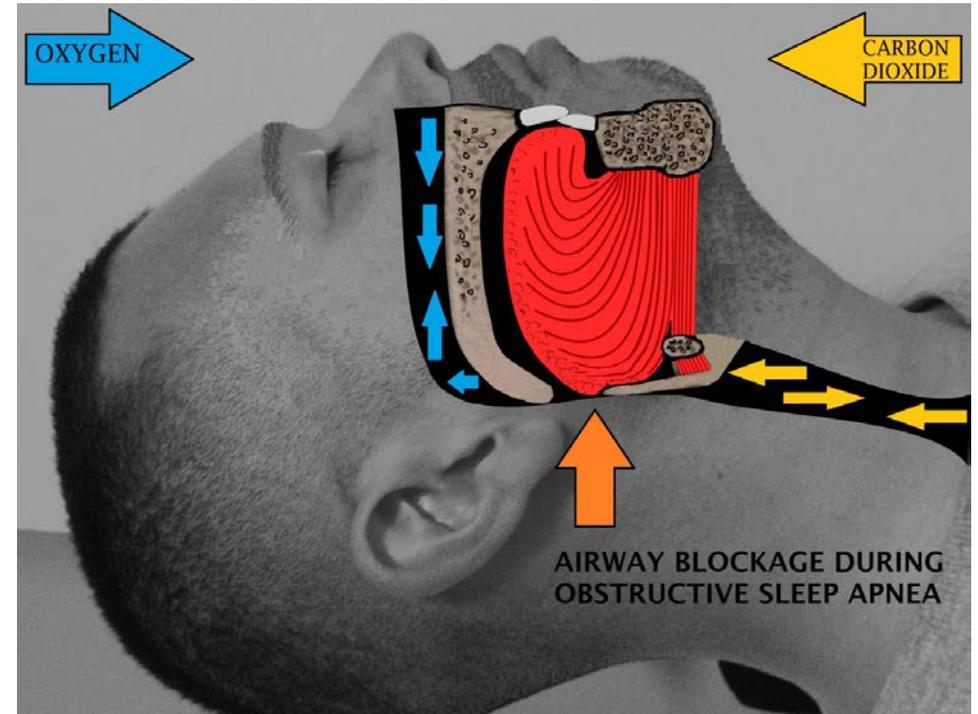
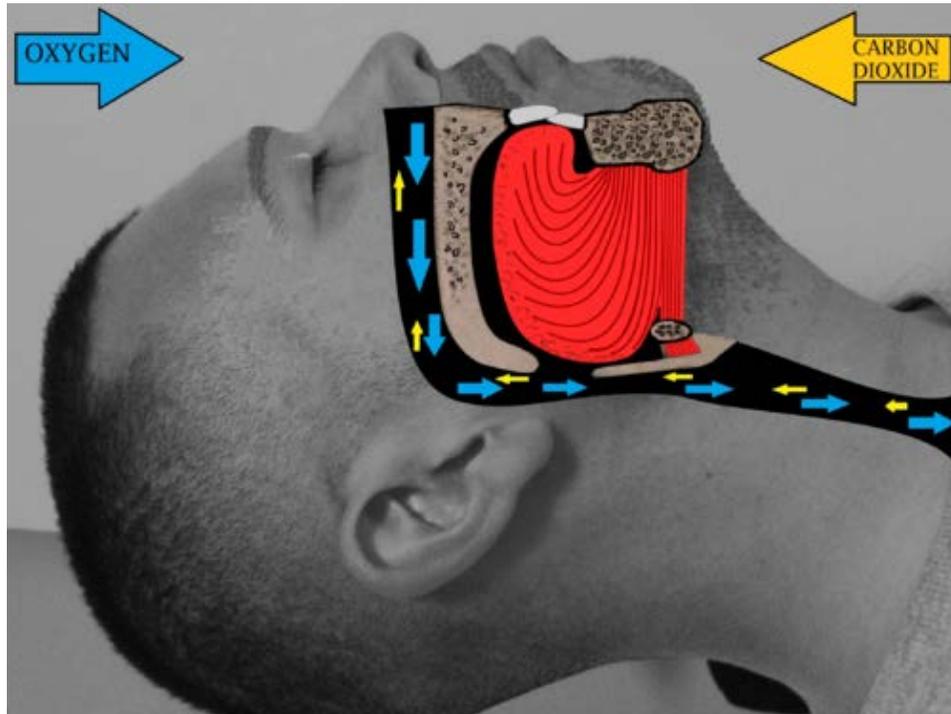




