Neuromuscular Electrical Stimulation for Treatment of OSA and Snoring

A daytime therapy for mild obstructive sleep apnea and snoring

FDA-AUTHORIZED (de novo) FEBRUARY 2021
Introduction and Disclosure
Background information
Background information

Mild OSA requires treatment

Mild OSA is common

• In the United States, ~54 million adults aged 30–69 years have OSA
• Of these, ~30.5 million fall in the mild range (AHI 5-14.9 events/hour)

Patients with mild OSA are...

• More likely to report poor quality of life than controls
  Sleep Heart Health Study: OR 1.2 after adjusting for age, gender, ethnicity, BMI, marital status, smoking, years of education, sleep medications, and co-morbidities

• 224% increased risk of developing hypertension than controls
  Penn State Cohort: HR 3.24 after adjusting for age, sex, race, smoking, BMI, OSA treatment, diabetes, and baseline blood pressure

• 59% more likely to have abnormal fasting glucose
  Multi-Ethnic Study of Atherosclerosis: OR 1.59 after adjusting for age, sex, and ethnicity

• 83% more likely to be diagnosed with diabetes
  Wisconsin Sleep Cohort: OR 1.83 after adjusting for age and sex

OSA tends to worsen over time

• Longitudinal studies suggest a slow, steady progression in OSA severity over time
Background information

Device-based therapy options require night-time use

<table>
<thead>
<tr>
<th>Primary Snoring</th>
<th>Mild OSA</th>
<th>Moderate OSA</th>
<th>Severe OSA</th>
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<tbody>
<tr>
<td>AHI 5 events/hour</td>
<td>AHI 15 events/hour</td>
<td>AHI 30 events/hour</td>
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</table>

Treatment Continuum

- Positional therapy devices
- Oral appliances
- If PAP is refused

With comorbidities

- Positive airway pressure: CPAP | APAP | BPAP
- Implanted devices: Hypoglossal nerve stimulation (2nd line)
Background information
Effectiveness of night-time therapy is limited by sub-optimal adherence

Efficacy ≠ effectiveness

• Efficacy: Treatment performance in ideal, controlled conditions
• Effectiveness: Treatment performance in real-world conditions

CMS definition of PAP adherence

• ≥4 hours/night on 70% of nights, over a consecutive 30-day period within the first 90 days of therapy

Approximately 54-75%\(^1\) of patients reach this threshold
Patients with mild OSA are 34% less likely to be adherent to PAP\(^4\)

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Introduction to eXciteOSA

PAP efficacy versus effectiveness

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10pm 8 hours of sleep 6am

<table>
<thead>
<tr>
<th>PAP worn for 4 hours</th>
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<td>Residual AHI (on-therapy) 5 events/hour</td>
<td>Off-therapy AHI 15 events/hour</td>
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5 events/hour is the cut-point for acceptable PAP treatment
15 events/hour is the cut-point for mild vs. moderate OSA

Full-night residual AHI 10 events/hour

Represents 33% effectiveness

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1. Ravesloot, MJL, de Vries, N. Reliable calculation of the efficacy of non-surgical and surgical treatment of obstructive sleep apnea revisited. Sleep 34(1):105-110 (2011). Image shown here is Figure 1 from Ravesloot & de Vries.
# Introduction to eXciteOSA

## PAP efficacy versus effectiveness

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<th>Time</th>
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<th>6am</th>
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| 10pm      | PAP worn for 4 hours  
Residual AHI (on-therapy) 5 events/hour | PAP removed for 4 hours  
Off-therapy AHI 15 events/hour | Full-night residual AHI 10 events/hour  
Represents 33% effectiveness\(^1\) |
|           | PAP worn for 4 hours  
Residual AHI (on-therapy) 5 events/hour | PAP removed for 4 hours  
Off-therapy AHI 10 events/hour | Full-night residual AHI 7.5 events/hour  
Represents 25% effectiveness |
|           | PAP worn for 5 hours  
Residual AHI (on-therapy) 5 events/hour | PAP removed for 3 hours  
Off-therapy AHI 10 events/hour | Full-night residual AHI 6.9 events/hour  
Represents 31% effectiveness |

