CENTRAL SLEEP APNEA: TO TREAT OR NOT TO TREAT

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Type of Potential Conflict	Details of Potential Conflict
Grant/Research Support	
Consultant	Jazz Pharma
Speakers' Bureaus	
Financial support	
Other	

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1.
2.
3.

OBJECTIVES

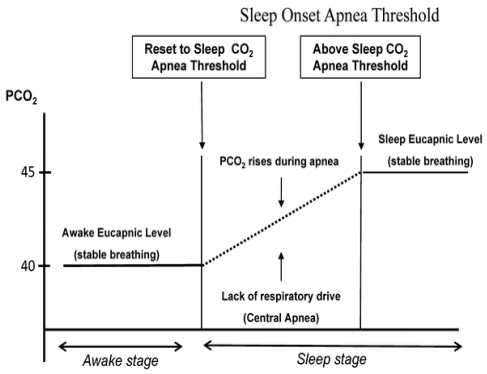
- Central sleep apnea: 101
- Treatment and outcomes

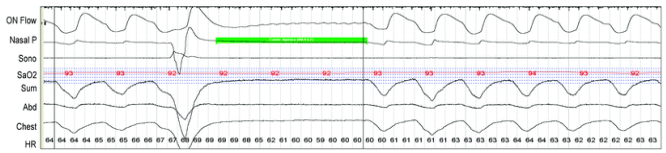
We are NOT talking about post-operative respiratory depression and impending respiratory failure*

PATHOPHYSIOLOGY

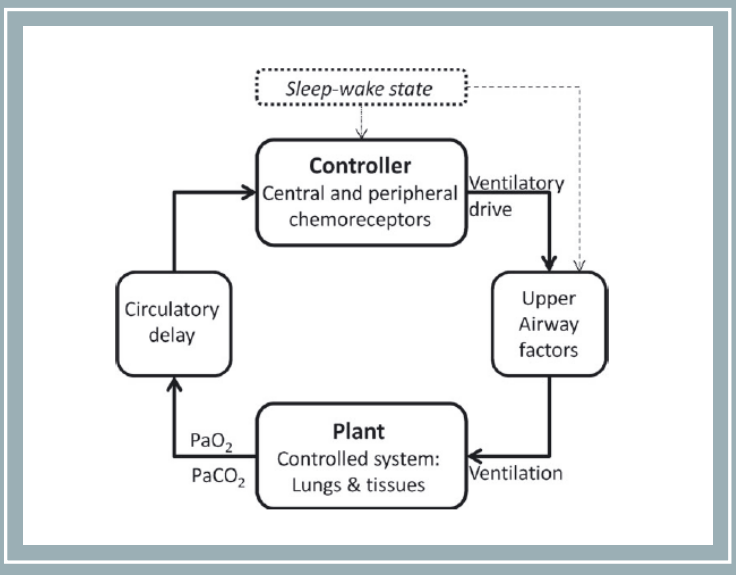
	Hypercapnic	Non-Hypercapnic
Ventilation	Hypoventilation during sleep and often wake (↑ PCO2)	Normal ventilation (normal PCO2)
Ventilatory response to hypercapnia	Decreased	Increased
Associations	Alveolar hypoventilation Respiratory depressants Neuromuscular disease	CSB High-altitude PB Primary CSA Treatment-Emergent CSA Sleep-onset/Post-arousal centrals