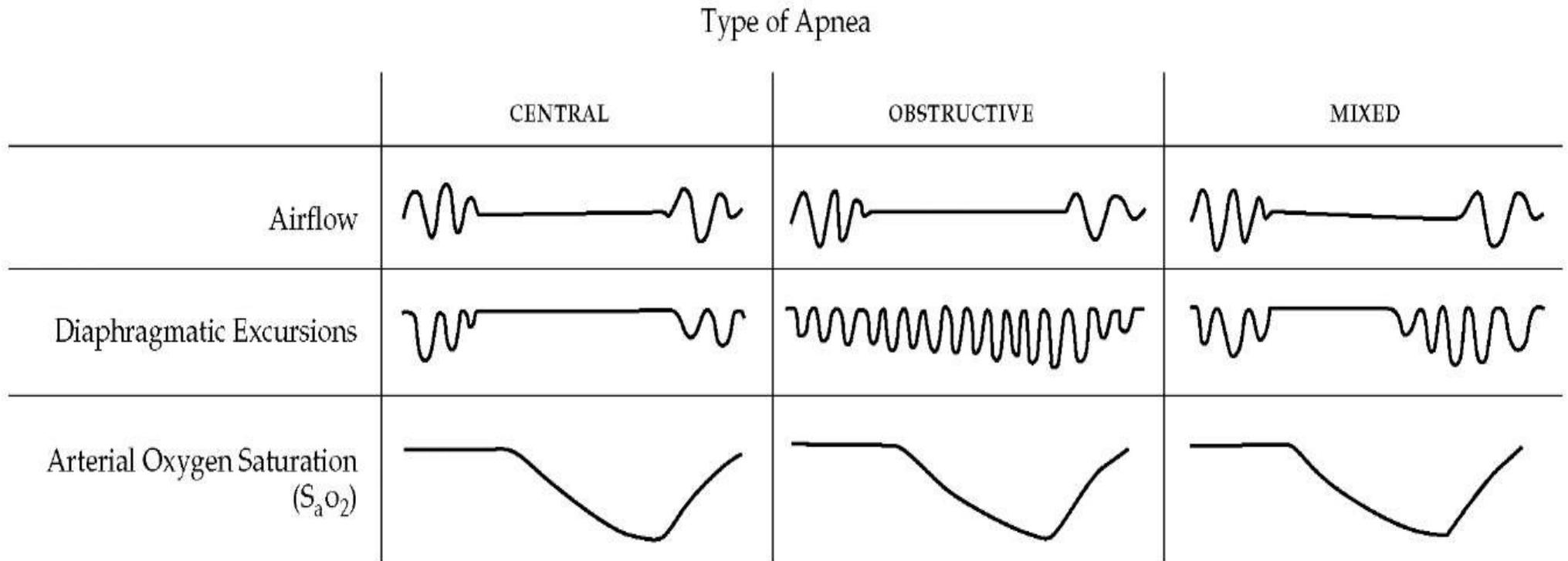




Airflow during sleep:



Respiratory abnormalities during sleep:



Opioid effects: Sleep and respiration

Opioids act at several receptor sites:

- Analgesia: *Mu, kappa, delta*
- Sedation: *Mu, kappa*
- Respiratory depression: *Mu*

Decreased respiratory rate

Decreased response to hypoxia and hypercapnia

Decreased pharyngeal muscle tone

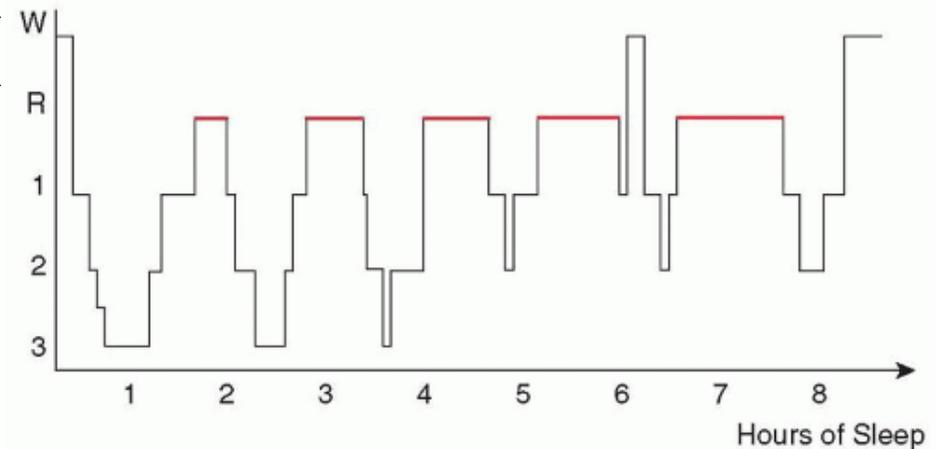
Effects of opioids on sleep architecture in opioid-dependent patients:

- Increased number of shifts in sleep-waking states
- Decreased sleep duration and efficiency
- Decreased the total sleep time, sleep efficiency
- Increased N2 sleep
- Decreased slow-wave (
- Decreased REM sleep

