



# **Obstructive Sleep Apnea 101 /** Why Sleep SMART?

First Investigator Meeting Background and Rationale February 22, 2019

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#### What is OSA?

# **Obstructive Sleep Apnea**

(Click to watch video)

#### Anatomy of OSA



## **OSA:** The Typical Patient

- Sleepiness
- •Male
- Overweight
- Loud snoring
- Middle age or older



## **OSA: The Typical Patient**

- Sleepiness
- •Male
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- Note: Stroke Patient
  *≠* Typical OSA Patient



## In-lab polysomnography (PSG): Not for Sleep SMART





#### Sleep Apnea Test (Nox T3): Use in Sleep SMART





<u>Obstructive Apnea</u>: Complete blockage of the airway despite effort to breathe. Chest movements gradually increase until airway opens.

#### CPAP



#### How does CPAP work?

http://www.mayoclinic.com/health/cpap/MM00716

#### **ResMed AirSense 10 AutoSet**



# How does automaticallyadjusting CPAP (aCPAP) work?

- Traditional approach:
  - CPAP titration in sleep laboratory
  - Rx for home CPAP at fixed pressure
- aCPAP
  - Adjusts pressure automatically, in real time
  - Responds to flow limitation, snoring, or apnea
  - Aims to give lowest effective settings on a continuous basis

#### Does OSA <u>need</u> to be treated? Specific outcomes linked to OSA

- Stroke
- Myocardial infarction
- Hypertension
- Hyperlipidemia
- Arrhythmias
- Heart failure
- Increased mortality

- Metabolic Syndrome
- Diabetes
- Erectile Dysfunction
- Depression
- Dementia
- ADHD
- Asthma

## **Logical Next Steps**

- "Should we put a sleep medicine physician in your stroke clinic?"
  - Ron Chervin to Devin Brown, last 10 years

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# **Logical Next Steps**

- "Should we put a sleep medicine physician in your stroke clinic?"
  - Ron Chervin to Devin Brown, last 10 years
- •"No"
  - Devin Brown to Ron Chervin, last 10 years
  - But: will gladly reconsider "when we have evidence that OSA treatment works for -- and is tolerated by -- my stroke patients"

#### What Informs Each Perspective?

• Plausible Biology

Suggestive Observational Data

Less Than Definitive Trials

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## How could OSA contribute to stroke risk?

- Sleep fragmentation
- Sympathetic activation
- Intermittent hypoxemia / oxidative stress
- Inflammation



Ali NJ et al. Chest 1992;101:1526-32.



FIGURE 1. Respiration (inductive plethysmography),  $tcPo_2$ ,  $tcPco_2$ , CVP, ICP (epidural), and AP during period with severe OSA (case 1).

Jennum P, Børgesen SE. Chest. 1989;95(2):279-83.

## How Could Untreated OSA Raise Risk for Stroke or TIA?





# How could OSA contribute to stroke risk?



# How could OSA impair stroke recovery?



## Plausible Biology is Reversible: CPAP Can Have Dramatic Impact

Hypnogram





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# OSA after Stroke: Epidemiology

- •About 3/4 stroke patients have sleep apnea
- Large majority have obstructive sleep apnea (OSA) rather than central sleep apnea
- Stroke patients seldom screened or treated for OSA

Johnson KG, Johnson DC. J Clin Sleep Med 2010; 6:131-137 Skolarus LE, et al. Stroke 2012; 43:1143-1145

## Observational data suggest OSA is a risk factor for:

- Ischemic stroke (incident or recurrent)
- Acute coronary syndrome (ACS)
- Death (and death after stroke)
- Post-stroke adverse functional outcomes

## OSA as Risk Factor for first-ever Stroke / ACS



N=967 women over ~7 years: untreated OSA (solid line) vs controls without OSA (dashed), incidence rate of stroke or coronary heart disease was 2.19 vs. 0.54 per 100 person-years; P < 0.0005. (Treated **OSA** shown in dotted line)

Campos-Rodriguez F, et al. Am J Respir Crit Care Med 2014; 189:1544-1550.

## OSA as Risk Factor for Recurrent CV Events



- N=223 poststroke patients
- Up to 7 years f/u
- Mod-Sev OSA patients who did not tolerate CPAP had more CVEs

Martinez-Garcia, et al. Eur Respir J 2012; 39: 906–912.