APNEA THRESHOLD



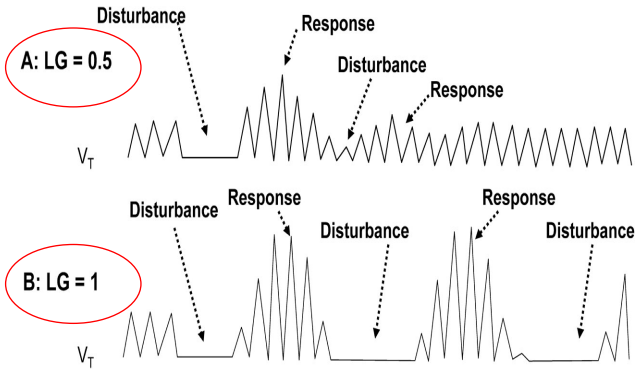


LOOP GAIN

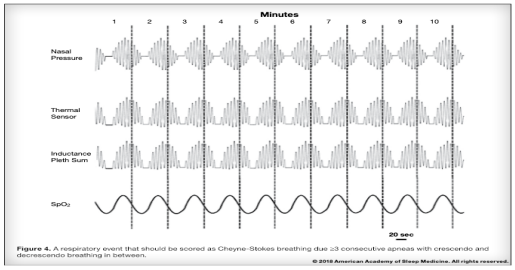


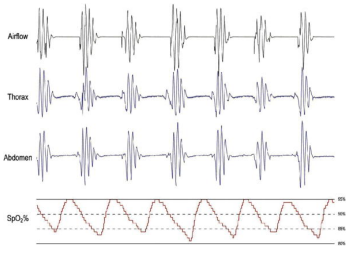
LOOP GAIN

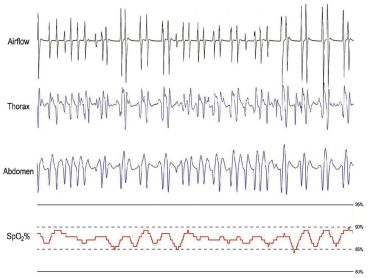
$$\text{Loop gain} = \frac{\text{Response to disturbance}}{\text{The disturbance itself}}$$



CENTRAL SLEEP APNEA: PHENOTYPES







CENTRAL SLEEP APNEA PHENOTYPES

	Central Sleep Apnea	Cheyne—Stokes Breathing
Cycle time	Short (< 40 sec)	Long (> 40 sec)
Apnea duration	Short	Long
Timing of arousals	At termination of apnea	At peak of hyperpnea
SpO2 nadir	At termination of apnea	Delayed
Hyperpnea duration	Short	Long
Morphology	Periodic breathing, Biots, Ataxic	Crescendo-decrescendo

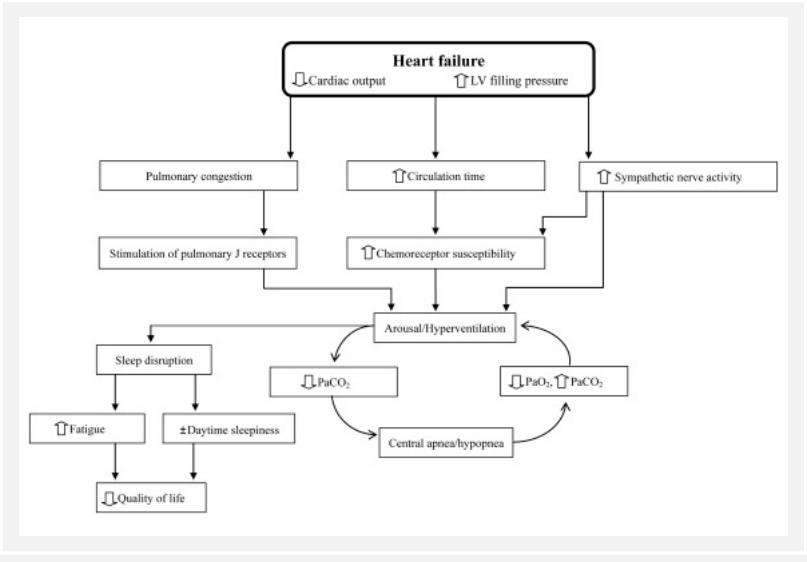
CENTRAL SLEEP APNEA SYNDROMES

- CSA with Cheyne-Stokes Respiration (Heart Failure)
- CSA due to a Medical Disorder without CSR (Arnold Chiari Malformation, Neuromuscular disorders)
- CSA due to Medication or Substances
- CSA due to High-Altitude Periodic Breathing
- Primary CSA
- Treatment-Emergent CSA
- Primary CSA of Infancy
- Primary CSA of Prematurity