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1. Ravesloot, MJL, de Vries, N. Reliable calculation of the efficacy of non-surgical and surgical treatment of obstructive sleep apnea revisited. *Sleep* 34(1):105-110 (2011). Image shown here is Figure 1 from Ravesloot & de Vries.
Background information

Introducing eXciteOSA for primary snoring and mild OSA

### Treatment Continuum

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#### eXciteOSA daytime therapy
Intraoral neuromuscular electrical stimulation

- **eXciteOSA is not labeled for use in moderate OSA**
- **Clinical research is ongoing**

- **Positional therapy devices**
- **Oral appliances**
- **With comorbidities**

- **If PAP is refused**
- **Positive airway pressure**
  - CPAP | APAP | BPAP

- **Implanted devices**
  - Hypoglossal nerve stimulation (2nd line)
Introduction to NMES and eXciteOSA
Introduction to eXciteOSA

The role of the genioglossus in OSA pathophysiology

- The largest upper airway muscle is the genioglossus
- The genioglossus is necessary and sufficient for maintaining upper airway patency\(^1\)
- As in all skeletal muscles, the genioglossus consists of:
  - Type I (slow twitch)
  - Type IIA (fast twitch; oxidative)
  - Type IIB (fast twitch; glycolytic)

Introduction to eXciteOSA

The role of the genioglossus in OSA pathophysiology

• The genioglossus of OSA patients has ↑ Type II and ↓ Type I fibers compared with controls\(^1,2\)

• This corresponds to increased \textit{in vitro} fatiguability of these fibers


Introduction to eXciteOSA

The role of the genioglossus in OSA pathophysiology

• The genioglossus of OSA patients has ↑ Type II and ↓ Type I fibers compared with controls¹,²

• This corresponds to increased in vitro fatiguability of these fibers

• Finally, both muscle fiber composition and function appear to be reversible with OSA treatment

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Introduction to eXciteOSA

The role of the genioglossus in OSA pathophysiology

Introduction to eXciteOSA

The role of the genioglossus in OSA pathophysiology

A direct measurement of localized muscle fatigue

Measured with custom-fit EMG electrode array placed on the tongue surface

Muscle fiber conduction velocity (normalized to initial value)

- Controls

- OSA patients

\( p = 0.03 \) between groups

\( p = 0.04 \) group-by-time interaction


Images shown here are Figures 1 and 3 from McSharry et al.
Introduction to eXciteOSA
Intraoral neuromuscular electrical stimulation

Apneas and hypopneas are caused by collapse of the upper airway

Studies have demonstrated that patients with OSA have reduced genioglossus endurance

eXciteOSA stimulates the genioglossus with targeted electrical current (3-20Hz)

NMES at similar frequencies causes fast-to-slow twitch muscle fiber transitions in skeletal muscles\(^1,2\)
It is hypothesized that intraoral NMES promotes a shift from Type IIa/b to Type I muscle fibers

eXciteOSA is associated with significant AHI reductions (see next slides)
A recent study reported increased genioglossus endurance associated with eXciteOSA

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The clinical experience
The clinical experience

Therapy phases

Phase 1
- 20 minutes a session
- 1 time each day
- 6 weeks

Phase 2
- 2 times per week or more
The clinical experience

Therapy phases
The clinical experience

Stimulation frequencies

- 3 Hz
- 10 Hz
- 20 Hz
- 10 Hz

[Image of stimulation frequencies]
The clinical experience

Stimulation levels

• Stimulation ranges from 1-15, controlled in the app

• Tolerance to stimulation varies by patient, and generally increases over time

• Patients should use therapy at their highest tolerable level
The clinical experience
eXciteOSA clinician portal
Overview of clinical trials

In the following slides, an asterix * refers to a post-hoc analysis of source data from the referenced study.
In all cases, the source data are maintained on file at Signifier Medical Technologies.
## Overview of clinical trials

