



7th Annual Meeting • October 19-20, 2017 • Boston, MA

# Pain and analgesia in the postoperative patient with obstructive sleep apnea

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## DISCLOSURE

I have no financial relationships with commercial support to disclose.

# Learning objectives

At the conclusion of this activity, participants should be able to:

Identify hyperalgesic phenotypes in obstructive sleep apnea

Evaluate the risk for altered pain perception in patients with OSA

Determine the risk for opioid-induced respiratory depression

Select appropriate analgesic regimens in the context of OSA

# Is obstructive sleep apnea hyperalgesic?

Nocturnal intermittent hypoxia

Sleep deprivation; sleep disruption

Excessive daytime sleepiness

Systemic inflammation

Comorbid insomnia

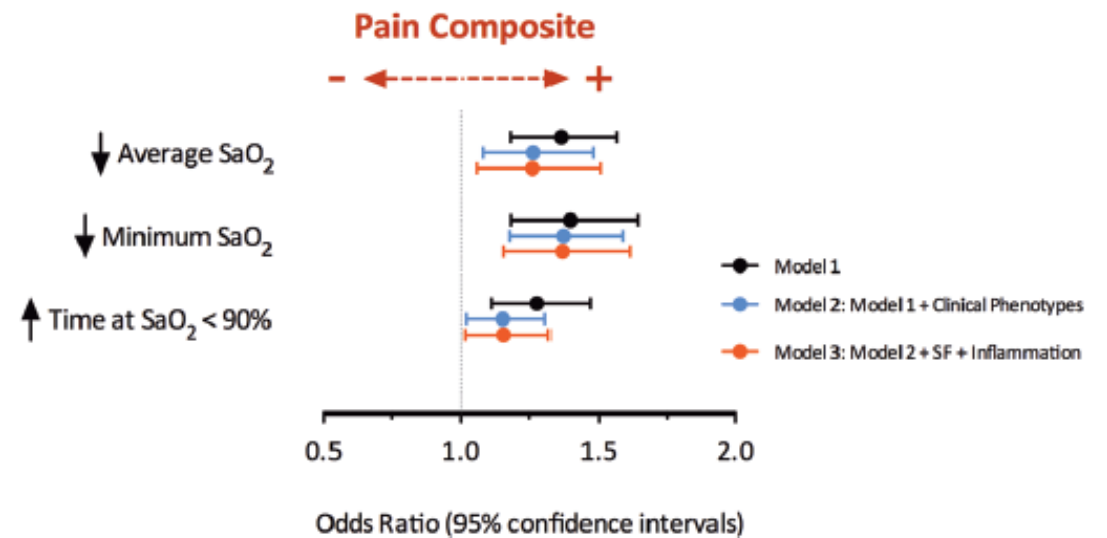
# Intermittent hypoxia

## Cleveland Family Study

- Family-based longitudinal cohort
- 634 OSA and controls
- 4 types of pain

## Nocturnal Intermittent Hypoxia Is Independently Associated with Pain in Subjects Suffering from Sleep-disordered Breathing

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A decrease in the minimum nocturnal SpO<sub>2</sub> from 92 to 75% almost doubled the odds for reporting pain

# Sleep deprivation and sleep disruption

Sleep deprivation promotes inflammation<sup>1</sup> and spontaneous pain<sup>2</sup> in healthy volunteers

Sleep disruption decreased central pain inhibition by 60% in healthy women<sup>3</sup>

CPAP (6-8 weeks) reduced sensitivity to heat pain by 40-100% in patients with severe OSA<sup>4</sup>

<sup>1</sup>Haack, Pain, 2007

<sup>2</sup>Haack, Pain, 2009

<sup>3</sup>Smith, Sleep, 2007

<sup>4</sup>Khalid, Sleep, 2011

# Excessive daytime sleepiness

“Sleepy” (MSLT 4.8 vs 12.6 min) pain-free volunteers have 40% lower pain thresholds than the non-sleepy ones<sup>1</sup>

In “sleepy” volunteers, an extended sleep opportunity increased pain thresholds by 25%<sup>2</sup>

Physiological sleepiness diminished the acute anti-nociceptive effect of codeine in healthy volunteers<sup>3</sup>

<sup>1</sup>Chhangani, Sleep, 2009

<sup>2</sup>Roehrs, Sleep, 2012

<sup>3</sup>Steinmiller, Exp Clin Psychopharmacol, 2010

# Systemic inflammation

OSA is a chronic inflammatory state

Both sleep fragmentation and intermittent hypoxia can trigger systemic inflammation via:

- Oxidative stress and sympathetic activation<sup>1</sup>

Cleveland Family Study

- Soluble IL-6 receptor levels were positively associated with nocturnal hypoxemia and arousal index<sup>2</sup>

<sup>1</sup>Arnardottir, Sleep, 2009

<sup>2</sup>Mehra, Arch Intern Med, 2006

# Insomnia comorbid with OSA

OSA and insomnia co-occur to a high degree<sup>1</sup>:

- 58% of OSA patients complain about insomnia
- 67% of patients with insomnia are also diagnosed with OSA

Experimental pain models have demonstrated:

- Insomnia decreased central pain inhibition<sup>2</sup>
- Insomnia and chronic pain synergistically increase pain<sup>3</sup>

<sup>1</sup>Luyster, J Clin Sleep Med, 2010

<sup>2</sup>Haack, Eur J Pain, 2011

<sup>3</sup>Sivertsen, Pain, 2015



# Opioid analgesia in patients with OSA

Animal and ex vivo models

Pediatric populations

Adult populations

# IH enhances opioid sensitivity in animals

Recurrent hypoxemia increased binding in the mu-opioid receptors (MOR) in rat's brainstem<sup>1</sup>

- Up-regulation of MOR?

Recurrent hypoxemia during development increased sensitivity to the respiratory effects of fentanyl in rats<sup>2</sup>

<sup>1</sup>Laferriere, Brain Res Bull, 2003

<sup>2</sup>Moss, Anesthesiology, 2006

# Tonsillectomy in children for OSA treatment

Nocturnal hypoxemia reduced morphine requirement for postoperative analgesia<sup>1</sup>

- Nadir nocturnal SpO<sub>2</sub> < 85%, decreased the dose of morphine by half<sup>2</sup>

Increased morphine requirement postoperatively in OSA<sup>3</sup>

- Higher incidence of respiratory complications

Racial disparity in the postoperative pain in OSA<sup>4</sup>

- Increased pain and morphine requirement in AA, compared with Caucasian children with OSA

<sup>1</sup>Brown, Anesthesiology, 2004

<sup>2</sup>Brown, Anesthesiology, 2006

<sup>3</sup>Sanders, Anesth Analg, 2006

<sup>4</sup>Sadhasivam, Pediatrics, 2012

# Adults with OSA and nocturnal hypoxemia

Nocturnal hypoxemia (lower nadir SpO<sub>2</sub>) was associated with higher analgesic potency of remifentanyl in experimental pain<sup>1</sup>

Nocturnal hypoxemia (fraction of sleep time with SpO<sub>2</sub> < 90%) was associated with decreased morphine requirement for postoperative analgesia in bariatric patients<sup>2</sup>

<sup>1</sup>Doufas, PLoS ONE, 2013

<sup>2</sup>Turan, PLoS ONE, 2015

# Pain and opioid analgesic effect in OSA

				Outcome	
Trials	N	Exposure		Pain	Analgesic Dose
EXPERIMENTAL	Khalid 2011	12	OSA diagnosis	↑	-
	Doufas 2013	43	Nadir SpO <sub>2</sub>	↓	↓
PROSPECTIVE	Brown 2006	22	Nadir SpO <sub>2</sub>	-	↓
	Sanders 2006	82	Respiratory distress index	-	↑
	Sadhasivam 2012	194	OSA diagnosis	↑	↑
RETROSPECTIVE	Brown 2004	46	Nadir SpO <sub>2</sub>	-	↓
	Doufas 2013	638	Nocturnal SpO <sub>2</sub>	↑	-
	Turan 2015	218	Time SpO <sub>2</sub> < 90%	-	↓

# Opioids and severe respiratory depression

## ADULTS

Death (55%) or permanent brain damage (22%), among 92 claims in the context of opioid analgesia<sup>1</sup>

- Established diagnosis or high risk for OSA (25%); obesity (66%); somnolence before the event (62%)

Congestive heart failure, postoperative ARF, OSA, and DM, prevalent among patients with life-threatening respiratory events<sup>2</sup>

OSA and respiratory events in PACU predict delayed respiratory depression<sup>3</sup>

- Chronic<sup>4</sup> and postoperative<sup>3</sup> use of benzodiazepines also predict respiratory depression

## CHILDREN

Death or neurologic injury post-tonsillectomy: 57% were at risk for OSA, based on ASA criteria<sup>5</sup>

- In at-risk-for-OSA children, adverse event was predominantly attributed to apnea than hemorrhage