CSA WITH CHEYNE STOKES RESPIRATION

- > 60 yrs
- 25-40% HF patients, male
- 25-50% acute stroke
- Atrial fibrillation
- Vast majority have HF, rare idiopathic or associated with renal failure
- Normal or low daytime PaCO2
- Longer respiratory phase is associated with longer circulation time and delay in SpO2 nadir
- Observed during N1 and N2, resolves in REM
- Can be seen w/ OSA
- Portends poor prognosis in HF

CSA WITH CHEYNE STOKES RESPIRATION



CSA DUE TO MEDICAL DISORDER (NOT CSR)

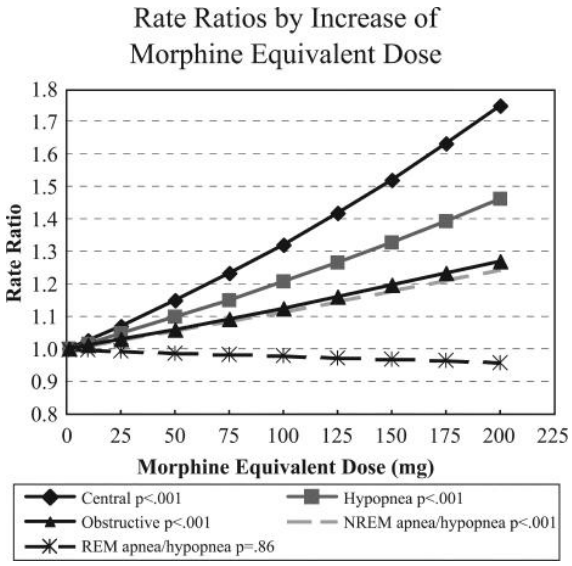
- Post-CVA
- Arnold Chiari Malformation
- Brainstem lesions
- Multi-System Atrophy
- Hypoventilation syndromes (e.g. NMD)

RISK FACTORS FOR SUBSTANCE RELATED CSA

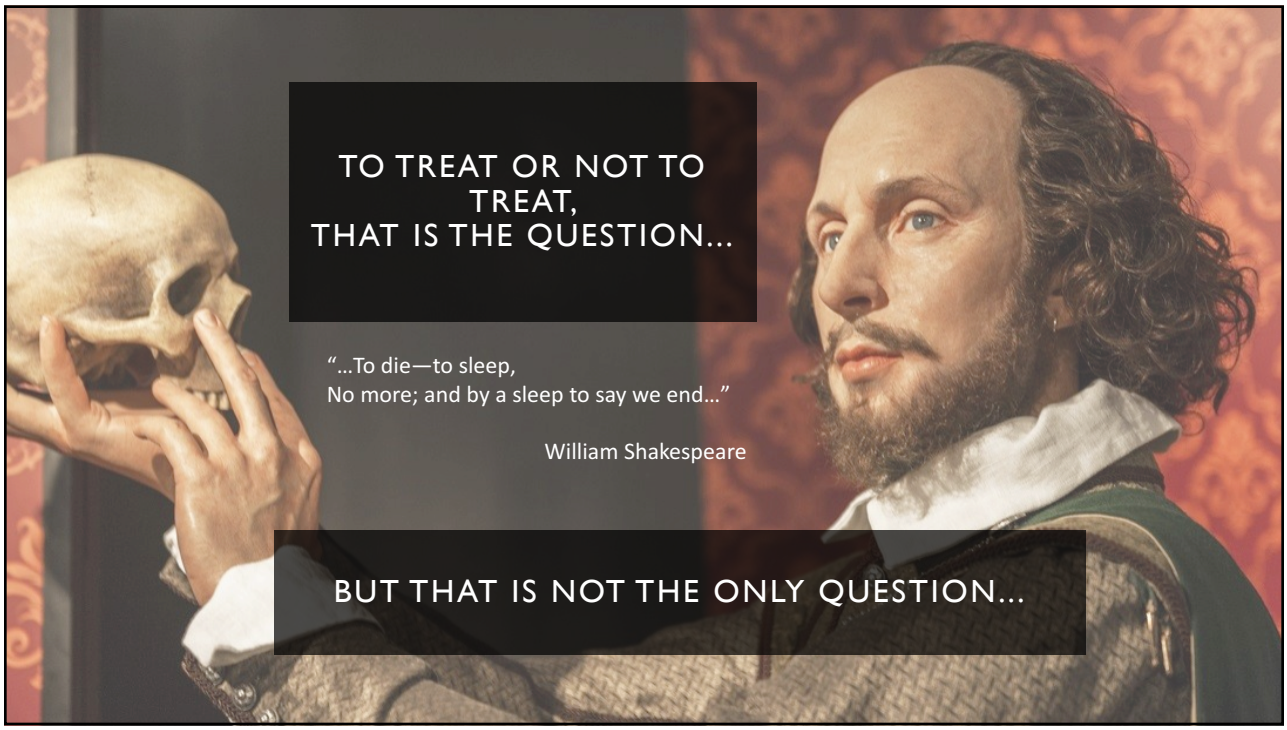
- Concurrent benzodiazepines
- Concurrent anti-depressants
- BMI inversely related to the severity of CSA
- Women may be at greater risk for CSA

