HYPOGLOSSLAL NERVE PACING FOR TREATMENT OF OBSTRUCTIVE SLEEP APNEA

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Speaker Disclosure

- Speaker for Xenoprot Pharmaceuticals
Objectives

- Understand basic obstructive sleep apnea signs and symptoms
- Understand the complications of obstructive sleep apnea
- Understand traditional therapies for sleep apnea
- Introduction to hypoglossal nerve pacing for treatment of sleep apnea
- Understand the proper patient for treatment with the hypoglossal nerve stimulator
Obstructive Sleep Apnea

- Recurrent episodes of partial or complete cessation of breathing during sleep.
  - 5 or more per hour of sleep
    - Apneic or hypopneic event last a minimum of 10 seconds
    - Episodes associated with oxygen desaturation.
18 - 20 million adults suffer from
- symptomatic OSA
- severe asymptomatic OSA
- Estimate that 82% of men and 92% of women with moderate-severe OSA have not been diagnosed.
Obstructive Sleep Apnea

- Affects 6% of the population in the U.S.
- Is under diagnosed
- Affects all aspects of life
- Associated with increased sick days and loss of productivity at work
In Flemons study, 40% of obese men and 50% of obese women have OSA.

Estimated life span of untreated OSA is 58 years (normal men 78 yrs., women 83 years).

John Hopkins study found severe OSA increased risk of dying by 46%
Symptoms of OSAS

- Snoring
- Excessive daytime sleepiness
- Fatigue
- Nocturnal awakenings and sleep maintenance insomnia
- Witnessed apnea
- Poor concentration
- Decreased memory especially short term
- Falling asleep or nodding off at inappropriate times
Symptoms of OSAS

- Change in personality or mood
- Weight gain
- Wakes up choking, short of or gasping for breath
- Wakes up from snoring
- Nocturia
- Morning headache
- Morning dry mouth
- Loss of libido or impotency
- Awakens fatigued in AM or after naps
Symptoms of OSAS

- Nighttime sweating
- Nighttime reflux
- Automatic behaviors
- Sleep drunkenness
FIGURE 1. Upper airway showing the different segments of the pharynx and indicating the variety of upper airway abnormalities reported to cause obstructive sleep apnea.
Mallampati Classification

Class I

Class II

Class III

Class IV
Complications of OSAS

- Hypertension
  - Untreated obstructive sleep apnea is associated with hypertension in 40 % of patients
  - 30 % of patients with idiopathic hypertension have OSAS

- Cardiac arrhythmias during sleep
  - Sinus arrhythmia, sinus bradycardia, atrial fibrillation, asystole, second-degree AV block, PVCs, and VT
Study included 488 patients from Mayo Clinic Cardioversion Clinic

Untreated OSA doubled the risk of recurrence of atrial fibrillation

Effective treatment of OSA with CPAP decreased risk of atrial fibrillation recurrence after cardioversion by 50%

Authors suggest patients with AF should be screened for OSA

Gami et al., Circulation 2004;110:364-367
Complications of OSAS

- Myocardial infarction
- CVA
- Type 2 Diabetes Mellitus
- Pulmonary hypertension
Obstructive Sleep Apnea and Stroke

- 2.24 increased risk of stroke in obstructive sleep apnea group compared to control group (p=0.004)
- When corrected for age, sex, smoking, alcohol consumption, BMI, DM, hyperlipidemia, A. Fib and HTN, the risk ratio was 1.97 (p=0.01)

Yaggi H, et al., NEJM 2005; 353: 2034-2041
Treatment of OSAS

- Exclude underlying medical conditions
  - Hypothyroidism
  - Acromegaly
  - Upper airway pathology
Treatment of OSAS

- Weight loss
- Avoid Alcohol and sedatives near bedtime
- CPAP/BIPAP
- Surgical
- Oral Devices
- Provent
- Positional Therapy
What if traditional therapy fails?

Hypoglossal Nerve Stimulator
Inspire
Upper Airway Stimulation™ System

Closed-Loop System Overview:

• Stimulation Lead
  • Encircles m-XII with cuff
  • Delivers stimulation from IPG to cuff-nerve interface

• Sensing Lead
  • Detects changing pressures of respiratory cycle
  • Conveys information to IPG

• Implanted Pulse Generator (IPG) or neurostimulator
  • Contains battery, computer and lead-connector block
  • Receives info from sense lead
  • Operates timing and output algorithms
  • Conveys energy to stimulation lead
  • Serves as return electrode for advanced stimulation configurations

N Engl J Med 2014;370:139-49; Figure 1, p 142
Inspire Implantable Components
Pathology of Obstructive Sleep Apnea

- Progressive loss of lingual and pharyngeal tone in the upper airway is the primary cause of OSA.
- Airway blockage is associated with reduction of lingual muscle tone and presumed inadequate neural signals from the hypoglossal nerve.
Tongue Functions

- Position of the posterior tongue is most relevant to the maintenance of the oropharyngeal patency.
- Anterior tongue is more involved in non-respiratory activities.
Position of the Tongue

- Extrinsic tongue muscles change position of the tongue
  - Genioglossus muscle considered the tongue protrusor
  - Geniohyoid innervated by the hypoglossal nerve provides the muscular floor of the tongue
  - Muscles that protrude and retract the tongue are coactivated during the respiratory drive.
    - Inspiration is always associated with tongue retraction force.