Kay et al., 1979

Pickworth et al., 1981

Staedt et al., 1996



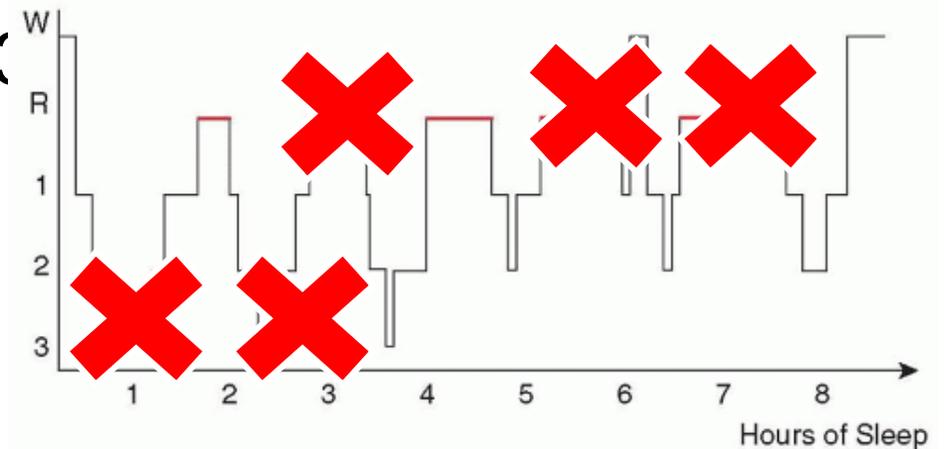
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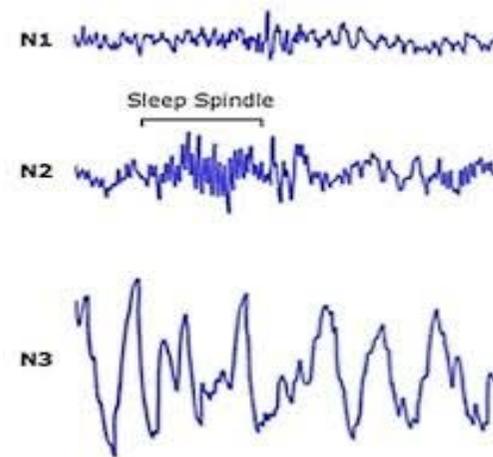
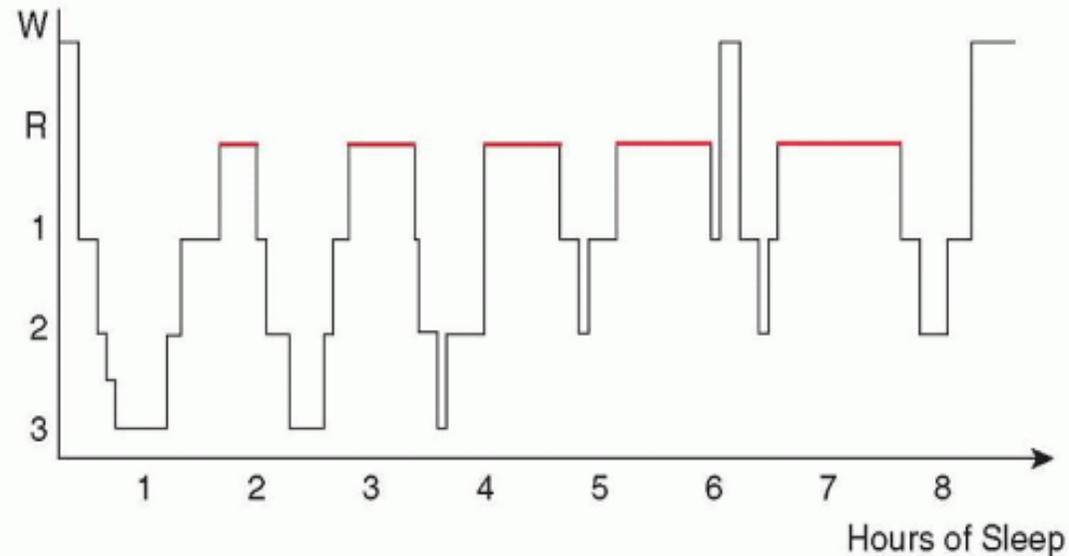


Sleep stage: N3 (slow-wave sleep)

Purpose of N3:

Restorative stage for repair of muscles and body tissues.

First part of night.

