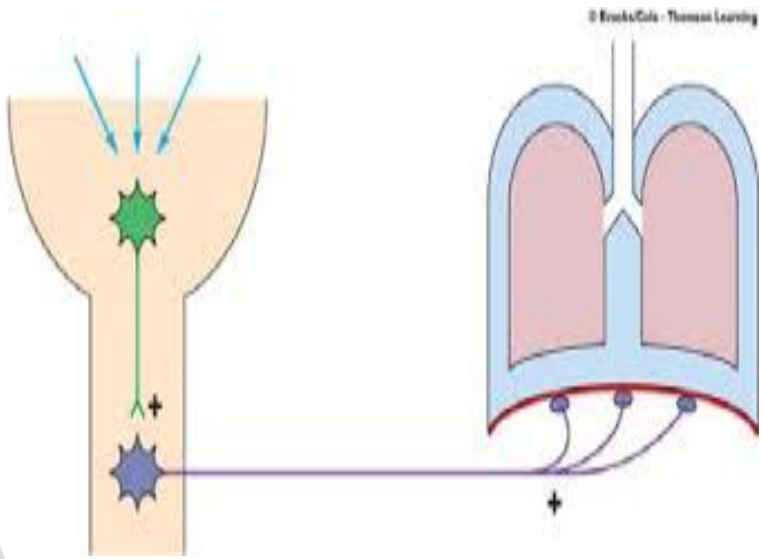
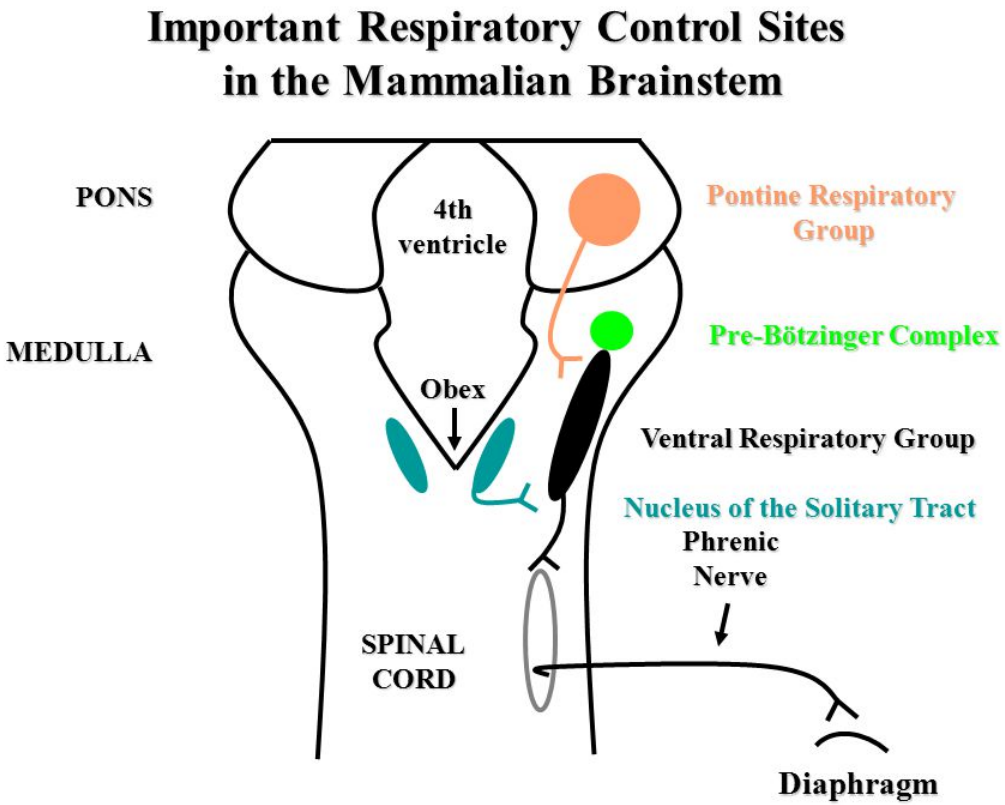
Opioids, Dyspnea and Risks