### Peer-reviewed manuscripts

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Single-center, single-arm trial</td>
<td>n=70 (AHI&lt;15) Subset: Interim analysis</td>
<td>n=115 (AHI&lt;15) Full participant sample</td>
<td>n=65 (AHI 5-14.9) Subset: Mild OSA only</td>
<td>n=20 (AHI&lt;15 during screening sleep test; PSG then performed for research)</td>
</tr>
<tr>
<td>Country</td>
<td>Germany &amp; UK</td>
<td>UK</td>
<td>UK &amp; Spain</td>
<td>UK &amp; Spain</td>
<td>USA</td>
</tr>
<tr>
<td>Duration</td>
<td>Six weeks treatment Home sleep test at baseline</td>
<td>Six weeks treatment Two home sleep tests pre- and post</td>
<td>4-6 weeks treatment PSG pre- and post</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Change in AHI (events/hr) | Not captured | Mild OSA subset: -5.1 /hour (from 9.8 to 4.7) | Not reported for mild OSA subset | Mild OSA: -3.4 /hour (from 10.2 to 6.8) | Mild OSA subset: -10.0 /hour (from 17.4 to 7.4) *
| Change in ESS (0-24 points) | Not captured | Mild OSA subset: -3.9 /24 (from 9.0 to 5.1) | Not reported for mild OSA subset | Mild OSA: -3.4 /24 (from 8.7 to 5.3) | Not reported for mild OSA subset |
| Change in snoring | Bed-partner reported snoring ↓44% | See full sample data | Objective snoring >40dB +14%; Bed-partner reported snoring ↓39% | See full sample data | No significant change in snoring |
| Sleep quality | Not captured | See full sample data | Self-reported sleep quality improvement (PSQI; p<0.001) Bed-partner reported sleep quality improvement (PSQI; p=0.02) | See full sample data | Self-reported sleep quality improvement (PSQI; p<0.03) Sleep efficiency during PSG increased from 75% to 84% (p<0.002) |
| Device usage / adherence | Not captured | Device used 83% of days, on average | Device used 83% of days, on average | Device used 85% of days, on average | 86% (percentage of days with ≥1 session) |

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* Post hoc analysis of Nokes et al. Physiological Reports (in press; 2022)
Overview of clinical trials

Impact of eXciteOSA on snoring

Statistically-significant reductions in bed-partner reported snoring assessed in a two-week diary

Statistically-significant reductions in objectively-measured snoring above thresholds of 40, 45, and 50dB

40dB is the threshold that the WHO uses to define night-time noise pollution

Overview of clinical trials
Impact of eXciteOSA on OSA severity

Amongst all participants with mild OSA at baseline, eXciteOSA was associated with a 33% reduction in the AHI on average 78% were identified as responders; these participants experienced a 52% reduction in the AHI on average.

- **Baseline**: 10.2
- **Follow-Up**: 6.8

**Responders (n=51 of 65; 78%)**
- **Baseline**: 10.4
- **Follow-Up**: 5.0

**Multi-center UK/EU trial**
- 46% of OSA patients normalized their AHI (<5 events/hour) over a full night*

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Clinical Presentation; Version 6 (30-June-2022)
Overview of clinical trials

Impact of eXciteOSA on OSA severity

Amongst all participants with mild OSA at baseline, eXciteOSA was associated with a 33% reduction in the AHI on average. 
78% were identified as responders; these participants experienced a 52% reduction in the AHI on average.

In a subsequent trial at UCSD, participants with mild OSA experienced a 57% reduction in the AHI on average (n=11; p>0.05)

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Amongst all participants with mild OSA at baseline, eXciteOSA was associated with a 33% reduction in the AHI on average (78% were identified as responders; these participants experienced a 52% reduction in the AHI on average).

In a subsequent trial at UCSD, participants with mild OSA experienced a 57% reduction in the AHI on average (*p*=0.28).