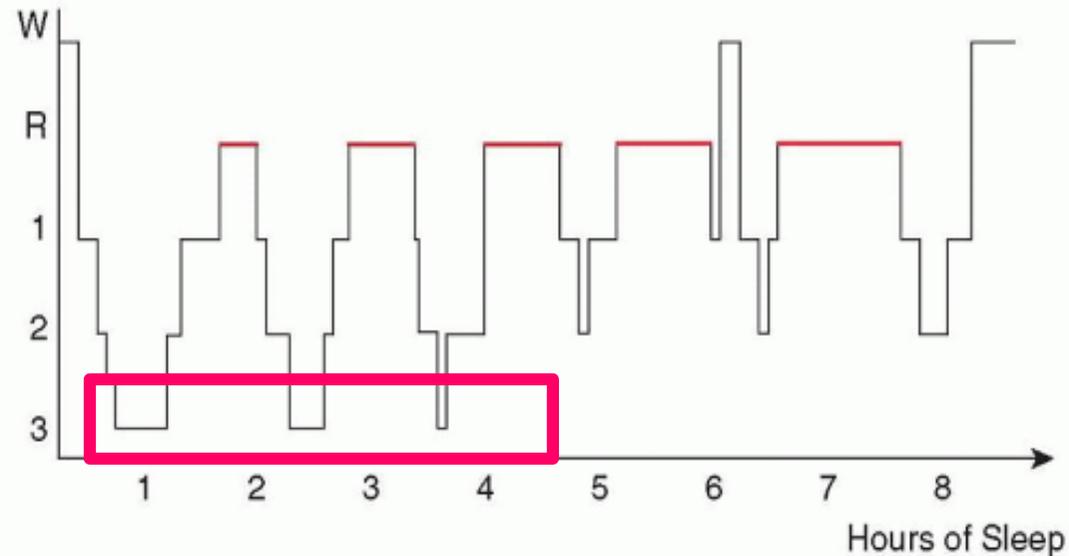


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Sleep Spindle

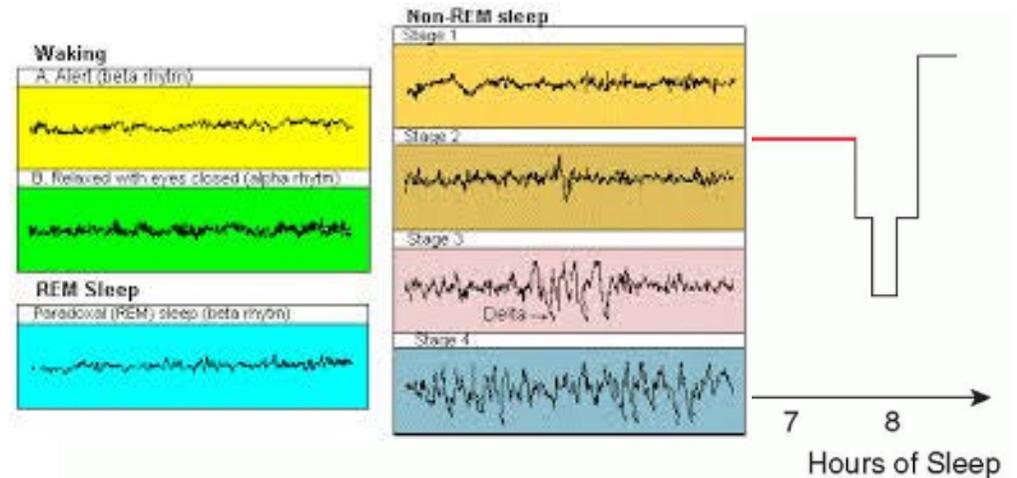


Sleep stage: REM (rapid-eye movement)

Purpose of REM:

Stimulates the area of the brain that is in charge of learning, making and retaining memories.

Longer episodes as the night progresses.