<sup>1</sup>Lee, Anesthesiology, 2015

<sup>2</sup>Ramachandran, J Clin Anesth, 2011

<sup>3</sup>Weingarten, Anesth Analg, 2015

<sup>4</sup>Ramachandran, Anesth Analg, 2017

<sup>5</sup>Coté, Anesth Analg, 2014

# Opioids worsen sleep-disordered breathing

Sleep-disordered breathing and oxygenation worsen after surgery in both OSA<sup>1,2</sup> and non-OSA<sup>3</sup> patients

- Large variation of effect<sup>1</sup>
- For OSA patients, age, preoperative AHI, and opioid dose were major predictors<sup>2</sup>

Among 833 patients recovering from non-cardiac surgery, hypoxemia is common and persistent<sup>4</sup>

- 21% averaged at least 10 min per hour with SpO<sub>2</sub> < 90%
- No difference between the use of long- or short-acting opioids<sup>5</sup>
- STOP-Bang questionnaire does not predict hypoxemia<sup>6</sup>

<sup>1</sup>Chung, Anesthesiology, 2014

<sup>2</sup>Chung, Anesthesiology, 2014

<sup>3</sup>Chung, Anesth Analg, 2015

<sup>4</sup>Sun, Anesth Analg, 2015

<sup>5</sup>Belcher, Anesth Analg, 2016

<sup>6</sup>Khanna, Anesth Analg, 2016

# Respiratory effects of opioids in OSA patients

A 0.5 mcg/kg bolus of fentanyl in children under general anesthesia led to apnea in 46% of OSA vs 5% of controls<sup>1</sup>

Remifentanyl infusion (0.075 mcg/kg/min) during a sleep study resulted in dramatic increase of central apnea in 4 out of 10 adults with OSA<sup>2</sup>

- “Opioid-emergent central sleep apnea”

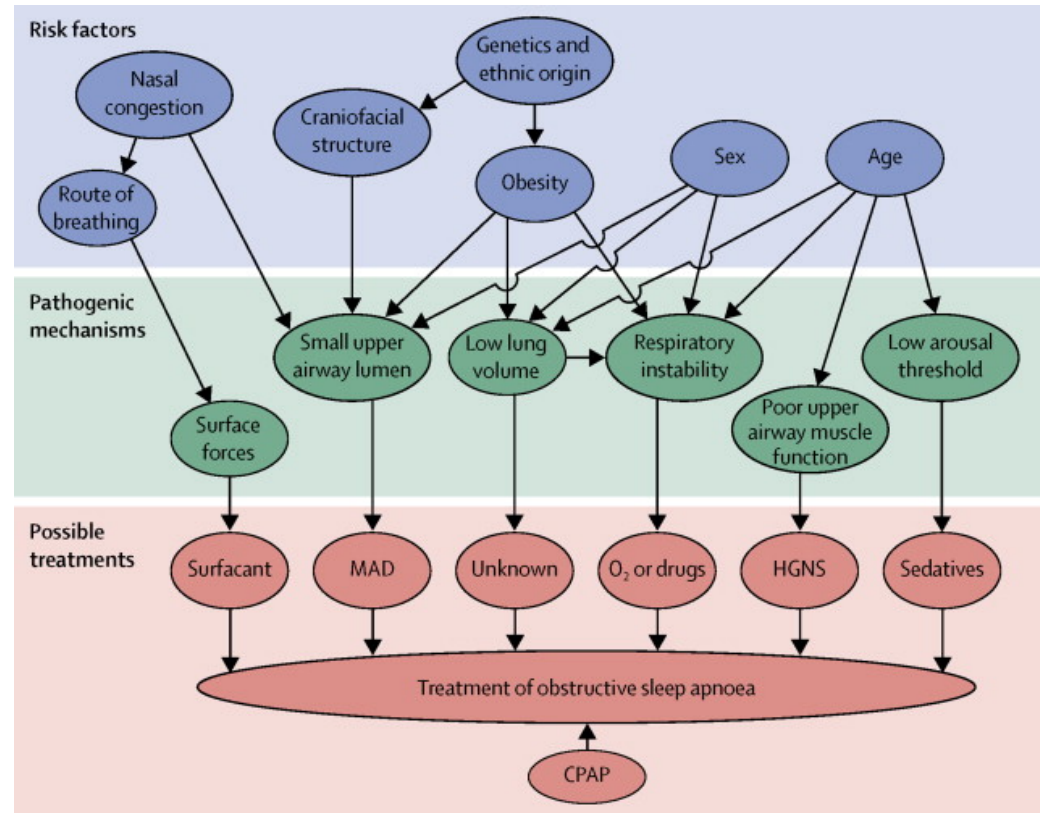
Variable effects of opioids on respiration in the context of OSA