Opioids and Respiration

- Opioids delay inspiration through hyperpolarization of pre-Botzinger complex neurons thereby slowing respiratory rate by delaying inspiration
- Tidal volume compensatorially increases when doses are low thereby maintaining minute ventilation which is lost with higher opioid doses
- An inspiratory cycle is missed (called quantal breathing or integer multiples of the control period of breathing in the absence of the opioid





Opioids and Respiration

- Opioids are not associated with Cheyne -Stokes respiration
- Hypoxic drive is depressed to a greater extent than hypercapnic drive and suppression is longer lasting
- Opioids blunt responses to hypoxia by binding to mu receptors within the Nucleus Tractus Solitarius , blocking neurotransmission from Glomus cells to the medulla

Opioids and Respiration

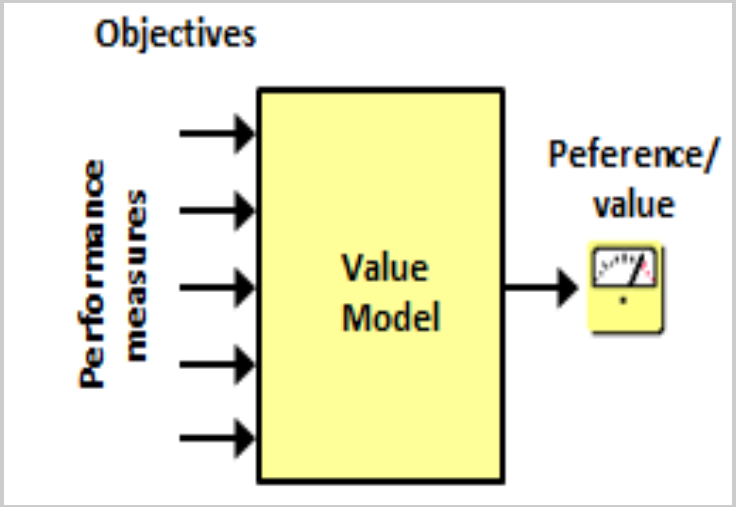
- Breath to breath tidal volume variability and delayed hyperventilation response to rising pCO2 levels suggests both a central and peripheral opioid effect
- Blunted respiratory response to context cues (breathholding) is increased

Not All Opioids Are The Same

Utility Function

UF allows objective and reliable characterization of individual opioid benefits and risks over time and dose in order to determine which opioid is safer to use and which dosing strategy places the patient at the least risk during opioid therapy

Kharasch E 2013



Buprenorphine, Fentanyl PK/PD

- D- prospective animal study
- P- Mouse model
- I- Buprenorphine and Fentanyl
- O- PK/PD
  - Plethysmography to quantitate ventilation
  - Tail flick antinociception
  - Respiratory depression-"yes/no" at 50% decline in ventilation
  - Antinociception-"yes/no" at tail flick latency >10 s
  - Concentration/effect odds ratio

Yassen A 2007

Buprenorphine, Fentanyl, PK/PD Effectiveness, Safety

- Buprenorphine antinociception OR 28.5 (6.9-50.1) favoring analgesia
- Buprenorphine respiratory depression OR 2.10 (0.71-3.49)
- Fentanyl antinociception OR 3.03 (1.87-4.21)
- Fentanyl respiratory depression OR 2.54 (1.26-3.82)
- OR (PA/PR) 13 to 1 in favor of buprenorphine (PA>PR)