**Usage:** 86% of days with ≥1 session (UCSD trial)

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Overview of clinical trials

Impact of eXciteOSA on OSA severity

Amongst all participants with mild OSA at baseline, the average Epworth Sleepiness Scale score dropped by 3.4 points
Amongst all participants with mild OSA at baseline, the average Epworth Sleepiness Scale score dropped by 3.4 points. The 4% ODI reduced by 30% on average amongst the responder group, the 4% ODI reduced by 50% on average.
Overview of clinical trials

Adverse events related to eXciteOSA

No serious adverse events were reported. 85% of study participants did not experience any related adverse events. Reported side effects were limited to each 20-minute therapy session, with no ongoing effects.

Overview of clinical trials

Mechanism of action

- Participants had primary snoring \((n=9)\) or mild OSA \((n=11)\) diagnosed in a previous HSAT
- Those with OSA experienced a 57% reduction in their AHI over 4-6 weeks *
- Participants experienced a significant increase in genioglossus endurance, but not strength, as anticipated
- No difference in genioglossus EMG (tonic or phasic; total sleep or NREM sleep)

![IOPI device measures tongue strength and endurance](https://iopimedical.com/)

![Graphs showing no change in tongue strength and significantly increased tongue endurance](https://iopimedical.com/)


*Post-hoc analysis of Nokes et al. *Physiological Reports* (in-press; 2022)
Overview of clinical trials
Considering the effective AHI

- **PAP worn for 4 hours**
  - Residual AHI (on-therapy) 5 events/hour

- **PAP removed for 4 hours**
  - Off-therapy AHI 15 events/hour

= Full-night residual AHI 10.0 events/hour
  - Represents 33% effectiveness

- **PAP worn for 4 hours**
  - Residual AHI (on-therapy) 5 events/hour

- **PAP removed for 4 hours**
  - Off-therapy AHI 10.2 events/hour

= Full-night residual AHI 7.6 events/hour
  - Represents 25% effectiveness

- **PAP worn for 5 hours**
  - Residual AHI (on-therapy) 5 events/hour

- **PAP removed for 3 hours**
  - Off-therapy AHI 10.2 events/hour

= Full-night residual AHI 7.0 events/hour
  - Represents 32% effectiveness

- **PAP worn for 5 hours**
  - Residual AHI (on-therapy) 5 events/hour

- **PAP removed for 3 hours**
  - Off-therapy AHI 10.2 events/hour

= Full-night residual AHI 10.2 events/hour
  - Represents 32% effectiveness

- **eXciteOSA requires no night-time use**

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### Overview of clinical trials

**Ongoing studies**  
Up to date as of June 2022

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Sample size</th>
<th>Site/s</th>
<th>Design</th>
<th>Aims</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild OSA (Multi-site) NCT04392765</td>
<td>n=80</td>
<td>Europe and Canada (Valencia, Pamplona, Amsterdam, Montreal, Vancouver, Berlin)</td>
<td>Single-arm trial</td>
<td>Aims to assess long-term efficacy of, and adherence to, eXciteOSA over up to 12 months</td>
</tr>
<tr>
<td>Mild OSA (Single-site) NCT04974515</td>
<td>n=40</td>
<td>United States (University of Miami, FL)</td>
<td>Randomized controlled trial; double-blinded</td>
<td>Aims to assess adherence to eXciteOSA (primary outcome) delivered at high vs. low stimulation over six weeks</td>
</tr>
<tr>
<td>Mild OSA (Multi-site) NCT05183009</td>
<td>n=102</td>
<td>United States (St. Louis MO, Birmingham AL, Baltimore MD, Colorado Springs CO, Columbia SC, Lehigh Acres FL, Columbus OH)</td>
<td>Randomized controlled trial; open-label</td>
<td>Aims to assess the impact of treatment (two doses) vs. no treatment on the REI (primary outcome) over six weeks</td>
</tr>
<tr>
<td>Moderate OSA (Multi-site) NCT05252156</td>
<td>n=62</td>
<td>United States (St. Louis MO, Birmingham AL, Baltimore MD, Colorado Springs CO, Columbia SC, Lehigh Acres FL, Columbus OH)</td>
<td>Randomized controlled trial; open-label</td>
<td>Aims to assess the impact of treatment vs. no treatment on the REI (primary outcome) over six weeks</td>
</tr>
<tr>
<td>…and further studies to understand the mechanism of action and which patients are most likely to respond</td>
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</table>

