Upper Airway Stimulation for Obstructive Sleep Apnea

Background, Mechanism and Clinical Data Overview

Michael Coleman, BA, RST, RPSGT

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Conflicts of Interest

• Employed at Inspire Medical Systems
• No other conflicts of interest
Learning Objectives

• Introduction to Upper Airway Stimulation (UAS)
• Clinical Evidence of UAS
• Indications and Contra-indications for UAS
• Understand mechanism of action for UAS
• Understand the titration process for UAS
Upper Airway Stimulation
Inspire II Systems

- Implantable Pulse Generator
- Stimulation Lead
- Respiratory Sensing Lead

Physician Programmer
Patient Remote
Feasibility of Hypoglossal Nerve Stimulation

Augmented muscle tone
Without causing arousals
Immediately stabilized airway
Improved Oxygenation

Schwartz et al, Arch Oto Head Neck Surg 2001
Mechanism of Action: Multi-level Effect

- Increased airway at palate and tongue-base
- Increased airway size with increasing stimulation energy

Safiruddin et al, ERJ 2015
Mechanism of Action: Site of Obstruction

Exclusion of complete concentric collapse (CCC) at palate for improved response

Vanderveken et al, J Clin Sleep Med 2013
Mechanism of Action: Hypoglossal Nerve Stimulation

Stimulation Site: Medial branch of the hypoglossal nerve, activates only protrusors (genioglossus, geniohyoid), distal to retractors (styloglossus and hyoglossus)

Mu and Sanders 2010
Palatoglossal Coupling
Upper Airway Stimulation Effect

No Stimulation  Stimulation Active
Inspire Clinical Evidence Development

**Inspire 1**
Proof of Principle

- 8 patients @ 4 centers
- 2001
- First in man
- 1 publication

**Inspire 2**
Feasibility Study

- 22 patients @ 4 centers
- 2009/10
- Patient selection
- Implant technique
- 1 peer reviewed publications

**Inspire 2 & 3**
Feasibility Studies

- 12 patients @ 7 centers
- 2010/11
- Safety / Efficacy
- 2 peer reviewed publications

**Inspire STAR**
Pivotal Trial (Phase 3)

- 126 patients @ 22 centers
- 2012/13
- Safety / Efficacy / FDA approval
- N Eng J Med (Jan 9, 2014)

*FDA full approval in May 2014*
## Inspire Phase III Pivotal Study
### The STAR Trial (n=126)

### Study Design
Prospective, multi-center single-arm trial with a randomized, controlled therapy withdrawal phase

### Key Patient Selection Criteria
**Inclusion:**
- CPAP failure or intolerant
- Moderate to severe OSA

**Exclusion:**
- BMI > 32 kg/m²
- Complete concentric collapse at the level of soft palate
- Significant central sleep apnea

### Study Endpoints
**Primary Endpoints at 12 months**
- AHI and ODI reductions

**Secondary Endpoints at 12 months**
- Quality of life questionnaires
- Randomized withdrawal effect

*Strollo et al, New Engl J Med, 2014*
Study Design and Rationale

- Use objective measures of OSA severity (AHI and ODI) for primary efficacy endpoint
- Long-term follow up at 12/18 months to evaluate sustained effect
- Randomized controlled withdrawal phase to confirm therapy effects
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>54.5 ± 10.2</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>105 (83%)</td>
</tr>
<tr>
<td>Race – White no. (%)</td>
<td>122 (97%)</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>28.4 ± 2.6</td>
</tr>
<tr>
<td>AHI – mean ± SD</td>
<td>32.0 ± 11.8</td>
</tr>
<tr>
<td>(range)</td>
<td>(13.3 – 65.1)</td>
</tr>
<tr>
<td>UPPP – no. (%)</td>
<td>22 (17%)</td>
</tr>
</tbody>
</table>

Mean ± SD
Implantation Procedure

- General anesthesia, sterile technique
- Average 2.5 hours duration
- Same day or second discharge
- Resume normal diet first day, restricted arm motion first week
Post-implant Pain Visual Analog Scale

Average post-op pain for UPPP ranges from 46 to 79 mm at one day post-op, and 55 to 88 mm at one week post-op (Troell, RJ 2000 and Rombaux, P 2003)

Inspire STAR data presented at the FDA Panel Review, 2014
Safety Summary

• Serious adverse events were rare (1.58%)
  – IPG repositioning to address discomfort (N=2)

• Time-limited tongue weakness related to surgical procedure and incision pain

• Stimulation side effects included discomfort and tongue abrasion and were resolved by reprogramming or therapy acclimatization

• Side effects did not affect overall therapy use
Reduced OSA severity

- Therapy significantly reduced OSA severity

*Strollo et al, New Engl J Med, January 2014*
Improved Quality of Life Measures

Increased daytime functioning

Reduced daytime sleepiness

<table>
<thead>
<tr>
<th>Median FOSQ Score</th>
<th>Baseline</th>
<th>Month-12</th>
<th>p &lt; 0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 126</td>
<td>N = 123</td>
<td>Normal &gt; 17.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p &lt; 0.0001</td>
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</table>