Webster et al, Pain Med 2008; Wang et al, Chest 2005; Mogri et al, Sleep Breath 2009; Farnet et al, Eur Respir J, 2013

MORPHINE-INDUCED CSA



Walker et al, JCSM 2007



AASM TREATMENT GUIDELINES

TREATMENT OF CENTRAL SLEEP APNEA SYNDROME IN ADULTS

http://dx.doi.org/10.5665/sleep.1580

The Treatment of Central Sleep Apnea Syndromes in Adults: Practice Parameters with an Evidence-Based Literature Review and Meta-Analyses

R. Nisha Aurora, MD[1]; Susmita Chowdhuri, MD[2]; Kannan Ramar, MD[3]; Sabin R. Bista, MD[4]; Kenneth R. Casey, MD, MPH[5]; Carin I. Lamm, MD[6]; David A. Kristo, MD[7]; Jorge M. Mallea, MD[8]; James A. Rowley, MD[9]; Rochelle S. Zak, MD[10]; Sharon L. Tracy, PhD[11]

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Sleep, 2012

JCSM
Journal of Clinical Sleep Medicine

SPECIAL ARTICLES

Updated Adaptive Servo-Ventilation Recommendations for the 2012 AASM Guideline: "The Treatment of Central Sleep Apnea Syndromes in Adults: Practice Parameters with an Evidence-Based Literature Review and Meta-Analyses"

R. Nisha Aurora, MD, MHS[1]; Sabin R. Bista, MD[2]; Kenneth R. Casey, MD, MPH[3]; Susmita Chowdhuri, MD[4]; David A. Kristo, MD[5]; Jorge M. Mallea, MD[6]; Kannan Ramar, MD[7]; James A. Rowley, MD[8]; Rochelle S. Zak, MD[9]; Jonathan L. Heald, MA[10]

JCSM, 2016

APAP
BPAP
iVAPS
CPAP
AVAPS
ASV

CSA RELATED TO CHF (CSB) - **CPAP**

- Improves AHI
- Improves LVEF (by 6%)

- CANPAP trial
  - CPAP had no direct effect on cardiac function or survival if SDB not well controlled
  - Post-hoc analysis – improved LVEF and Transplant-free Survival

