Results of the ADHERE Upper Airway Stimulation Registry and Predictors of Therapy Efficacy

ADHERE Registry Summary (n=1,017 enrolled)
E Thaler, R Schwab, J Maurer, et al
Laryngoscope, Sept 2019
Publication Link [open access]
OSA Treatment Background

While CPAP is the gold standard treatment of OSA, 30-50% cannot tolerate CPAP\(^1\)

Untreated OSA associated with daytime sleepiness, higher cardiovascular risk

There is a need for treatment options for CPAP-intolerance

Upper Airway Stimulation – surgical option, shown to be safe and effective in multiple studies

1. Rose, SLEEP 2012, Home-PAP study
Inspire Therapy
A Treatment for Obstructive Sleep Apnea Patients Who Are Unable to Use CPAP

Safe Outpatient Procedure
Sleep Remote
Nightly Adherence Monitoring (Quality Measures)
ADHERE Registry

• Goal: Collect real-world outcomes data
• International multi-center, standard-of-care registry
• Eligibility – prospective patients receiving UAS for OSA
  • CPAP intolerant or non-compliant
  • AHI between 15-65, and fewer than 25% central apneas
  • Absence of velum complete concentric collapse on DISE

1,400 enrollments as of Sept 2019

Enrollment Goal: 2,500 patients
Registry Data Collection
Follows Clinical Protocol

Baseline
Medical Record
• Demographics
• OSA History
• AHI
• ESS
• Implant Time
• Adverse Events

Post-Titration (6mo.)
• Titration PSG (AHI)
• ESS
• Therapy Usage
• Clinical Global Impression
• Patient Experience

Implant

Annual Visit (12mo.)
• HSAT / PSG AHI
• ESS
• Therapy Usage
• Clinical Global Impression
• Patient Experience

AHI: apnea-hypopnea index (4%);
ESS: Epworth sleepiness scale;
AE: adverse event;
PSG: in-lab polysomnography;
HSAT: home sleep apnea test
Study Enrollment Status
At Manuscript Completion

- Study is on-going, continues to capture data through patient follow-up

- This paper (n=1,017) extends the work from ADHERE-500¹

ENROLLMENT STATUS
Oct 2016 – Feb 2019

- Enrolled: 1017
- Completed 6-month: 640
- Completed 12-month: 382

¹ Heiser, Eur Resp J 2019
ADHERE Registry Goals
Report outcomes and new findings

UPDATE CLINICAL OUTCOMES (AHI, ESS, USAGE) AND SAFETY

DISSEMINATE NEW FINDINGS AS ENROLLMENTS PROGRESS
ADHERE Registry
Demographics: middle aged, male, severe OSA (n=1,017)

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60 ± 11 (22-86)</td>
</tr>
<tr>
<td>Sex</td>
<td>74% Male</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>96% Caucasian</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>29.3 ± 3.9</td>
</tr>
<tr>
<td>Baseline AHI</td>
<td>36 ± 15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline Co-morbidities</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>47%</td>
</tr>
<tr>
<td>Depression</td>
<td>22%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13%</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>6%</td>
</tr>
<tr>
<td>Heart Attack</td>
<td>4%</td>
</tr>
<tr>
<td>Stroke</td>
<td>3%</td>
</tr>
</tbody>
</table>
ADHERE Registry: Consistent effectiveness

**Apnea Hypopnea Index (AHI)**

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Median AHI (events/hour)</th>
<th>AHI response at 12 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (n=881)</td>
<td>32.8</td>
<td>AHI ≤ 5: 32%</td>
</tr>
<tr>
<td>Post-Titration (n=535)</td>
<td>6.3</td>
<td>AHI ≤ 10: 53%</td>
</tr>
<tr>
<td>Final Visit (n=439)</td>
<td>9.5</td>
<td>AHI ≤ 15: 67%</td>
</tr>
</tbody>
</table>

Mean AHI reduced from baseline of 35.8 ± 15.4 to 14.2 ± 15.0 at 12 months (p < 0.001)

**Epworth Sleepiness Scale (ESS)**

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Median ESS</th>
<th>Normalized Daytime Sleepiness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (n=881)</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>Post-Titration (n=535)</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>Final Visit (n=439)</td>
<td>6.0</td>
<td></td>
</tr>
</tbody>
</table>

Mean ESS reduced from baseline of 11.4 ± 5.6 to 7.2 ± 4.8 at 12 months
Reference: ESS < 10 considered free of symptoms for excessive daytime sleepiness

