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