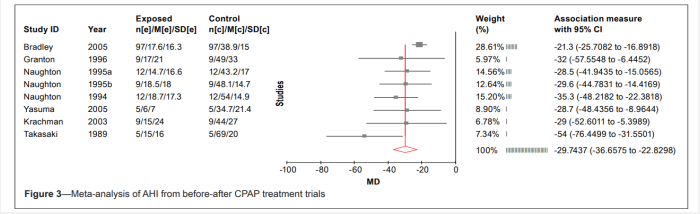

Figure 3—Meta-analysis of AHI from before-after CPAP treatment trials

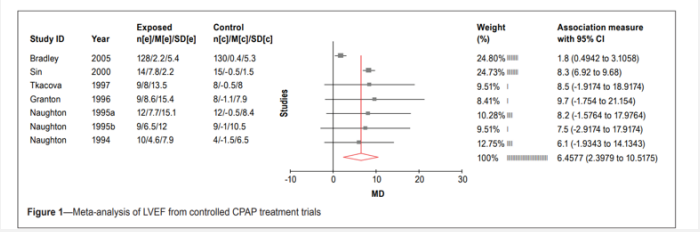

Figure 1—Meta-analysis of LVEF from controlled CPAP treatment trials

Sleep 2012

CSA RELATED TO CHF (CSB) - **OXYGEN**

- Mechanisms:
  - Reduce CO2 sensitivity
  - Reduce controller gain
- Improves LVEF (by 1%)
- Improves AHI (not as much as CPAP)

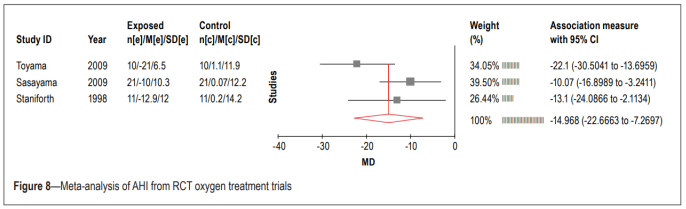

Figure 8—Meta-analysis of AHI from RCT oxygen treatment trials

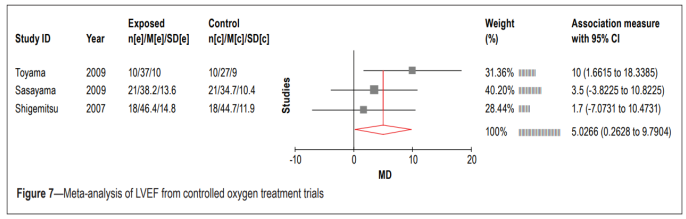

Figure 7—Meta-analysis of LVEF from controlled oxygen treatment trials

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CSA RELATED TO CHF (CSB) - **ASV**

- Moderate data for improvement in AHI and LVEF (by 6%)
- SERVE-HF Trial…

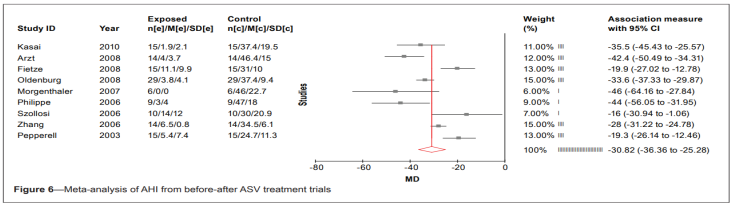

Figure 6—Meta-analysis of AHI from before-after ASV treatment trials

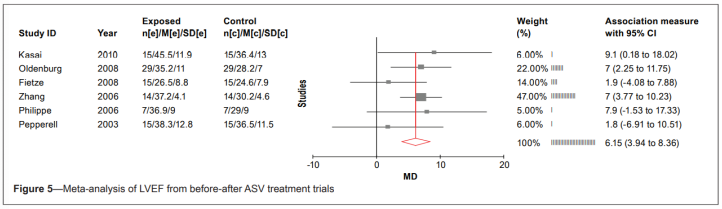

Figure 5—Meta-analysis of LVEF from before-after ASV treatment trials

Sleep 2012

ASV CONTRAINDICATIONS

SERVE-HF Trial 2015 demonstrated increased mortality in symptomatic HF patients with reduced EF using ASV