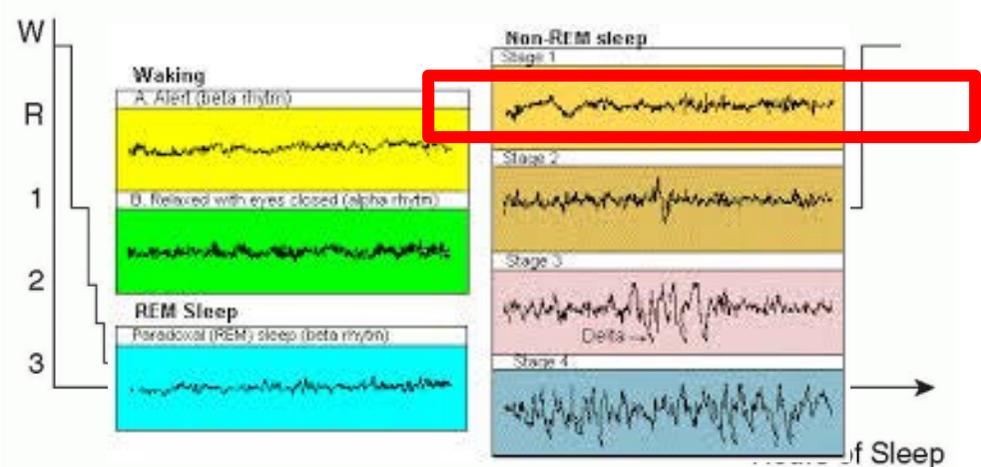


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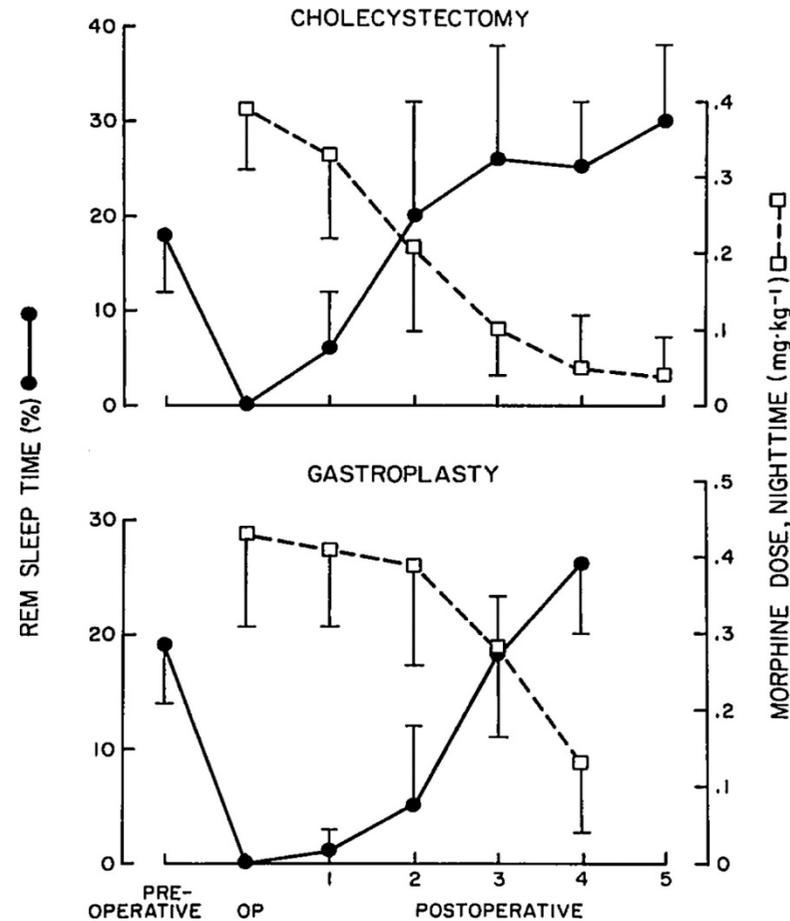
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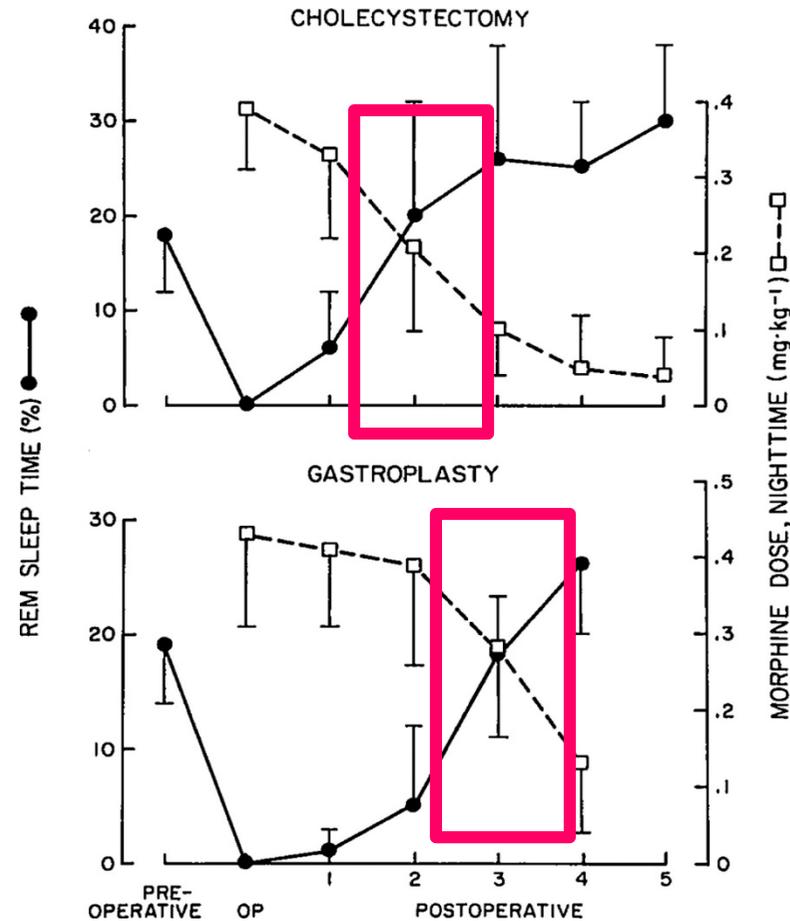
Effects of morphine on post-operative patients:

Knill et al., Anesthesiology, 1990



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Sleep in Critical Illness

Sleep and medication in critical illness:

- Reduction in REM sleep can occur with narcotics, SSRI, antidepressants, and vasopressors.
- In post-operative and critically ill patients, delirium generally occurs during days 3-5.
- This coincides with the period of REM rebound.