<table>
<thead>
<tr>
<th>Median ESS Score</th>
<th>Baseline</th>
<th>Month-12</th>
<th>p &lt; 0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 126</td>
<td>N = 123</td>
<td>Normal &lt; 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p &lt; 0.0001</td>
</tr>
</tbody>
</table>

Increased daytime functioning

Reduced daytime sleepiness
Therapy randomization demonstrated the therapy effect is due to stimulation

- First 46 consecutive participants with a therapy response were randomized 1:1 to therapy maintenance or therapy withdrawal for 1 week after 12-month visit
- PSG was repeated after 1 week, and compared against the 12-month
- The therapy withdrawal group had a significant increase in AHI while maintenance group remained low

Therapy Withdrawal and Reactivation

Mean and S.E.  *p<0.05 vs. baseline; # p<0.05 vs. 12 month ; ## p<0.05 vs. RCT.

Woodson et al, Otolaryngology – Head and Neck Surgery, 2014
Long-term Outcome at 18 months

Median AHI

Baseline: 29.3
Month-12: 9.0
Month-18: 9.7

N = 126
N = 124
N = 121

Median ODI

Baseline: 25.4
Month-12: 7.4
Month-18: 8.6

N = 126
N = 124
N = 121

Median FOSQ Score

Baseline: 14.6
Month-12: 18.2
Month-18: 18.4

N = 126
N = 123
N = 123

Median ESS Score

Baseline: 11.0
Month-12: 6.0
Month-18: 6.0

N = 126
N = 123
N = 123

Strollo et al, SLEEP 2015
36 Month Follow Up

![Graphs showing changes in AHI, ODI, FOSQ, and ESS over 36 months.](image)
Self-report Nightly Use

Nightly Use (%)

12 Month
N = 124
86%

24 Month
N = 117
81%

36 Month
N = 108
81%
Self and Partner-Report Snoring

### Self Report Snoring

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n = 123)</th>
<th>12M (n = 120)</th>
<th>M36 (n = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No snoring</td>
<td>24%</td>
<td>33%</td>
<td>49%</td>
</tr>
<tr>
<td>Soft snoring</td>
<td>3%</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>Loud snoring</td>
<td>3%</td>
<td>37%</td>
<td>49%</td>
</tr>
<tr>
<td>Very intense snoring</td>
<td>11%</td>
<td>53%</td>
<td>49%</td>
</tr>
<tr>
<td>Bed partner leaves room</td>
<td>11%</td>
<td>53%</td>
<td>49%</td>
</tr>
</tbody>
</table>

### Partner Report Snoring

- **“Partner leaves room” reduced from 30% to 5%**
- **“No or Soft Snoring” increased from 17% to 85%**
Mortality and CV Risks associated with Severe OSA

1. Young et al, SLEEP 2008, Wisconsin Sleep Cohort
Multi-disciplinary Longitudinal Management

Screen:
- Consultation
- Sleep study
- DISE

Office Visit and In-lab PSG:
- Activation
- Home use and acclimatization
- In-lab sleep titration

Office Visit:
- Battery
- Usage
- Therapy Adjustment

Long-term:
1-3 month

Annual
Titration – Basic Algorithm

Arousal Threshold

Therapeutic Amplitude Range

≥ 30 minutes in the patient’s preferred sleep position with minimum occurrence of events, preferably with REM sleep observed

Increase amplitude by 0.1 to 0.2 volts if ≥ 5 obstructive apneas or hypopneas or loud, unambiguous snoring

Start at:
FT - 0.2 V

Reduce amplitude by 0.1 to 0.2 volts if stimulation causes persistent arousals or is poorly tolerated

Amplitude (volts)

Time (minutes)

≥ 10 min

*Adapted from current practice guidelines established for CPAP titration by the American Academy of Sleep Medicine, ref: *Journal of Clinical Sleep Medicine, Vol. 4, No 2, 2008*
Titration – Stimulation Artifact

- chin EMG signal
- stimulation artifact
- flow cannula signal
- inhalation
Titration – Acute Flow Changes (Flow Effect)

Look for increases in airflow associated with stimulation, as shown here (usually seen in the PTAF)
When therapy is turned on at therapeutic amplitude, you may see a dramatic effect. In this case, breathing, respiratory effort and SaO2 immediately stabilize.
Increasing the stimulation strength is similar to increasing CPAP pressure. As stimulation strength is increased, airway patency is also increased.
Middlesex Hospital - Sleep Laboratory

Therapy OFF – severe OSA

Therapy ON – OSA resolved
The next 10 epochs

Continuation of epochs, showing sustained response @ 2.2 volts while supine
Upper Airway Stimulation
Clinical Evidence Map

Safety and Effectiveness
• Pivotal study: safety and efficacy
• Feasibility studies
• Randomized withdrawal study
• Long-term outcome at 18- and 24-month
• Cost effectiveness analysis

Mechanism of Action
• Multi-level effects
• Patient selection

Clinical Practice
• Standardized implant techniques
• Device programming

8 peer reviewed publications supporting upper airway stimulation for OSA