ASV for CSAS Related to CHF

- Recommendation 1: ASV targeted to normalize the AHI should not be used for the treatment of CSAS related to CHF in adults with an EF ≤ 45% and moderate or severe CSA predominant, sleep-disordered breathing. (*STANDARD AGAINST*)
- Recommendation 2: ASV targeted to normalize the AHI can be used for the treatment of CSAS related to CHF in adults with an EF > 45% or mild CHF related CSAS. (*OPTION*)

CSA RELATED TO CHF (CSB) - BPAP-S, BPAP-ST (OPTION)

- Little data for BPAP-S
- BPAP-ST may improve AHI, but no good data on clinical outcomes
- CPAP vs BPAP-ST equally effective in reducing AHI

CSA RELATED TO CHF (CSB) - PHARMACOLOGICS (OPTION)

- Limited studies on acetazolamide and theophylline
- Benefit vs Harms
- Requires very close follow up

CSA DUE TO DRUG OR SUBSTANCE (OP-CSA)

- AASM Treatment Guidelines has No Recommendations
- CPAP, BPAP, ASV, NIV

TO TREAT, OR NOT TO TREAT?

- The clinical significance of Op-CSA and related hypoxemia or ataxic breathing is unknown without further studies
- The indications and clinical outcomes of treatment of Op-CSA is unknown

*****This is a different category than respiratory depression and impending respiratory failure*****

OP-CSA TREATMENT

No clear consensus on how best to manage opioid-induced SDB, apart from using the lowest effective opioid dose

Options include:

Withdrawal opioids, using non-opioid analgesics	Reducing opioid dose	Selecting an opioid that with less toxicity (e.g. buprenorphine instead of methadone)	Avoidance of potentially aggravating concurrent drugs	Supplemental oxygen	PAP	Pharmacologic therapy (e.g. acetazolamide, theophylline, carbon dioxide)

OP-CSA: OXYGEN

- Hypoxemia without sleep apnea may occur in >10% of chronic opioid users
- Oxygen may improve hypoxemia without effect on ataxic breathing or hypoventilation
- No systematic study of supplemental oxygen and effect on Op-CSA

Mogri et al, Sleep Breath 2009; Farney et al, Chest 2003

	Subjects	Results
Farney et al, 2008	22 OSA + CSA	• CPAP and ASV improved OAI • CPAP worsened CAI • ASV did not improve CAI, hypopneas or hypoxemia
Javaheri et al, 2008	5 CSA only	• CPAP worsened CAI • ASV eliminated CAI • ASV did not help with hypopneas
Allater et al, 2009	6 case-series; mod-severe CSA (50% also with OSA)	• 4/5 failed CPAP • 4/4 improved on BPAP ST • 3/4 required O2
Ramar et al, 2012	47 CSA due to CHF and Opioids	• Complete descriptive data for opioid patients were not reported, but as a whole CPAP treated OSA but worsened CAI
Javaheri et al, 2014	20; 4 with OSA only, 16 with OSA + CSA	• 9/16 had persistent CSA after 4-8 weeks of CPAP • ASV was effective in eliminating CSA in all patients
Troitino et al, 2014	34 OSA + CSA	• 24% resolved with CPAP • 67% of those tried on BPAP resolved • 60% of those tried on ASV resolved (those that failed BPAP also failed ASV; ataxic breathing did not respond to ASV)

OP-CSA: CPAP

Summary: CPAP eliminates Op-CSA in only minority of patients, may even worsen CAI