Neuromodulation 2012
Inspire 1 - Proof of Principle Trial

- 8 patients in 4 centers

Results
- Improved from AHI 52 +/- 20.4 to 22.6 +/- 12.1
- Improved oxygen desaturation

Choosing the Airway

- Drug induce sleep endoscopy
  - Midazolam +/- propofol

Anteroposterior collapse

Concentric collapse

Surgical Insertion
Cuff Electrode Location Introduction

Stimulation Site for Optimal Protrusion

**Objectives:**

- Place cuff where STAR trial showed best results
- Exclude retractorors
- Recruit protrusors

Base diagram and content adapted from Mu & Sanders, Clin Anat. 2010 October; 23(7): 777–791.
Incision Planning Placement Landmarks

Stimulation Lead Incision

Sensor Lead Incision
Inferior to 4\textsuperscript{th} rib and Superior to 6\textsuperscript{th} rib

IPG Pocket Incision:
2-4 finger widths inferior to clavicle
Obtain Post-Implant X-rays x 2

Document Implant Positions & Integrity

Lateral view, showing stim cuff electrode include vertebrae and chin

AP view, showing IPG/lead wrap and sensing lead include IPG and sensor lead

**Precaution:** Utilize CXR to validate the absence of pneumothorax
Intraoperative Tongue Motion Examples

Videos from Actual implants, Germany, 2013 (upper left) and 2014 (upper right and lower)
Inspire Therapy Tongue Protrusion

0.9 V

1.0 V

1.2 V

1.4 V
Multi-level Mechanism of Action

Therapeutic effect is evident at both the palate and tongue-base.

More prominent response with increasing stimulation energy – within therapeutic range.
Inspire Therapy affects the airway at multiple levels
Inspire 2 & 3 – Feasibility Studies

- 34 patients at 8 centers
- Responders
  - BMI < 32
  - AHI < 50
  - Did not have complete concentric palatal collapse
- 8 patients from responders
  - Improved from AHI 38.9 +/- 9.8 to
  - 10 +/- 11 at 6 month post implant
  - Improved ESS and FOSQ (Functional Outcomes of Sleep Questionairre)

Laryngoscope. 2012 Jul; 122(7): 1626-33
CLINICAL EVIDENCE – STAR TRIAL RESULTS
Inspire STAR

- 126 patients (86% men) at 22 centers
  - AHI >15/hr
  - BMI <32
  - Not concentric narrowing of airway
  - Intolerant to CPAP

- Baseline PSG → Implant device → Repeat baseline PSG → Activate stimulator

- Follow up
  - Outpatient visits at months: 2, 3, 6, 9, 12 with device interrogation
  - PSG at months: 2, 6, 12

Stimulator Programming

- Unit adjusted with a programmer unit via telemetry at polysomnogram at 2 and 6 months.
  - Adjusted variables: stimulation voltage, rate and pulse rate and the timing of electrical stimulation.

Inspire STAR

- **Primary Outcomes**
  - AHI reduction by 50% and < 20/hr
  - ODI (number per hour of sleep that oxygen decreased by 4 percentage points from baseline) reduced by 25% from baseline score

- **Secondary outcomes**
  - Improvement in ESS
  - Improvement in FOSQ by 2 or more points

STAR Trial Results

Upper-Airway Stimulation for Obstructive Sleep Apnea

Patrick J. Strollo, Jr., M.D., Ryan J. Soose, M.D., Joachim T. Maurer, M.D., Nico de Vries, M.D., Jason Cornelius, M.D., Oleg Froymovich, M.D., Ronald D. Hanson, M.D., Tapan A. Padhya, M.D., David L. Steward, M.D., M. Boyd Gillespie, M.D., B. Tucker Woodson, M.D., Paul H. Van de Heyning, M.D., Ph.D.,

PRIMARY OUTCOMES

The scores on the AHI and ODI (primary outcome measures) were lower (indicating fewer episodes of sleep apnea) at 12 months than at baseline. The median AHI score decreased 68%,

SECONDARY OUTCOMES

Scores on the FOSQ and Epworth Sleepiness Scale indicated significant improvement at 12 months, as compared with baseline. The increase in the
## Inspire STAR

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline</th>
<th>12 months</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI (median)</td>
<td>29.3</td>
<td>9.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ODI (median)</td>
<td>25.4</td>
<td>7.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FOSQ (median)</td>
<td>14.6</td>
<td>18.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESS (median)</td>
<td>11.0</td>
<td>6.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

STAR trial Primary Outcomes: AHI and ODI (n = 124)

AHI

ODI

UAS significantly reduced OSA severity after 12 months

*Median and error bar in standard error
Randomized Controlled Therapy Withdrawal Study

The RCT study confirmed therapeutic effects at 12 month

*mean and error bar in standard error
Secondary Outcome: Quality of Life Measures