Yassen A 2007

PK/PD Respiratory Effects Fentanyl and Buprenorphine

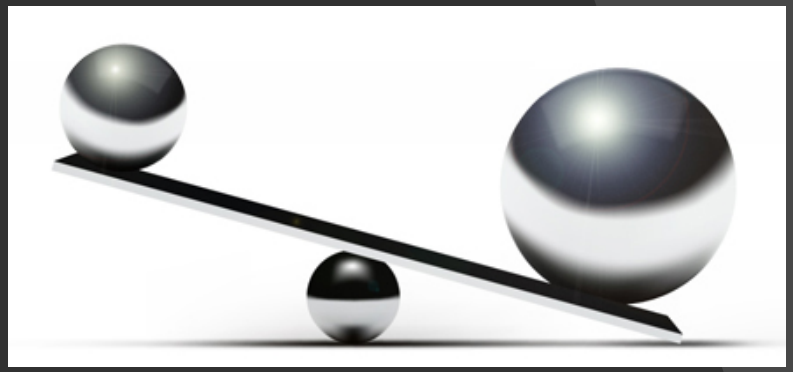
- D- Prospective study
- P- Healthy volunteers (n=74)
- I- Buprenorphine doses 0.05 to 0.6mg, fentanyl doses 0.075 to 0.5mg
- O-Respiratory response to PetCO2 at 50%

  PK/PD modeling

Yassen A 2007

PK/PD Buprenorphine , Fentanyl Respiratory Depression

- Biophase equilibrium-16 vs. 75 minutes (buprenorphine)
- Buprenorphine was a partial agonist with intrinsic activity of 0.51 and ceiling effect
- Fentanyl was a full agonist with an intrinsic activity of 0.91



Yassen A 2007


Vulnerable
Populations

Chronic Pain, SDB w/wo Opioids

- A comparison of patients on opioid therapy for chronic pain and a similar cohort of patients with chronic pain not on opioids found a AHI of 41 in those on opioids and 22 in those not on opioids ($p=0.018$).
- In a subset who underwent opioid taper, the AHI decreased to 16-17 ($p<0.01$).
- Central sleep apnea resolved off opioids. Hypoxia during REM sleep which had occurred in 27% of individuals before opioid taper also improved significantly ($p<0.01$)

COPD and SDB

- Those with SBD and comorbid COPD (overlap syndrome) or those with cardiovascular disease are at greater risk of for arrhythmias at night.
- The overlap syndrome compounds the risk of nocturnal arrhythmias relative to COPD or SDB alone.
- Those with the overlap syndrome have a 2.5-fold greater risk of tachyarrhythmias relative to those with OSA alone

Cardiovascular Disease and SDB

- Patient with a pre-existing cardiovascular disease and SDB have higher healthcare costs and a greater risk for adverse cardiovascular events with an odds ratio (OR) of 4.1 (95%CI 1.8 – 9.3) compared with matched controls without SDB
- The number of obstructive events and the degree of hypoxemia during sleep strongly predicts for occurrence of an arrhythmia

Author (Reference)	Numbers	Benefits / Risks	NNT	Comments
Elkstrom M	N=271	Dyspnea relief	7-9	All but I study< 30 days in duration
Barnes H	Systematic review of 26 studies with N=526	Dyspnea relief	9-10	All but I study< 30 days in duration
Vozoris NT	N=130,979	Risks	HR/NNH	Opioid
	Matched-cohort study	Hospitalizations	HR1.5 / NNH 66	Short-acting opioids
		COPD/pneumonia related mortality	HR 4.79 /NNH 77	Short-acting opioids
		All-cause mortality	HR 3.38 / NNH 28	Mortality related to cardiac events
Vozoris NT	N=22,912	Hospitalizations	HR 1.73 /NNH 71	Morphine dose<30mg/day
	Matched-cohort study	COPD/pneumonia related mortality	HR 7.55 / NNH 71	Morphine dose<30mg/day
		All-cause mortality	HR 5.19 / NNH 17	Morphine dose<30mg/day

Summary

- Opioids adversely influence respiratory function and worsen sleep disordered breathing rendering certain populations at risk for sudden deaths and cardiovascular deaths.
- Physicians rarely screen individuals for risks
- Not all opioids are the same but further clinical studies need to explore this