OP-CSA: BILEVEL PAP

- A recent systematic review reported the effectiveness of BPAP with backup rate in eliminating CSA in 62%, and ASV in 58% of patients taking chronic opioids
- BPAP with a backup rate (BPAP-ST), was effective for treating CSA unresponsive to CPAP

Reddy et al, J Opioid Manag 2014; Guilleminault et al, Lung 2010

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OP-CSA: SERVO-VENTILATION

ASV may treat CSA associated with chronic opioid use unresponsive to CPAP

OP-CSA: ASV VERSUS BPAP-ST

- ASV improved total AHI
- ASV improved CAI
- ASV improved RAI
- Normalization of respiration in 83% vs 33%
- No diff in mean or nadir SpO2
- No diff in PAP95% for IPAP or EPAP
- Satisfaction Q: ASV felt more awake, alert
- No diff in comfort questionnaire

Cao et al. JCSM, 2014

OP-CSA: MEDICATION MODIFICATION

- Effects of partial opioid agonists (e.g. buprenorphine)
  - 63% subjects had AHI ≥ 5, mostly CSA
  - CSA more frequent in females
  - Ataxic breathing common
- *Summary: Partial opioid agonists still risk for Op-CSA*
  - many patients also on BZD, muscle relaxants
  - Long term effect not ascertained

Farney et al, Eur Respir J, 2013

SUMMARY FOR OP-CSA

Treatment

- Current data regarding PAP therapy is inconclusive
- CPAP appears to be mostly ineffective in reducing central apneas
- BPAP-ST may eliminate Op-CSA in as many as 60%
- ASV has produced some conflicting results
- Presence of ataxic breathing predicts poor response to any of these PAP modes

TO TREAT OR NOT TO TREAT?

Treat based on severity

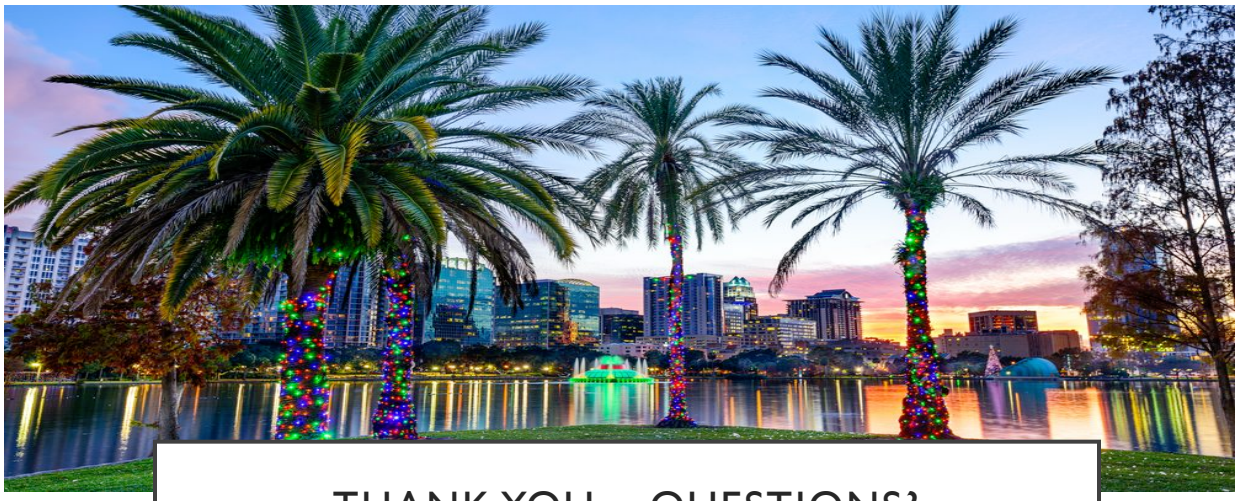
- Desaturations
- Number of events

Treat based on risk factors

- co-morbidities

Treat based on symptoms

- EDS
- Sleep fragmentation



THANK YOU – QUESTIONS?

#WonChristine