(Weinhouse et al. Crit Care Clin 25:539, 2009)

Sleep Disorders Caused by Opiate Addiction:

Insomnia

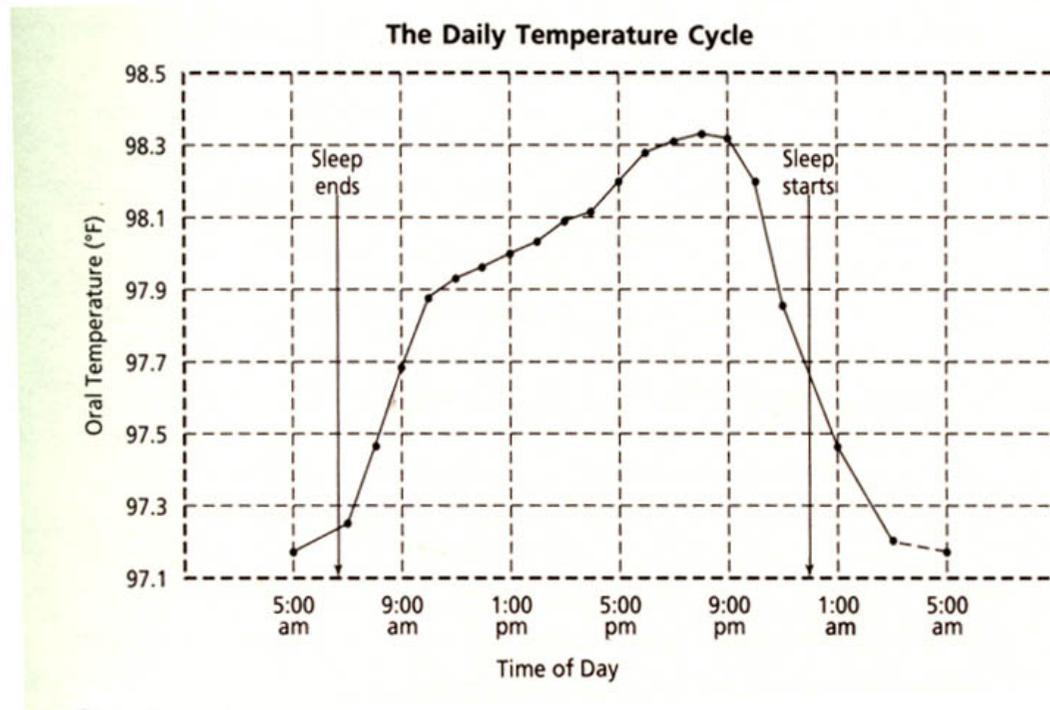
Individuals taking opioids suffer from sleep deprivation due to sleep-onset or sleep-maintenance insomnia and reduced deep sleep.

Parasomnia

Parasomnia is a group of sleep disorders that disrupt sleep and lead to sleep deprivation, such as sleepwalking and REM Sleep Behavior Disorder. Opioids interfere with sleep patterns and can also cause individuals to engage in abnormal behaviors during sleep that are characteristic of these disorders.