ESS Scale
Daytime Sleepiness

FOSQ Score
Daytime Functioning

UAS normalized daytime sleepiness and daytime functioning after 12 months

*Median and error bar in standard error
Partner-Reported Level of Snoring

<table>
<thead>
<tr>
<th>Level of Snoring</th>
<th>Baseline</th>
<th>12-Months</th>
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</thead>
<tbody>
<tr>
<td>Bed partner leaves room</td>
<td>18%</td>
<td>85%</td>
</tr>
<tr>
<td>Intense snoring</td>
<td>28.7%</td>
<td>49.0%</td>
</tr>
<tr>
<td>Loud snoring</td>
<td>24.1%</td>
<td></td>
</tr>
<tr>
<td>Soft Snoring</td>
<td>11.1%</td>
<td></td>
</tr>
<tr>
<td>No snoring at all</td>
<td>6.5%</td>
<td></td>
</tr>
</tbody>
</table>

- Baseline: n=108
- 12-Months: n=100
Analyses into therapy response sought actionable findings

Figure S3. AHI Changes in Responders and Non-responders

Chart Citation Supplement to: Strollo PJ Jr, Soose RJ, Maurer JT, et al. Upper-airway stimulation for obstructive sleep apnea. N Engl J Med 2014;370:139-49. DOI: 10.1056/NEJMoa1308659, Figure S3, p 11.
Inspire Therapy Effect

No Stimulation  Stimulation Active
Therapy Off Test

Stimulation OFF

OSA Resumes
Acute Flow-Response following Titration

PSG
Stimulation Titration: Baseline
Stimulation Titration:
Amplitude Increase $\rightarrow$ Flow Increase

3.2 volts

3.4 volts
Stimulation Titration: Final Settings
Inspire® Upper Airway Stimulation
- An physiologic therapy for OSA -

No anatomy alteration
Works with patients physiology
Standardized implant technique
Fast post operative recovery

No facial apparatus
Patients start, stop or pause therapy using sleep remote

Therapy is titrated non invasively under the care of a sleep physician
Patient Programmer Controls

- Amplitude Increase
- Amplitude Decrease
- Open Battery Door
- Therapy On / Pause (Pauses when Therapy is On)
- Therapy Off
- Position Programmer Tip Directly over IPG To Make Changes
Potential Alternative Stimulator

[Image of a medical device with "aura 6000" and "ImThera" branding]
Stimulation delivered through a six contact self-sizing cuff electrode secured around the hypoglossal nerve at level of the submandibular gland.

Selective activating some of the six contacts to gain the desired tone and movement.

Minimum of two contacts are active

One area stimulated at a time to allow the muscle in the other area(s) that are stimulated to recover before re-activation to avoid fatigue.
Treatment with Aura6000

- A sleep session starts with a 30–45-min “startup delay phase” allowing the patient to fall asleep.
- After the delay, the first contact (contact 1) begins to stimulate (“adaptation phase”)
  - The threshold amplitude slowly ramps up for the duration of the ramp until at the conclusion of the ramp and the beginning of the plateau phase
- The plateau phase
  - The stimulation current amplitude has reached its target level “treatment phase”.
After the plateau duration is complete for the contact 1, the stimulation begins to ramp back down.

At the conclusion of the ramp down duration, the first contact is deactivated and the ramp up phase of the second contact is activated.

Process is repeated for all active contacts (Cycle 1)

When all of the active contacts have been stimulated, the cycle repeats again beginning with the first contact (Cycle 2) all through the sleep until the end of the sleep therapy.
Imthera Pilot Study

- 14 patients
- 13 successfully implanted with Aura 6000
  - Electrode positioned around trunk of hypoglossal nerve and connected to impulse pulse generator
  - Generator stimulates nerve causing activation of dilation

European Resp J. May 2012
Imthera Pilot Study

- Endpoints were improvement at 3 months and maintained to 12 months.
- Demonstrated safe and effective treatment for patients intolerant to CPAP.
# ImThera Pilot Study

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<th>Outcome</th>
<th>Baseline</th>
<th>12 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI</td>
<td>45 +/- 18</td>
<td>21 +/- 17</td>
</tr>
<tr>
<td>ODI</td>
<td>29 +/- 20</td>
<td>15 +/- 16</td>
</tr>
<tr>
<td>ESS</td>
<td>11 +/- 7</td>
<td>8 +/- 4</td>
</tr>
</tbody>
</table>

European Resp J. May 2012
Differences between Inspire and Aura6000

- **Inspire**
  - sensing lead to monitor respiration
  - One lead
  - Approved by the FDA

- **Aura**
  - no sensing lead to monitor respiration
  - Six contacts
  - Currently in trials
Objectives

- Many signs and symptoms of obstructive sleep apnea
- Cardiovascular complications of obstructive sleep apnea
- Traditional therapies for sleep apnea
  - CPAP, oral appliances, surgery, Provent
- Hypoglossal nerve pacing for treatment of sleep apnea is effective for some patients
- Proper patient
  - BMI < 32, AHI > 15/hr but < 50/hr
  - Not concentric narrowing
  - Intolerant of CPAP
QUESTIONS?