Thaler, et al. Laryngoscope 2019
ADHERE Registry: Strong safety profile

<table>
<thead>
<tr>
<th>Type</th>
<th>Post-Titration</th>
<th>Final Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># of Events</td>
<td>% of Patients</td>
</tr>
<tr>
<td>Tongue Weakness</td>
<td>3</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Swallowing or speech related</td>
<td>4</td>
<td>1%</td>
</tr>
<tr>
<td>Discomfort (incision/scar)</td>
<td>14</td>
<td>4%</td>
</tr>
<tr>
<td>Discomfort (device)</td>
<td>10</td>
<td>3%</td>
</tr>
<tr>
<td>Infection</td>
<td>2</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Post-Op – Other</td>
<td>14</td>
<td>4%</td>
</tr>
<tr>
<td>Stimulation related discomfort</td>
<td>41</td>
<td>12%</td>
</tr>
<tr>
<td>Tongue abrasion</td>
<td>12</td>
<td>3%</td>
</tr>
<tr>
<td>Insomnia/Arousal</td>
<td>10</td>
<td>3%</td>
</tr>
<tr>
<td>Revision interventions (including explant)</td>
<td>1</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Other Discomfort</td>
<td>12</td>
<td>3%</td>
</tr>
<tr>
<td>Activation - Other</td>
<td>37</td>
<td>3%</td>
</tr>
<tr>
<td>Total</td>
<td>161</td>
<td>46%</td>
</tr>
</tbody>
</table>
Adhere Registry Physician Global Impression: 92% of patients had improvement at 12-months

92% reported improvement

Final Visit (418)

- 46% Very much improved
- 34% Much improved
- 12% Minimally improved
- 4% No change
- 2% Minimally worse
- 3% Much worse
- 1% Very much worse
High Patient Satisfaction

How does Inspire compare against your previous experience with CPAP? (n=378)

- Inspire is much better than CPAP: 88%
- CPAP is a little better than Inspire: 7%
- Inspire and CPAP are about the same: 7%
- CPAP is a little better than Inspire: 20%
- CPAP is much better than Inspire: 26%

I would recommend Inspire to a friend or family member (n=390)

- Strongly agree: 96%
- Agree: 70%
- Neither agree or disagree: 21%
- Disagree: 7%
- Strongly disagree: 3%

Given the chance, I would choose to receive Inspire again (n=390)

- Strongly agree: 94%
- Agree: 74%
- Neither agree or disagree: 20%
- Disagree: 7%
- Strongly disagree: 4%

Overall, how satisfied are you with Inspire? (n=391)

- Strongly agree: 93%
- Agree: 72%
- Neither agree or disagree: 21%
- Disagree: 7%
- Strongly disagree: 5%
High Patient Adherence
Usage of 5.6 hr/night is higher than CPAP clinical trials

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Usage Hours / Night at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspire ADHERE @ 12-months</td>
<td>5.6</td>
</tr>
<tr>
<td>(n=421)</td>
<td></td>
</tr>
<tr>
<td>APPLES trial @ 6-mo</td>
<td>4.2</td>
</tr>
<tr>
<td>(n=442)</td>
<td></td>
</tr>
<tr>
<td>SAVE Trial @ 12-mo</td>
<td>3.5</td>
</tr>
<tr>
<td>(n=1346)</td>
<td></td>
</tr>
</tbody>
</table>

Therapy Usage Hours / Night at 12 months

References:
1. ADHERE-1000: Thaler, Laryngoscope 2019
2. APPLES: Kushida, Sleep 2012
4. Medicare PAP "guideline" is 4 hours / night, 5 nights per week, within a 30 consecutive day period
Improved understanding of approaching the hypoglossal nerve
Locating digastric & mylohyoid can prevent “mistaken identity” of mylohyoid nerve vs. hypoglossal nerve

Previous understanding – digastric runs horizontal

Current understanding – digastric fibers run more vertical

1 - Retract digastric muscle
2 – Retract Mylohyoid muscle
3 – HGN at anterior SMG, under mylohyoid

Heiser, Update on Operative Techniques, Laryngoscope 2016
Example: Clinica Navarra Case Report of mistaken nerve

**Introduction**
Surgical challenges during hypoglossal nerve stimulation surgery aren’t common and they are usually related to identification of the medial division branches. We report an unusual case of an undescribed setback in which the mylohyoid nerve was confused for the hypoglossal nerve.

**Clinical Case**
62-year old man with a five-year history of OSA, with CPAP intolerance. A body mass index (BMI) of 24, an Epworth Sleepiness Scale 9/24, and AHI of 47/hour, and history of tonsillectomy during childhood. Physical examination, awake endoscopy and drug-induced sleep endoscopy (DISE) revealed an antero-posterior soft palate and tongue base collapse. Having met surgical implantation criteria, upper airway stimulation surgery and an Inspire system implant were indicated.