<sup>1</sup>Waters, J Appl Physiol, 2002

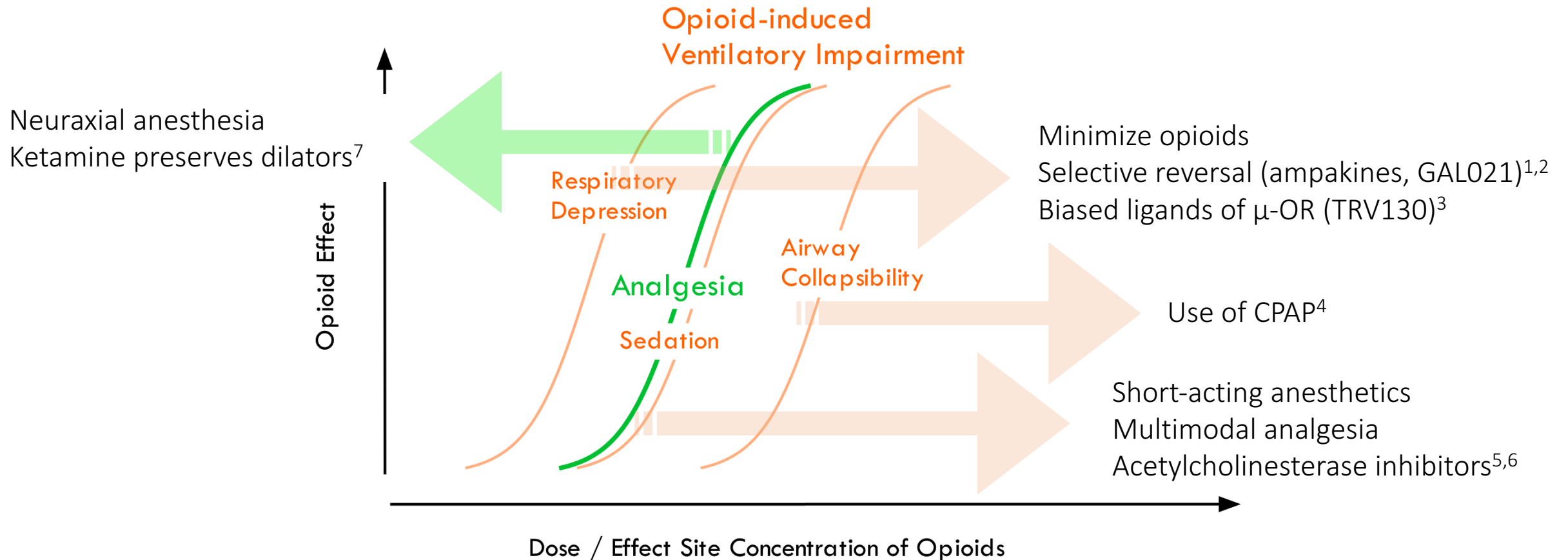
<sup>2</sup>Bernards, Anesthesiology, 2009



# Variability in OSA pathogenic mechanisms



# Mitigation of opioid side effects



<sup>1</sup>Oertel, Clin Pharmacol Ther, 2010

<sup>2</sup>Roozkrans, Anesthesiology, 2014

<sup>3</sup>Soergel, Pain, 2014

<sup>4</sup>Liao, Anesthesiology, 2013

<sup>5</sup>Meuret, Anesthesiology, 2000

<sup>6</sup>Hedner, Am J Respir Crit Care Med, 2003

<sup>7</sup>Eikermann, Anesthesiology, 2012

# Neuraxial & regional anesthesia in OSA

Analysis of more than 1,000,000 cases of total hip and knee arthroplasties between 2006 and 2013<sup>1</sup>:

- Increase in the use of peripheral nerve block from 9 to 15%
- Decrease in the daily prescription of opioids by 17%

Among 30,024 patients with OSA undergoing total joint arthroplasty<sup>2</sup>

- 11% neuraxial, 15% combined and 74% general anesthesia
- Less complications with neuraxial vs general anesthesia; OR: 0.83 (95% CI: 0.74 - 0.93)

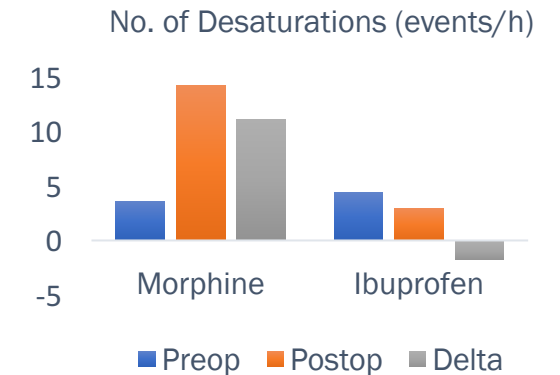
<sup>1</sup>Cozowicz, Anesth Analg, 2017