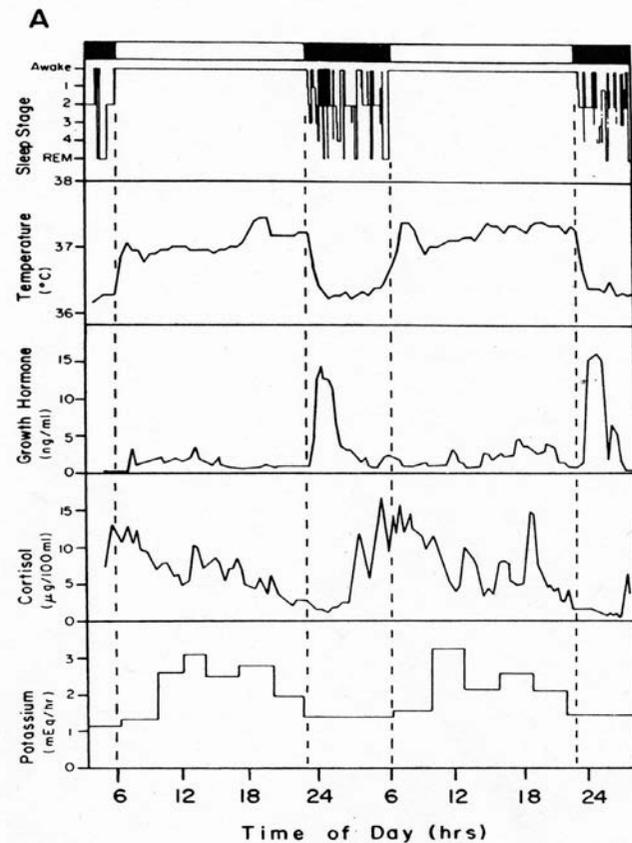
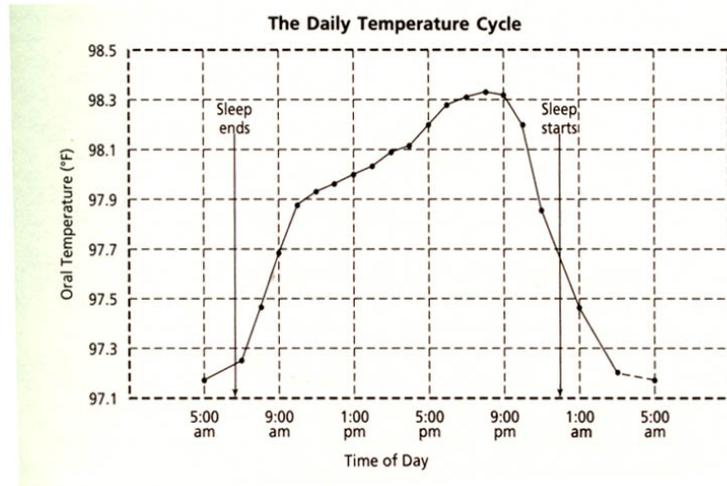
Sleep Disorders Caused by Opiate Addiction:

Opiate-induced abnormalities in circadian rhythms:



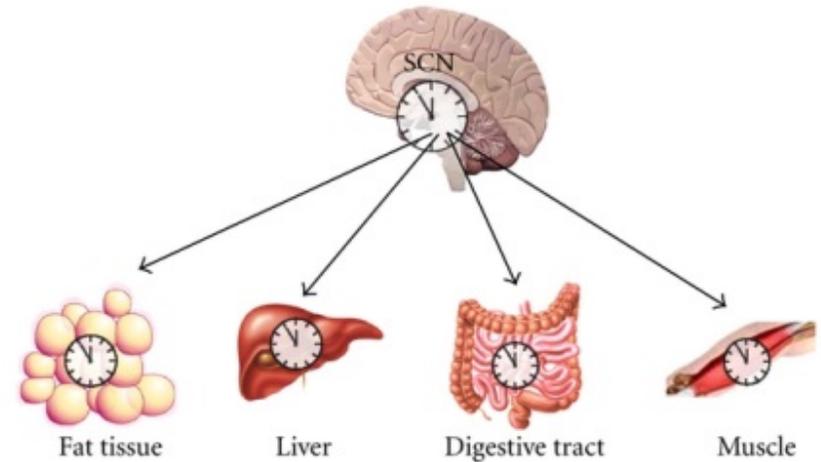
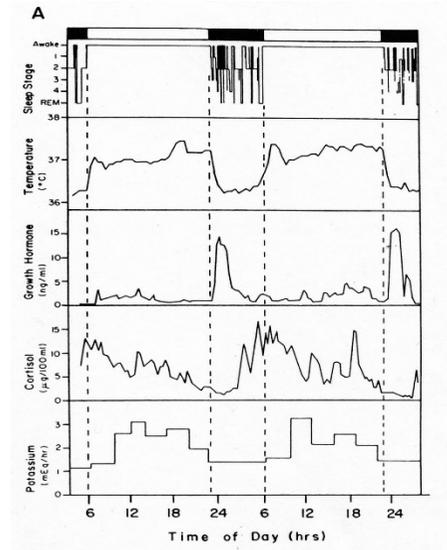
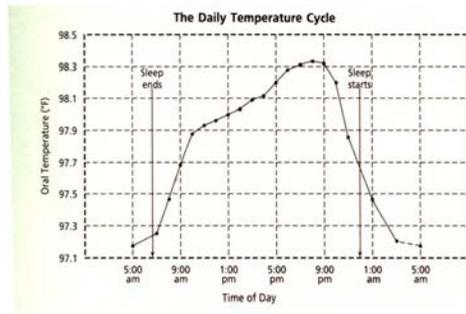
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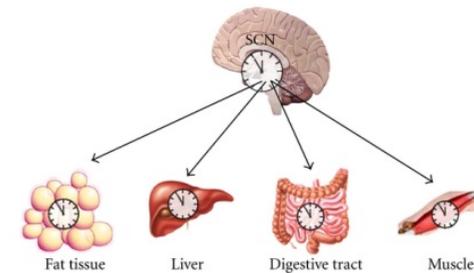
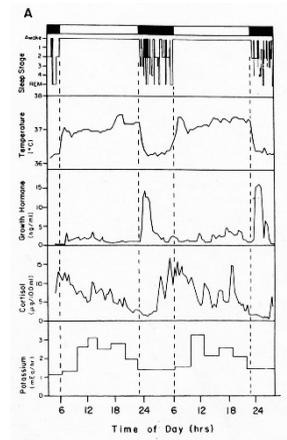
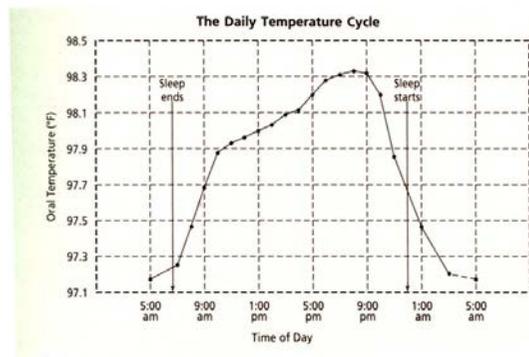
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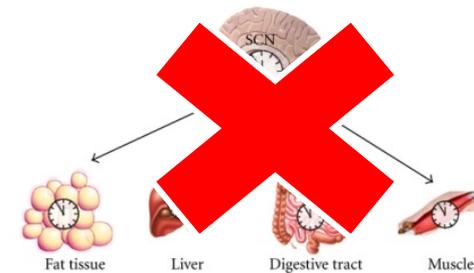
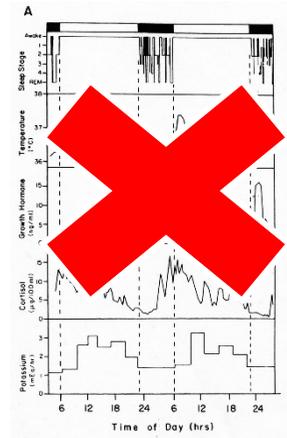
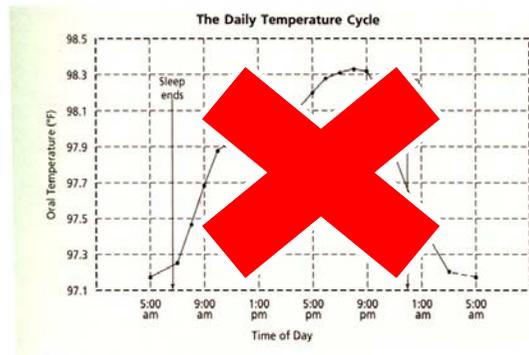
Opioids and opioid withdrawal disrupt the temporal organization of sleep and cause disruption of clock genes.