- Mylohyoid nerve (MHN) runs along the mylohyoid muscle, similar path as HGN, but is smaller in caliber
- NIM testing of mylohyoid can also appear to have tongue protrusion
- Hypoglossal nerve (HGN) is deep to the mylohyoid muscle
- Clear identification of muscle layers can avoid ‘mistaken identity’ of MHN for HGN
Post-hoc predictors of therapy response

- Multiple ways to define response to therapy (AHI, ESS, usage, or combination of these)

- Sleep surgeons measure success by the “Sher Response Rate”
  - 50% decrease in AHI, and \( \leq 20 \) events/hour

- STAR 1-year responder rate: 66%
- ADHERE-1000 1-year responder rate: 69%

- Can we identify potential predictors of increased response?
All subpopulations showed significant success
Females, and lower BMI had greater magnitude improvement

- Univariate / multi-variate regression of demographics vs. AHI response (Sher Criterion)

- Predictors of highest success were:
  - Female Gender - 94% increased odds of favorable response vs males (ie, 80% vs 67% Response)
  - Lower BMI - every 1pt. decrease in BMI associated with 8% higher odds of favorable AHI response

- Age nor baseline AHI did not predict response

- Suggests a biological mechanism or phenotype that is more sensitive to UAS

These are retrospective findings and not intended to change patient selection

Univariate model for therapy response

Therapy response is defined as at least 50% reduction of AHI to less than 20.
Both genders had significant reduction in AHI
ADHERE Registry Update Summary

**Largest** real-world data collection of upper airway stimulation for treatment of OSA to date

Reduced OSA severity, sustained through 12-months, **consistent** with multiple other studies

Improved patient symptoms, and **high satisfaction**

Maintained high therapy **adherence** after 12 months
Multi-variate model with stepwise selection – gender and BMI were retained as predictors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariable Results</th>
<th>Multivariable Results</th>
<th>Multivariable Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (p-value)</td>
<td>95% CI for OR</td>
<td>OR (p-value)</td>
</tr>
<tr>
<td>Sex (Female vs Male)</td>
<td>1.943 (0.0457)</td>
<td>1.013, 3.729</td>
<td>3.634 (0.0041)</td>
</tr>
<tr>
<td>Age at consent</td>
<td>1.014 (0.1862)</td>
<td>0.993, 1.034</td>
<td>1.000 (0.9998)</td>
</tr>
<tr>
<td>BMI at baseline</td>
<td>0.915 (0.0028)</td>
<td>0.863, 0.970</td>
<td>0.913 (0.0108)</td>
</tr>
<tr>
<td>Baseline AHI</td>
<td>0.993 (0.2914)</td>
<td>0.979, 1.006</td>
<td>1.006 (0.5198)</td>
</tr>
<tr>
<td>Tongue motion</td>
<td>P = 0.6414</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral protrusion vs. Right protrusion</td>
<td>1.312 (0.3488)</td>
<td>0.743, 2.318</td>
<td>1.554 (0.1645)</td>
</tr>
<tr>
<td>Bilateral or right protrusion vs. Other</td>
<td>0.963 (0.9244)</td>
<td>0.442, 2.100</td>
<td>-</td>
</tr>
<tr>
<td>Other vs. Right protrusion</td>
<td>1.284 (0.5843)</td>
<td>0.525, 3.141</td>
<td>1.339 (0.6320)</td>
</tr>
<tr>
<td>Therapy hours per week at 6-mo</td>
<td>1.011 (0.2457)</td>
<td>0.993, 1.029</td>
<td>1.004 (0.8103)</td>
</tr>
<tr>
<td>&lt;28 hours vs ≥28 hours at 6-months</td>
<td>0.726 (0.3864)</td>
<td>0.352, 1.498</td>
<td>1.130 (0.8362)</td>
</tr>
<tr>
<td>Therapy hours per week at 12-mo</td>
<td>1.017 (0.0390)</td>
<td>1.001, 1.033</td>
<td>1.001 (0.9668)</td>
</tr>
<tr>
<td>&lt;28 hours vs ≥28 hours at 12-months</td>
<td>0.622 (0.0769)</td>
<td>0.367, 1.053</td>
<td>0.651 (0.3732)</td>
</tr>
</tbody>
</table>

- Gender, baseline BMI, and binary therapy use (<28 hours vs ≥28 hours) at final follow-up were entered into the model in the first, second, and third step. No other variable met the chi-square score of 0.2 significance level for entry into the model.