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Clinical Presentation; Version 6 (30-June-2022)
Real-world evidence
Real world evidence

FDA authorized in February 2021, Commercial release in US April 2021

- **Uptake and usage:**
  - United States
    - 4045 Patients
    - 83% Adherence
    - 463 Clinics
    - 228,000 Sessions completed
    - 4.60 Million Minutes of therapy
eXciteOSA Case Study

44 year old male with mild OSA (AHI 11.4) and snoring, otherwise healthy and normal weight

Tried CPAP and MAD, unable to tolerate

Unrefreshed sleep, daytime fatigue, overall low energy

Managed symptoms by napping daily

Pre eXciteOSA, the snore app shows:
Nearly 2 hours of snore time
Majority of snore intensity is loud

Began eXciteOSA therapy May 14
June 13

After 29 sessions, this Day view shows snore time reduced to 13 minutes, 30 seconds.

The majority of the snore intensity is light.
eXciteOSA Therapy, June 1

After 17 therapy sessions, the Month view shows an average 46 minutes and 31 seconds of snore time, and it has become quieter.

Note the decrease in light and loud snore Intensity denoted by the red and yellow segments in the bar graph.
June 29

Phase 1 of eXciteOSA therapy is complete

Note how little Loud snore time is reported

Monthly average snore time is 31 minutes and 26 seconds

Symptoms improved! More energy, sleeps better, no problem waking up and no nap required
Further resources
Further resources

Regulatory information; United States us

- eXciteOSA was FDA-authorized (de novo; DEN200018) on February 5th, 2021
- **Regulation:** 21 CFR 872.5575; Neuromuscular tongue muscle stimulator for the reduction of snoring and obstructive sleep apnea
- **Regulatory Class:** Class II
- **Intended Use:** eXciteOSA is intended for the reduction of snoring and mild obstruction sleep apnea by strengthening tongue muscles via electrical muscle stimulation
- **Indications for Use:** eXciteOSA is a removable tongue muscle stimulation device that delivers neuromuscular stimulation to the tongue in order to reduce mild obstructive sleep apnea (AHI <15) and snoring for patients that are 18 years or older
- **Contraindications**
  - Confirmed or suspected pregnancy
  - Pacemaker or implanted electrodes
  - Temporary or permanent metal implants, dental braces, intraoral metal prosthesis/restorations/appliances, or dental jewelry in the mouth
  - Suffering from mouth ulcers
  - Confirmed or suspected AHI ≥ 15 events/hour

Please refer to the Instructions for Use for complete guidance
**Further resources**

**Reimbursement:** [https://exciteosa.com/support-hub/reimbursement/](https://exciteosa.com/support-hub/reimbursement/)

<table>
<thead>
<tr>
<th>Commercial Payer Patients</th>
<th>Medicare Patients</th>
<th>Medicaid Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Here you’ll find a complete set of resources dedicated to eXciteOSA® submissions to Commercial Payers.</td>
<td>Please use these templated materials and letters of medical necessity and appeals for Medicare</td>
<td>Please use these templated materials and letters of medical necessity and appeals for Medicaid</td>
</tr>
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| Medicare Documentation Checklist for Physicians | Download |
| Medicare Documentation Checklist for DME suppliers | Download |
| Payer Summary Reference | Download |
| Patient Reimbursement Guide for eXciteOSA | Download |

reimbursement@signifiermedical.com
Further resources

Physician resources

Visit www.exciteosa.com for resources including:

Instructions for use; brochures; case studies
Patient screening questionnaire
Patient education resources
Marketing resources
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DAYTIME THERAPY FOR YOUR MILD OSA & SNORING PATIENTS

exciteOSA