Sleep Disorders Caused by Opiate Addiction:

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Risk Factors for Opiate-Related Sleep Disordered Breathing

Opiate effects on respiration during sleep:

Risk factors

These are NOT classical risk factors for sleep apnea.

- Low-to-normal body mass index
- Morphine equivalent doses of ≥ 200 mg
(the type of opioid used is less important than the dose)
- Concurrent benzodiazepine and antidepressant use

Management of Opiate-Related Sleep Disordered Breathing

Opiate effects on respiration during sleep: Management

- Lowering the opioid dose below 200 mg morphine equivalent
- Reduce other concurrent medications with respiratory depressant effects
- Positive airway pressure
- CPAP is less effective than Adaptive Servo Ventilation (ASV) or rate-controlled bilevel positive airway pressure
- Concurrent oxygen use, but only with positive airway pressure
- Repeat polysomnography and titration if opioid dosing is increased

Opiate effects on respiration during sleep: Management

Ampakines:

Experimental drugs which have been shown to improve opioid-induced ventilation without loss of the analgesic effect

Ampakines modulate the action of the glutamate neurotransmitter, decreasing opiate-induced respiratory depression

[Clin Pharmacol Ther. 2010 Feb;87\[2\]:204-11](#)

Effects of other sedative/anxiolytics on sleep:

Benzodiazepines: Increased N2, decreased N1 and N3

Non-benzodiazepine receptor agonists: Maintain sleep architecture

Orexin receptor antagonists: Increased REM sleep, no effect on NREM sleep

Melatonin and receptor agonists: Reduced N1, otherwise maintained NREM/REM cycles

Atypical antipsychotics: Suppress REM sleep, increase N3

SSRI: Increase or no effect on N3, decreased REM

TCAs: Increased N3, Increased REM

Conclusions:

- Chronic opioid therapy is associated with abnormalities in respiratory control during sleep and wakefulness.
- Hypoventilation, central and obstructive sleep apnea, and irregular (ataxic) breathing patterns can occur with opioid use, with increasing risk if morphine equivalent dosing is ≥ 200 mg.
- Management includes lowering opioid dose and avoiding other concomitant respiratory depressants. When needed, respiratory augmentation with positive airway pressure should be utilized.