<sup>2</sup>Memtsoudis, Reg Anesth Pain Med, 2013

# Opioid-sparing post-tonsillectomy in OSA

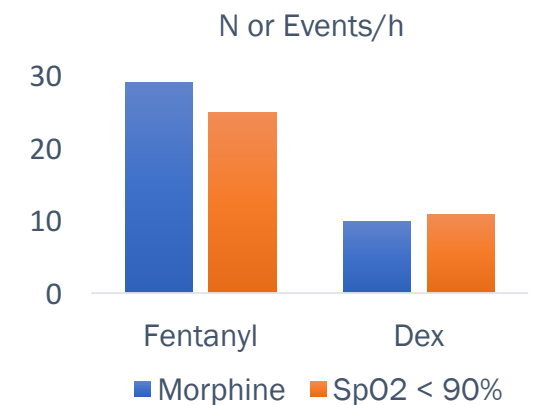
## Postoperative ibuprofen is effective analgesic<sup>1</sup>

- Randomized to morphine (N=30, 0.1 - 0.35 mg/kg, Q 4h), or ibuprofen (N=26, 10 mg/kg, Q 6h)
- No difference in pain; decreased number of desaturations events with ibuprofen



## Intraoperative dexmedetomidine (Dex) infusion<sup>2</sup>

- Randomized to Dex (N=61, 2 mcg/kg bolus, 0.7 mcg/kg/min), or Fentanyl (N=61, a bolus of 1 mcg/kg)
- Decreased postoperative opioid analgesia and desaturation events in Dex vs Fentanyl groups
- Maximum pain was higher in the F than Dex groups (5 vs 3, OPS)



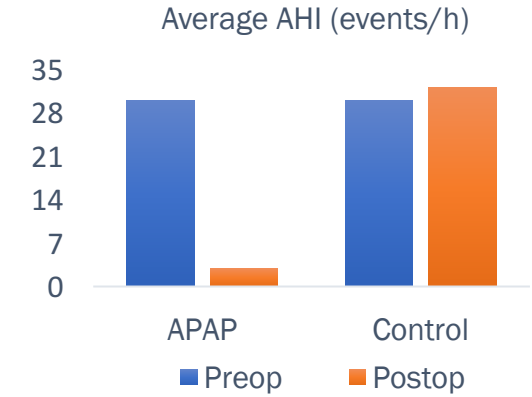
<sup>1</sup>Kelly, Pediatrics, 2015

<sup>2</sup>Patel, Anesth Analg, 2010

# Support airway patency postoperatively

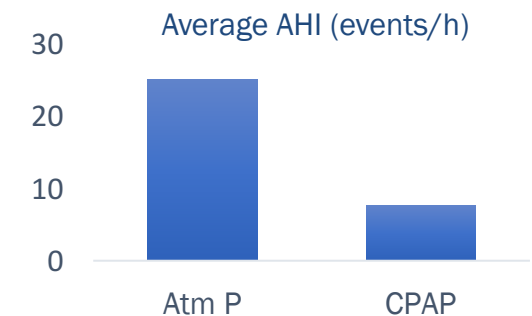
## Postoperative positive airway pressure (PAP)<sup>1</sup>

- 177 patients were randomized to receive Auto-titrated PAP or routine care for 5 postoperative nights
- APAP decreased AHI by 89% on 3<sup>rd</sup> postoperative night



## CPAP early after bariatric surgery<sup>2</sup>

- Crossover randomization of 38 bariatric (BMI: 46 kg/m<sup>2</sup>) patients to atmospheric pressure (AP), or CPAP in PACU
- CPAP treatment decreased AHI during opioid analgesia in the PACU by 69%
- Total morphine-equivalent dose administered 2.9 vs 2.5 mg



<sup>1</sup>Liao, Anesthesiology, 2013

<sup>2</sup>Zaremba, Anesthesiology, 2016

# Summary

Several OSA-related phenotypes might enhance pain perception

Nocturnal intermittent hypoxemia in OSA might be associated with reduced requirement for opioid analgesia

Postoperative opioids may aggravate sleep-disordered breathing

- A direct link with life-threatening respiratory events is yet to be demonstrated

Mitigating respiratory depression during postoperative analgesia

- Maintaining arousal responses, minimizing opioids, and/or supporting the airway via mechanical means