#### OSA as Risk Factor for Mortality (Gen Population)

- N=1651 men
- Followed annually for average of 10 yrs
- Fatal and non-fatal cardiovascular events were more common in severe OSA than less severe, or treated subjects



Marin JM, et al. Lancet 2005; 365:1046-1053.

#### OSA as Risk Factor for Mortality (After Stroke)

- N=166 post-stroke patients
- Studied 2 months post-stroke; followed for 5 years
- Mod-Sev OSA patients who did not tolerate CPAP had higher mortality



Martinez-Garcia, et al. Am J Respir Crit Care Med 2009; 180:36–41.

# OSA after Stroke → Worse Functional Outcomes

#### •OSA is associated with:

- increased dependence after stroke
- longer acute rehabilitation stays
- poorer functional outcomes at admission and discharge from rehabilitation
- poor longer-term functional outcomes

Cherkassky T, et al. Am J Phys Med Rehabil 2003; 82:452-455 Good D, et al. Stroke 1996; 27:252-259 Kaneko Y, et al. Sleep 2003; 26:293-297 Turkington PM, et al. Thorax 2004; 59:367-371

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#### 5 pilot RCTs of CPAP for OSA after <u>acute</u> stroke

- Total N = 307
- Median hrs/night CPAP use:
  - ~ 4 hours on average
  - ~ 5 hours on nights used, or in subjects who accepted PAP
- Results sometimes positive despite inadequate power:
  - Intent to treat analysis of intervention vs controls
  - CPAP adherent vs controls
  - Per protocol analysis

Bravata DM, et al. Sleep 2011; 34:1271-1277 Parra O, et al. Eur Respir J 2011; 37:1128-1136 Minnerup J, et al. Stroke 2012; 43:1137-1139 Brown DL, et al. J Stroke Cerebrovasc Dis 2013; 22:1216-1224 Bravata DM, et al. J Am Heart Assoc 2018; 7:e008841

#### 5 pilot RCTs of CPAP for OSA after <u>sub</u>acute stroke or in rehab period

- Greater improvement in intervention vs control group in:
  - Stroke-related impairment (Canadian Neurologic Scale); motor function (Functional Independence measure, motor) (one study)
  - Depression (one study)
  - Cognition (two studies)

Hsu CY, et al. J Neurol Neurosurg Psychiatry 2006; 77:1143-1149 Ryan CM, et al. Stroke 2011; 42:1062-1067 Sandberg O, et al. Eur Respir J 2001; 18:630-634 Aaronson JA, et al. Sleep 2015; 38:1431-1437 Khot SP, et al. J Clin Sleep Med 2016; 12:1019-1026

#### 1 Pilot RCT of CPAP for OSA after TIA

- 2% in intervention group had recurrent vascular events or death vs 12% in control group (p=0.13)
  - Follow-up at 90 days
  - Was underpowered for these outcomes

Bravata DM, et al. Stroke 2010; 41:1464-1470

## Safety of CPAP and aCPAP after stroke or TIA

 Across the 5 pilot trials in the acute stroke/TIA period, 307 subjects showed only one SAE related to treatment, and it was expected

• BP reduction is modest (about 2 mm Hg)

#### So ... should we put a sleep physician in Devin's stroke clinic?

• AHA/ASA secondary stroke prevention guidelines:

"Given these generally promising albeit mixed results across the randomized trials and the observational cohort studies, what is clearly needed is a randomized trial with adequate sample size to examine whether and the extent to which treatment of sleep apnea with CPAP improves outcomes such as stroke severity, functional status, and recurrent vascular events."

Kernan WN, et al. Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2014; 45:2160-2236.

#### **Equipoise to Perform RCT?**

- Treatment of OSA reduces sleepiness, HTN
- Does CPAP help similarly, after stroke?
- Do stroke patients tolerate CPAP?
- Sleep SMART protocol:
  - Participants unlikely to have OSA addressed outside trial
  - Controls forgo OSA treatment for limited period (6 months)
  - Peer-reviewed
  - IRB-approved
  - DSMB-approved

Brown DL, et al. J Clin Sleep Med. 2011 Feb 15;7(1):103-8





#### **Welcome to Sleep SMART!**

(click to play video)